E-ISSN 2757-7392

2026 Vol 7 Issue 3

HEPATOLOGY FORUM



FEATURED IN THIS ISSUE

Turkish Association for the Study of the Liver

MASLD GUIDANCE

ISSN: 1307-5888 / E-ISSN 2757-7392

Editorial Board

Editor-in-Chief

Ulus Salih Akarca
ulus.salih.akarca@ege.edu.tr

Associate Editors (Alphabetically)

Ali Riza Caliskan
Department of Gastroenterology, Adiyaman Training and Research Hospital, Adiyaman, Türkiye
komamir02@hotmail.com

Berna Savas
Department of Pathology, Ankara University School of Medicine, Ankara, Türkiye
bernasavas@gmail.com

Cem Simsek
Department of Gastroenterology, Hacettepe University School of Medicine, Ankara, Türkiye
cemsimsek90@gmail.com

Cemal Nuri Ercin
Department of Gastroenterology, Saglik Bilimleri University Gulhane School of Medicine, Ankara, Türkiye
cnercin@hotmail.com

Coskun Ozer Demirtas
Department of Gastroenterology, Marmara University School of Medicine, Istanbul, Türkiye
coskun_demirtas10@hotmail.com

Cumali Efe
Department of Gastroenterology, Harran University Faculty of Medicine, Sanliurfa, Türkiye
scumaliefe@gmail.com

Dilara Turan Gokce
Department of Gastroenterology, Ankara University School of Medicine, Ankara, Türkiye
dilaraturan89@yahoo.com

Fatih Guzelbulut
Department of Gastroenterology, Haydarpasa Numune Training and Research Hospital, Istanbul, Türkiye
fguzelbulut@hotmail.com

Gokhan Kabacam
Department of Gastroenterology, Guven Hospital, Ankara, Türkiye
gokhankabacam@yahoo.com

Gupse Adali
Department of Gastroenterology, University of Health Sciences Istanbul Umraniye Training and Research Hospital, Istanbul, Türkiye
gupseadali@gmail.com

Hale Gokcan
Department of Gastroenterology, Ankara University, Ankara, Türkiye
halesumer@yahoo.com

Ilker Turan
Department of Gastroenterology, Ege University School of Medicine, Izmir, Türkiye
ilkerturan@gmail.com

Mujdat Zeybel
Department of Gastroenterology, Koc University School of Medicine, Istanbul, Türkiye
mzeybel@ku.edu.tr

Nuray Yazihan
Department of Pathophysiology, and Internal Medicine Ankara University School of Medicine, Ankara, Türkiye
Ankara University, Institute of Health Sciences, Interdisciplinary Food, Metabolism and Clinical Nutrition Department, Ankara, Türkiye
nurayyazihan@yahoo.com

Serkan Yaras
Department of Gastroenterology, Mersin University School of Medicine, Mersin, Türkiye
drserkan1975@hotmail.com

Suna Yapali
Department of Gastroenterology, Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Türkiye
sunayapali@yahoo.com

Yasemin Balaban
Department of Gastroenterology, Hacettepe University School of Medicine, Ankara, Türkiye
ybalaban@hacettepe.edu.tr

Yusuf Yilmaz
Department of Gastroenterology, Recep Tayyip Erdogan University, School of Medicine, Rize, Türkiye
dryusufyilmaz@gmail.com

Zarife Kuloglu
Department of Pediatrics, Ankara University School of Medicine, Ankara, Türkiye
zarifekuloglu@yahoo.com

International Associate Editors (Alphabetically)

Ahmet Gurakar, USA
Department of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, Baltimore, USA
aguraka1@jhmi.edu

Alexandre Louvet, France
University Hospital of Lille, France
alexandre.louvet@chru-lille.fr

Ali Canbay, Germany
Department of Gastroenterology, Hepatology, and Infectious Diseases, Magdeburg University Hospital, Magdeburg, Germany
ali.canbay@med.ovgu.de

Ashok Kumar Choudhury, India
Associate Professor of Hepatology and Liver Transplant Institute of Liver & Biliary Sciences D-1 Vasant Kunj New Delhi, India
Ashokkumar123@gmail.com

Azra Husic-Selimovic, Bosnia and Herzegovina
General Hospital Abdulah Nakas
husic_azra@yahoo.com

Eda Kaya, Germany
Department of Medicine Universitätsklinikum Knappschaftskrankenhaus Bochum, Germany
edakaya93@gmail.com

Georgios Papatheodoridis, Greece
Department of Gastroenterology and Hepatology, National and Kapodistrian University of Athens Medical School, Athens, Greece
gepapath@med.uoa.gr

Jasmohan Bajaj, USA
Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, Virginia, USA
jasmohan.bajaj@vcuhealth.org

Jordan Feld, Canada
Department of Gastroenterology and Center for Liver Diseases, University of Toronto, Toronto, Canada
jordan.feld@uhn.ca

Ming-Hua Zheng, China
MAFLD Research Center, Department of Hepatology, the First Affiliated Hospital of Wenzhou Medical University, China
zhengmh@wmu.edu.cn

Patrick Kamath, USA
Department of Gastroenterology and Hepatology, Mayo Clinic College of Medicine, Rochester, MN, USA
kamath.patrick@mayo.edu

Paul Kwo, USA
Department of Gastroenterology and Hepatology, Stanford University Medical Center, CA, USA
pkwo@stanford.edu

Senem Ceren Karatay, Germany
Department of Medicine II, Saarland University Medical Center, Saarland University, Homburg, Germany
senem.oezen-karatayli@uks.eu

Sevda Agayeva, Azerbaijan
Department of Gastroenterology, Baku Medical Plaza Hospital, Baku, Azerbaijan
seva_agayeva@yahoo.com

Sukru Emre, USA
Transplant and Immunology Center Yale School of Medicine, New Haven, CT, USA
sukru.emre@yale.edu

Timucin Taner, USA
Department of Surgery, Mayo Clinic College of Medicine, Rochester, MN, USA
taner.timucin@mayo.edu

Managing Editor

Cumali Efe
Department of Gastroenterology, Harran University Faculty of Medicine, Sanliurfa, Türkiye
scumaliefe@gmail.com

Consulting Biostatistician

Beyza Doganay
Department of Biostatistics, Ankara University School of Medicine, Ankara, Türkiye
bdoganay@medicine.ankara.edu.tr

Editors Emeriti

Nurdan Tozun, Founding Editor
Department of Gastroenterology, Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Türkiye
nurdantozun@hotmail.com

Bulent Degertekin
Department of Gastroenterology, Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Türkiye
degertekinb@hotmail.com

TASL Governing Board 2025–2027

Bulent Degertekin
Department of Gastroenterology, Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Türkiye
degertekinb@hotmail.com

Gupse Adali
Department of Gastroenterology, University of Health Sciences, Istanbul Umraniye Training and Research Hospital, Istanbul, Türkiye
gupseadali@gmail.com

Suna Yapali
Department of Gastroenterology, Acibadem Mehmet Ali Aydinlar University, School of Medicine, Istanbul, Türkiye
sunayapali@yahoo.com

Remzi Adnan Akdogan
Department of Gastroenterology, Recep Tayyip Erdogan University, School of Medicine, Rize, Türkiye
remzi.akdogan@erdogan.edu.tr

Cumali Efe
Department of Gastroenterology, Harran University Faculty of Medicine, Sanliurfa, Türkiye
scumaliefe@gmail.com

Onur Keskin
Department of Gastroenterology, Hacettepe University School of Medicine, Ankara, Türkiye
onurkeskin81@gmail.com

Ramazan Idilman
Department of Gastroenterology, Ankara University School of Medicine, Ankara, Türkiye
ramazan.idilman@medicine.ankara.edu.tr

Information for Authors

Hepatology Forum welcomes original articles, reviews, case reports, clinical images, and letters. All manuscripts must be submitted via the online submission system at **www.hepatologyforum.org**. Please consult the website for the most current instructions, formatting guidelines, and ethical policies.

Abstracting and Indexing

Hepatology Forum is indexed in **PubMed**, **PubMed Central**, **Web of Science (ESCI)**, **EBSCO**, **ProQuest**, **Open Ukrainian Citation Index**, **CAS, MIAR (2024), TUBITAK TR Index (2022)** and **Türkiye Citation Index**.

Contact

Editor in Chief: Prof. Ulus Salih Akarca
Address: EKD, 184 S, 1/4, 35100, Bornova, Izmir
E-mail: ulus.salih.akarca@ege.edu.tr

Turkish Association for the Study of the Liver
Address: Inonu mah. Cumhuriyet cad. No: 131 Mutlu apt. Kat: 4 D: 5 Harbiye, Istanbul/Türkiye
Phone: +90 212 244 30 71
Fax: +90 212 234 19 60
Web: www.tasl.org.tr
E-mail: tasl@tasl.org.tr

Publisher: Kare Media
Address: Goztepe Mahallesi, Fahrettin Kerim Gokay Caddesi, No: 200, Daire: 2, Kadikoy, Istanbul/Türkiye
Phone: +90 216 550 61 11
Fax: +90 216 550 61 12
Web: www.karepb.com
E-mail: kare@karepb.com

Volume 7 Issue 3 July 2026

Contents

Practice Guidance

TASL practice guidance for the diagnosis and management of metabolic dysfunction-associated steatotic liver disease (MASLD) 177
Yilmaz Y, Adali G, Ergenc I, Kaya E, Turan Gokce D, Keklikkiran C, Zeybel M, Dogay Us G, Degertekin B, Idilman R, Turkish Association for the Study of the Liver (TASL) Obesity and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) Special Interest Group (SIG): Akarca US, Karasu Z, Kaymakoglu S, Tozun N, Uygun A

Invited Editorial

Body composition in glucagon-like peptide-1 receptor agonist therapy: Absolute loss, relative changes, and outcomes.....215
Chen S, Liu W-Y, Targher G, Byrne CD, Yilmaz Y, Zheng MH

Systematic Reviews

Duration of vasoconstrictors after endoscopic variceal ligation in acute variceal bleeding: A systematic review and network meta-analysis.....218
Giri S, Panda S, Singh A, Varghese J, Ingawale S, Tapper EB, Rockey DC, Choudhury A

Large language models in hepatology: A systematic review 227
Suenghataiphorn T, Tribuddharat N, Danpanichkul P, Kulthamrongsri N

Reviews

WHO 2024 Hepatitis B Guidelines: No more gray zone for low- and middle-income countries? An evaluation.....236
Saravanan S, Vignesh R, Shankar EM, Sivadoss R, Sivamalar S, Velu V, Balakrishnan P, Venkateswaran AR

MELD 3.0: Exploring and expanding its utility beyond transplantation.....241
Reddy Kalluru PK, Buhulaigah HE, Allikesam KK, Kuchi D, Muqtadir A, Onteddu N, Cherukuri A, Allagadda T, Kamakkagari M, Rajali H

Original Articles

Artificial intelligence-based multiclass classification of etiologies in patients with elevated liver enzymes: A prospective cohort study.....249
Ozden Y, Yuzugulen O, Buyukberber NM

Acetaminophen toxicity: Patterns of liver injury, effects on hospital length of stay, and the need for inpatient psychiatric care 256
Ozturk NB, Da BL, Ezaz G, Schiano TD

Shifts in liver biopsy indications and histopathological diagnoses: A report from a tertiary care center in Türkiye 262
Dalkilic YE, Parlar YE, Simsek C, Kiki Z, Dag O, Sokmensuer C, Balaban HY

Endoscopic ultrasound strain elastography in MASLD: Evaluation against transient elastography and non-invasive markers 269
Helal AE, ElBasiony M, Abdel-Razik A, Mousa N, Shiha G

Discriminative performance of non-invasive scoring systems for VCTE-defined steatosis and fibrosis in patients with psoriasis 277
Yuksel S, Ergun T, Ozdogan OC, Ozen Alahdab Y, Yilmaz V, Atmaca G, Kara U, Demirtas CO

Case Reports

Acute on chronic liver failure in erythropoietic protoporphyria: A case report and review of the literature 288
Viswanath A, Thomas RT, Kumar ES, Zachariah UG, Jose SK, Thomas M, Kodiatte TA

A fructose-intolerant patient with acute liver injury: Not only the active ingredient, but also excipients matter 292
Kaya E, Zedginidze A, Baraksei D, Canbay A, Tannapfel A, Goetze O

A rare but lethal hepatic infection: Emphysematous hepatitis – Case report and literature review 296
Okut G, Ugur MA, Yildiz H, Takci H, Dogan SM

Suspected azathioprine-induced hypersensitivity pneumonitis in a patient with autoimmune hepatitis: A rare case report.....302
Ketenci YB, Demiroz H, Akca M, Avcioglu U

Letters to the Editor

Albumin in hepatic encephalopathy: Evidence, prioritization, and the affordability gap in decompensated cirrhosis.....306
Alam MS, Khatoon N

Reply

Reply to the Letter to the Editor: "Albumin in hepatic encephalopathy: Evidence, prioritization, and the affordability gap in decompensated cirrhosis" 308
Covre Coan AC, Antunes VLJ, Prata AA, Milioli NJ, Correa TL, Martins OC, Romeiro P, Júnior ESB, Reis AM, Fernandes MV

Effects of rifaximin in fructose-induced steatohepatitis in rats 310
Kiyak M

Reply

Reply to the Letter to the Editor: "Effects of rifaximin in fructose-induced steatohepatitis in rats".....311
Cabuk Celik N, Yilmaz Goc R, Bahcecioglu IH, Ozercan IH, Tuzcu M, Ilhan N, Sahin K

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 177–214 DOI: 10.14744/hf.2026.44190

PRACTICE GUIDANCE

TASL practice guidance for the diagnosis and management of metabolic dysfunction-associated steatotic liver disease (MASLD)

Yusuf Yilmaz[1,2], Gupse Adali[3], Ilkay Ergenc[4], Eda Kaya[5], Dilara Turan Gokce[6], Caglayan Keklikkiran[1], Mujdat Zeybel[7], Gediz Dogay Us[8], Bulent Degertekin[9], Ramazan Idilman[6], Turkish Association for the Study of the Liver (TASL) Obesity and Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) Special Interest Group (SIG): Ulus Salih Akarca[10], Zeki Karasu[10], Sabahattin Kaymakoglu[11], Nurdan Tozun[12], Ahmet Uygun[13]

1: Department of Gastroenterology, Faculty of Medicine, Recep Tayyip Erdogan University, Rize, Türkiye
2: Dijitalpark Teknokent, İstanbul, Türkiye
3: Department of Gastroenterology, University of Health Sciences, Istanbul Umraniye Training and Research Hospital, Istanbul, Türkiye
4: The Roger Williams Institute of Liver Studies, King's College Hospital, London, UK
5: Department of Medicine, University Hospital Knappschaft Kliniken Bochum, Ruhr University Bochum, Bochum, Germany
6: Department of Gastroenterology, Ankara University Faculty of Medicine, Ankara, Türkiye
7: Department of Gastroenterology and Hepatology, Koc University Faculty of Medicine, Istanbul, Türkiye
8: School of Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, The Netherlands
9: Division of Gastroenterology and Hepatology, Acibadem Mehmet Ali Aydinlar University Faculty of Medicine, Istanbul, Türkiye
10: Department of Gastroenterology and Hepatology, Faculty of Medicine, Ege University, Izmir, Türkiye
11: Division of Gastroenterohepatology, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye
12: Department of Gastroenterology, Acibadem Mehmet Ali Aydinlar University Faculty of Medicine, Istanbul, Türkiye
13: Department of Gastroenterology, Gulhane Faculty of Medicine, Ankara, Türkiye

Points to Note

- **Synthesis of Current Evidence:** 99% of former NAFLD cases align with new MASLD criteria, and TASL 2026 guidance focuses on improving clinical approaches to management.
- **Major Controversies:** Debates continue over replacing liver biopsies with NITs (FIB-4/VCTE) and defining ideal patient profiles for new MASH therapies like resmetirom.
- **Future Directions:** Efforts focus on expanding Turkish epidemiological data, defining cancer screening strategies for non-cirrhotic MASLD, and monitoring long-term drug efficacy.

ABSTRACT

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide and represents a major and growing public health challenge in Türkiye. This guidance provides an updated, clinically oriented overview of the definition, epidemiology, screening, diagnosis, risk stratification, and management of MASLD, with particular emphasis on evolving nomenclature, non-invasive diagnostic pathways, and current treatment strategies. The document addresses the full clinical spectrum of disease, from steatosis and metabolic dysfunction-associated steatohepatitis (MASH) to advanced fibrosis, cirrhosis, hepatocellular carcinoma, and liver transplantation. The guidance also incorporates evidence and practice considerations relevant to the Turkish population, including local epidemiology, resource availability, and implementation challenges in real-world care. Finally, areas of uncertainty and evidence gaps are highlighted to support future research and locally relevant policy development.

Keywords: Cirrhosis, fibrosis, MASLD, MASH, metabolic dysfunction, steatotic liver disease.

How to cite this article: Yilmaz Y, Adali G, Ergenc I, Kaya E, Turan Gokce D, Keklikkiran C, et al. TASL practice guidance for the diagnosis and management of metabolic dysfunction-associated steatotic liver disease (MASLD). Hepatology Forum 2026; 7(3):177–214.

Received: June 19, 2026; **Revised:** June 29, 2026; **Accepted:** July 03, 2026; **Available Online:** July 27, 2026

Corresponding author: Yusuf Yilmaz; Department of Gastroenterology, Recep Tayyip Erdogan University Faculty of Medicine, Rize, Türkiye; **E-mail:** dryusufyilmaz@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Guidance development and Methodology

The Turkish Association for the Study of the Liver (TASL) Governing Board commissioned the development of this guidance in February 2026. An Executive Committee was appointed by the TASL MASLD Special Interest Group and it comprised Turkish hepatologists with recognized clinical and academic expertise in MASLD, including clinical trials, ensuring balanced representation across different levels of clinical and academic experience, from early career investigators to senior experts in the field. An Advisory Board was subsequently selected by the TASL Governing Board based on prolonged clinical and academic expertise in hepatology and MASLD.

The guidance was developed in accordance with the methodological principles for trustworthy guidelines articulated by the National Academy of Medicine (formerly the Institute of Medicine), the Guidelines International Network (GIN)–McMaster Guideline Development Checklist, and the Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument. The Executive Committee was responsible for formulating the clinical questions, supervising the evidence review, drafting the recommendations, and assigning the level of evidence and strength of the recommendations for each statement. The Advisory Board independently reviewed the full draft for scientific content, balance, and applicability to Turkish clinical practice. To mitigate intellectual and financial conflicts of interest, members who declared a relevant interest neither served as lead authors nor had a deciding vote on recommendations concerning the relevant product class.

The draft guidance was presented for open discussion at a hybrid TASL İstanbul meeting in April 2026 and was subsequently revised in response to feedback and suggestions received during the TASL National Congress in May 2026. Following the revision, the manuscript was circulated to the Advisory Board and finalized after incorporating additional comments and feedback.

The recommendations were developed independently and were not directly adopted from existing international guidance documents. Instead, the available evidence was identified, critically appraised, synthesized, and graded according to the standardized methodology detailed below, with particular consideration of its applicability to the Turkish population.

Scope and Target Audience

This practice guidance addresses the definition, epidemiology, screening, diagnosis, risk stratification, treatment, and long-term management of metabolic dysfunction-associated steatotic liver disease (MASLD) across its full clinical spectrum. It includes the use of non-invasive diagnostic tools, lifestyle and pharmacological treatment options, bariatric and endoscopic interventions, and the management of cirrhosis, hepatocellular carcinoma, and liver transplantation-related issues. The guidance is primarily intended for hepatologists, gastroenterologists, endocrinologists, internal medicine physicians, primary care physicians and other healthcare professionals involved in the multidisciplinary care of patients with MASLD in Türkiye.

Clinical Questions Addressed by this Guidance

This guidance was developed to address the following key clinical questions:

Each key question was structured a priori by the Executive Committee using the PICO framework (Population, Intervention or index test, Comparator, Outcome). Patient-important outcomes were prioritized and pre-specified, namely all-cause and liver-related mortality, progression to cirrhosis, hepatic decompensation, hepatocellular carcinoma, major adverse cardiovascular events, and diagnostic accuracy of non-invasive tests for advanced fibrosis. These PICO questions defined the eligibility criteria for the literature search and the structure of the corresponding recommendations.

- What is the current definition and classification of MASLD, including its relationship with steatotic liver disease (SLD), MASH, metabolic dysfunction and alcohol-related liver disease (MetALD)?
- Which individuals should be screened for MASLD and advanced fibrosis?
- What is the preferred diagnostic pathway for MASLD in routine clinical practice, including the role of non-invasive tests and liver biopsy?
- Which lifestyle interventions should be recommended, and what degree of weight loss is clinically meaningful?
- What is the role of liver-directed therapy, antidiabetic agents, lipid-lowering treatment, bariatric surgery, and endoscopic interventions?
- How should associated metabolic comorbidities and cardiovascular risk be assessed and managed?
- How should cirrhosis, portal hypertension, hepatocellular carcinoma risk, and liver transplantation-related issues be managed in patients with MASLD?

Literature Review

A structured literature review was conducted using PubMed/MEDLINE, Embase, Web of Science, and Scopus. The search strategy incorporated combinations of the following terms: MASLD, MASH, SLD, MAFLD, NAFLD, MetALD, fibrosis, cirrhosis, hepatocellular carcinoma, non-invasive tests, obesity, type 2 diabetes mellitus, dyslipidemia, hypertension, cardiovascular disease, chronic kidney disease, bariatric surgery, endoscopic therapy, and liver transplantation. All relevant evidence published up to April 2026 was considered.

Priority was given to systematic reviews, meta-analyses, randomized controlled trials, large observational cohort studies, and international clinical practice guidelines. Where available, particular consideration was given to epidemiological and clinical data from Türkiye to ensure the relevance and applicability of the recommendations to the Turkish population.

Search Strategy

The electronic search combined controlled vocabulary (MeSH/Emtree) with free-text keywords, linked by Boolean operators ("OR" with-

Table 1. Classification of evidence levels based on study designs and source types

Level	Definition (source types)
High	Consistent evidence from well-conducted randomized controlled trials, or systematic reviews/meta-analyses of such trials, or large robust prospective cohort studies; further research is unlikely to change confidence in the estimate.
Moderate	Real-world and registry data, retrospective cohorts, smaller or methodologically limited randomized trials, post-hoc or subgroup analyses, or indirect evidence; further research may change the estimate.
Low	Expert opinion, case series or case reports, mechanistic or physiological reasoning, narrative reviews, or substantial extrapolation from indirect populations.

in concepts, "AND" across concepts), and was adapted to the syntax of each database. The search covered the period from database inception to 30 April 2026, with no start-date restriction, and was limited to records in English. The electronic search was supplemented by (i) hand-searching of the reference lists of included articles and of relevant international guidelines, (ii) screening of recent congress proceedings (EASL, AASLD, and the TASL National Congress), and (iii) targeted searches of regulatory sources (EMA and FDA) and trial registries for the licensing status of MASH-directed therapies. Records were exported to a reference manager and de-duplicated prior to screening. The full database-specific search strings are available from the corresponding author upon request.

Study Selection and Screening

Titles and abstracts were screened against the pre-specified PICO criteria, and potentially eligible records were assessed in full text. Each step was performed by at least two committee members, with disagreements resolved through discussion or by a third reviewer. Studies were eligible if they reported on adults (or, where stated, children) with MASLD/MASH or its antecedent terms (NAFLD/NASH/MAFLD) and addressed one or more of the pre-specified questions and outcomes. Editorials, narrative commentaries without primary data, non-peer-reviewed preprints, and studies judged to be at high risk of bias were used only as supportive context and not as a basis for graded recommendations. When several studies addressed the same question, the evidence base was prioritized hierarchically: meta-analyses and systematic reviews, randomized controlled trials, large prospective cohorts, retrospective/real-world studies, and mechanistic data or expert opinion. Where contemporary international guidelines addressed an identical question, they were appraised as secondary sources and reinterpreted for the Turkish context rather than adopted verbatim.

Critical Appraisal and Evidence Synthesis

Included studies were critically appraised for methodological quality and risk of bias using design-appropriate considerations (randomization and blinding for trials; selection, attrition, and confounding for observational studies; spectrum, and reference-standard adequacy for diagnostic-accuracy studies). Because the body of evidence was clinically and methodologically heterogeneous, evidence was synthesized narratively rather than by *de novo* meta-analysis, and quantitative estimates were reported as published. For each PICO question, the committee summarized the direction, magnitude, consistency, and certainty of the effect, together with its directness and applicability to routine Turkish practice, and this structured summary formed the explicit basis for the level of evidence and the strength of the recommendation assigned below.

Rating the Level of Evidence

Because the guidance was finalized after the formal meetings and a further consensus/voting round could no longer be convened, the Executive Committee applied a structured, pre-defined framework—adapted from the GRADE approach and from the evidence-rating schemes of contemporary EASL and AASLD MASLD guidance—to grade every recommendation *post hoc*. Each recommendation was assigned one of three levels of evidence (High, Moderate, or Low), reflecting the certainty that the estimated effect is correct. The level reflects the study design as a starting point and is then modified by the risk of bias, inconsistency, indirectness, imprecision, and publication bias (which may lower it) and by a large, consistent effect or a clear dose–response relationship (which may raise it) (Table 1).

Rating the Strength of Recommendation and Verb Conventions

The strength of each recommendation was determined by integrating five domains: (1) level of evidence; (2) balance between desirable and undesirable effects (benefit–harm); (3) clinical necessity and impact on prognosis or patient-important outcomes; (4) applicability in Türkiye, including access, cost, tiered healthcare system, and practicality of implementation; and (5) availability of alternatives and burden imposed on the patient. Two strengths were used: Strong and Conditional. Consistent with the GRADE approach, a strong recommendation may accompany moderate- or low-level evidence when the benefit–harm balance or the imperative to avoid harm is decisive. Conversely, high-level evidence may yield only a conditional recommendation when applicability, cost, or patient burden is limited (Table 2).

Updating Policy

This guidance is intended to function as a living document. An update is planned after the initial approval of a MASH-specific pharmacological therapy in Türkiye or within 3 years of publication, whichever occurs first. Earlier revision may also be considered if major new evidence emerges that is likely to influence diagnostic pathways, treatment recommendations, or the management of metabolic comorbidities and long-term outcomes.

Table 2. Strength of recommendations, clinical interpretations, and corresponding operative wording

Strength	Interpretation	Operative wording (verb)
Strong	Desirable effects clearly outweigh undesirable effects and burden; applies to most patients in most circumstances.	"is recommended", "should", "must"
Conditional	Desirable effects probably outweigh undesirable effects, but the balance is closer, the evidence weaker, or the applicability/feasibility constrained; shared decision-making is appropriate.	"is suggested", "may be considered", "can be"
Conditional (against)	Undesirable effects probably outweigh desirable effects in most situations; however, exceptions exist.	"is not generally recommended", "is better avoided"
Strong (against)	The undesirable effects clearly outweigh the desirable effects; therefore, the intervention should not be used.	"is not recommended", "should not", "is contraindicated"

Conflict of Interest and Financial Disclosure

No external financial support was received for the preparation of this guidance. No pharmaceutical company or commercial entity had any role in the conception, drafting, review, or approval of this document. Yusuf Yilmaz has served as a consultant and/or advisory board member for Zydus, Echosens, and Novo Nordisk. All other authors declare that they have no conflicts of interest relevant to the content of this guidance.

In line with the conflict-of-interest management described above, authors with a declared relevant interest were recused from leading and from final adjudication of the recommendations addressing the corresponding product class (vibration-controlled transient elastography, GLP-1 receptor agonists, and saroglitazar/PPAR agents); these recommendations were drafted and graded by non-conflicted committee members.

Introduction

Since it was first defined in the 1980s, the term non-alcoholic fatty liver disease (NAFLD) has been used to describe a spectrum of conditions encompassing non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). However, in recent years, the terminology has been increasingly debated since it defines the condition by the absence of significant alcohol consumption rather than by its underlying pathophysiology. In 2020, a group of experts from 22 different countries reached a consensus and proposed renaming NAFLD as metabolic dysfunction-associated fatty liver disease (MAFLD).[1] In 2023, through a Delphi consensus, a group of researchers gathered all causes of metabolic fatty liver disease under the umbrella term "Steatotic Liver Disease" (SLD),[2] and reclassified the previously-defined MAFLD as Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Under this framework, the presence of intrahepatic fat accompanied by at least one cardiometabolic risk factor is defined as MASLD. This nomenclature has been accepted as a more affirmative and pathophysiologically relevant description of the disease. Similarly, for cases accompanied by an active inflammatory process, the term "MASH" (Metabolic Dysfunction-Associated Steatohepatitis) is used instead of "NASH".[3] The old term NAFLD has been abandoned due to both the exclusionary nature of the "non-alcoholic" expression and the stigmatizing effect of the word "fatty".[2]

In recent years, particularly following the change in nomenclature, our understanding of the disease has evolved substantially. Screening strategies have advanced, and we are now entering an era in which MASLD can also be treated pharmacologically. In light of these developments, an updated guidance tailored to the Turkish population is warranted. This guidance aims to provide a comprehensive overview of the current evidence on the diagnosis, screening, management, and treatment of MASLD, while addressing challenges specific to clinical practice in Türkiye. In addition, we discuss emerging therapeutic approaches and future directions in the field, with the goal of supporting healthcare professionals in the optimal care of individuals with MASLD.

Definition, Epidemiology, Natural Course and Risk Factors of MASLD

Definition

SLD is the umbrella term that encompasses MASLD, which refers to the accumulation of fat (steatosis) in the liver due to any cause and includes a broad spectrum of liver disorders (Fig. 1).[1] The primary goal of this terminological change was to define the disease through an affirmative approach based on the presence of existing metabolic dysfunction rather than solely on the absence of alcohol consumption. Simultaneously, with this new classification, alcohol-related liver disease and alcohol consumption have been more clearly defined, and steatosis due to other causes has been addressed.

Validation studies conducted during the transition to the new terminology have shown that most patients meeting the former NAFLD criteria are fully compatible with the new MASLD definition. In large-scale cohort analyses, 95% to 99% of patients previously diagnosed with NAFLD are directly included in the MASLD category because they present with at least one cardiometabolic risk factor.[4] This high concordance rate demonstrates that the change in terminology does not disrupt the continuity of past scientific data; on the contrary, it improves diagnostic accuracy by emphasizing the presence of metabolic risk factors.[5,6] While only 1–3% of patients previously diagnosed with NAFLD are reclassified into the "Cryptogenic SLD" category, the designation of patients with both metabolic dysfunction and moderate alcohol consumption as Metabolic dysfunction and alcohol-as-

sociated liver disease (MetALD) has enabled a clearer distinction for clinical management.[7]

Subcategories are defined according to the underlying etiology of steatosis, as outlined below.

MASLD

This category represents the largest subgroup of SLD.

- MASLD: This condition is defined by the presence of hepatic steatosis combined with at least one cardiometabolic risk factor. These risk factors include obesity, type 2 diabetes, hypertension, and dyslipidemia.
- MASH: Standing for metabolic dysfunction-associated steatohepatitis, is considered the more severe and progressive form of MASLD. While MASLD refers to the presence of fat, MASH occurs when fat is accompanied by liver inflammation and cellular damage, often characterized by "ballooning" of the liver cells.

MetALD

One of the most critical categories in the new terminology is MetALD, which describes individuals who simultaneously meet the criteria for MASLD and consume alcohol above specified thresholds. This category is unique because it recognizes the combined and potentially synergistic effects of metabolic dysfunction and alcohol consumption on liver health. The diagnosis specifically applies to individuals whose daily alcohol intake is between 20–50 g for women and 30–60 g for men. By establishing these clear alcohol thresholds alongside metabolic indicators, this classification allows clinicians to better identify and manage patients who face a "double hit" of liver injury from both lifestyle and metabolic sources.[8] The proposal of this subcategory has introduced a new diagnostic framework and addressed a previously unmet gap.

ALD (Alcohol-Associated Liver Disease)

This category defines a condition in which the primary driver of liver fat accumulation is excessive alcohol consumption rather than metabolic factors. To be classified in this category, alcohol intake must exceed the following high thresholds: >50 g/day for women and >60 g/day for men. Unlike the previous categories, this diagnosis focuses on the direct toxic impact of high-level alcohol use on the liver.

Specific Etiology SLD

This group includes cases where the underlying cause of liver fat is a specific condition other than metabolic factors or excessive alcohol use, as shown in Table 3.

Cryptogenic SLD

This category refers to cases in which hepatic steatosis is present, but the underlying cause remains unknown. It is characterized by the absence of identifiable factors; specifically, steatosis cannot be attributed to metabolic dysfunction, significant alcohol consumption, or any other known cause. Essentially, it serves as a classification for individuals who do not fit within the established metabolic, alcohol-associated, or specific etiological categories of steatotic liver disease.

Table 3. Secondary causes of hepatic steatosis

Category	Conditions
Infections	Chronic HCV infection
Nutritional/ Intestinal-related	• Coeliac disease • Small intestinal bacterial overgrowth
Endocrine disorders	• Polycystic ovary syndrome • Hypothyroidism • Hypopituitarism • Growth hormone deficiency
Genetic Diseases	• A1AT deficiency • Wilson's disease • Haemochromatosis • Congenital lipodystrophy • Abeta- and Hypobetalipoproteinemia • Familial hypercholesterolemia • Glycogen storage diseases • Cholesterol ester storage disease • Hereditary fructose intolerance
Pregnancy-associated	Acute fatty liver of pregnancy
Steatosis-associated risk gene variants	PNPLA3 p.I148M

HCV: Hepatitis C virus; A1AT: Alpha-1-antitrypsin.

Diagnosis of MASLD

The diagnosis of MASLD is established by the presence of hepatic steatosis detected by a validated method, together with at least one cardiometabolic risk factor. Accordingly, the diagnostic evaluation is based on three key components: the presence of hepatic steatosis, the identification of at least one cardiometabolic risk factor, and the assessment of other potential causes or contributors to liver disease.[2]

Assessment of Hepatic Steatosis

The first step in the diagnostic process is to establish the presence of hepatic steatosis. This can be achieved using the following methods:

- Non-invasive tests (NITs): Several diagnostic scores, including the fatty liver index, hepatic steatosis index, and triglyceride–glucose index, are available.[9,10] In settings where imaging modalities are not accessible, these blood-based NITs may be considered as alternative screening tools.
- Imaging Methods: Ultrasonography is the most used imaging modality. For more detailed assessment, Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF), a non-invasive specialized MRI technique used to accurately quantify the fat fraction in the liver, or computed tomography (CT) may be used.

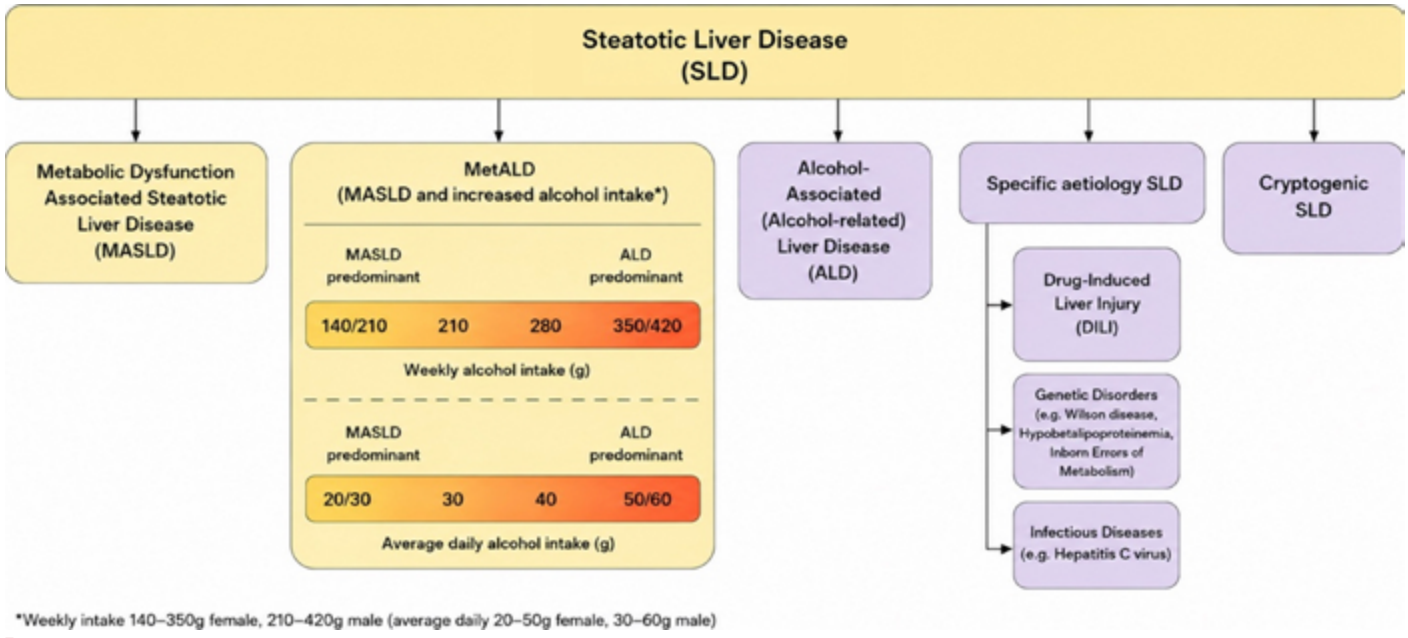


Figure 1. Classification of steatotic liver disease (SLD) according to the updated nomenclature. Adapted from [2].

SLD: Steatotic liver disease; MASLD: Metabolic dysfunction-associated steatotic liver disease; MetALD: Metabolic dysfunction and alcohol-related liver disease; ALD: Alcohol-related liver disease; DILI: Drug-induced liver injury.

- Vibration-Controlled Transient Elastography (VCTE): A non-invasive method that quantitatively assesses both hepatic steatosis through the Controlled Attenuation Parameter (CAP) and liver fibrosis through Liver Stiffness Measurement (LSM).
- Biopsy: Although considered the "reference standard" for definitive diagnosis, it is not routinely performed due to its invasive nature. It may be considered when accompanying causes of liver disease are suspected, or when there is concern regarding disease severity and progression.

Identification of Metabolic Risk Factors

The identification of at least one cardiometabolic risk factor is a prerequisite for the diagnosis of MASLD in individuals with hepatic steatosis. The five qualifying cardiometabolic risk categories and their respective diagnostic criteria are summarized in Figure 2:

Exclusion of Other Causes

To confirm a diagnosis of MASLD, alternative causes of hepatic steatosis should be excluded, including excessive alcohol consumption (defined as an average daily intake of ≥20 g for women and ≥30 g for men), viral hepatitis (e.g., hepatitis B or C), and drug-induced liver injury. The clinical algorithm for MASLD terminology is summarized in Figure 2.

Epidemiology

The prevalence of MASLD is increasing worldwide in parallel with the rising prevalence of obesity and other cardiometabolic risk factors. Current estimates suggest that approximately 1.3 billion people worldwide are affected by MASLD.[11–13] The disease is more common in men than in women, with reported prevalence rates of approximately 40% and 25%, respectively.[14] Furthermore, MASLD has emerged as one of the leading indications for liver transplantation in many parts of the world.[15] In 2021, mortality due to MASLD-related cirrhosis was reported as 97,403 cases, and hepatocellular carcinoma (HCC)-related deaths reached 40,925 cases.[11] This indicates that the incidence of the disease will continue to rise for both genders in the coming years. Projections suggest that an additional 667 million cases of MASLD will occur by 2045, highlighting the substantial and growing global burden of the disease.[16] Moreover, MASLD is not limited to adults but also affects children, with disease processes potentially beginning as early as the fetal stage and continuing throughout the lifespan into late adulthood. The global prevalence of MASLD in children is estimated to be approximately 7%, increasing to around 14% among adolescents.[17] A recent meta-analysis based on data from Turkish pediatric populations reported a markedly higher prevalence of up to 50%; however, this estimate was derived from cohorts of children with obesity or those with elevated liver transaminases. Consequently, these findings are not representative of the general pediatric population, for which robust prevalence data remain limited.[18] In contrast, a previous autopsy-based liver biopsy study conducted in children and adolescents aged 2–20 years reported a prevalence of approximately 6%, which is consistent with estimates from the broader literature.[19]

The prevalence of cardiometabolic risk factors, particularly type 2 diabetes mellitus (T2DM) and obesity, has increased substantially in Türkiye over recent decades. According to World Health Organization estimates, the age-standardized prevalence of obesity among adults in Türkiye was 33.3% in 2022.[20] Data from TURDEP-I and TURDEP-II,

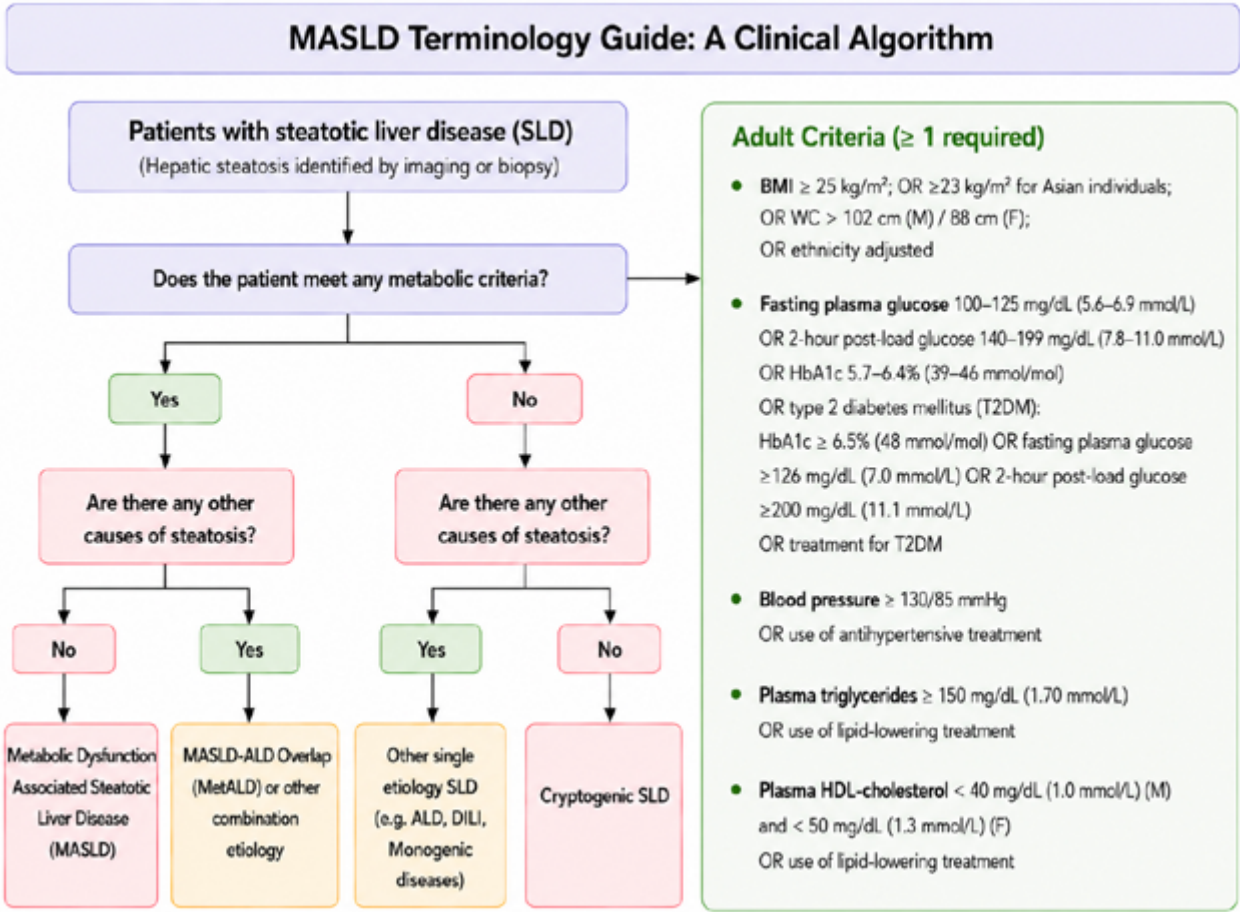


Figure 2. Clinical algorithm for the diagnosis and classification of steatotic liver disease (SLD) according to the MASLD nomenclature. Modified from [2].

SLD: Steatotic liver disease; MASLD: Metabolic dysfunction-associated steatotic liver disease; MetALD: Metabolic dysfunction and alcohol-related liver disease; BMI: Body mass index; WC: Waist circumference; T2DM: Type 2 diabetes mellitus; HDL: High-density lipoprotein.

which monitored the course of metabolic diseases in the adult population of Türkiye, revealed that over a 12-year period between 1998 and 2010, the prevalence of T2DM increased from 7.2% to 16.5%, and the prevalence of obesity rose from 22% to 36%.[21,22]

Parallel to this metabolic increase in the population, MASLD prevalence in Türkiye is projected to exceed 30%. Türkiye has thus become one of the countries with the highest global prevalence of hepatic steatosis in the world in line with the increase in metabolic risk factors. In a community-based study, the ultrasonographic prevalence of SLD was reported as 60.1%, while a multi-center screening study found the MASLD prevalence to be 45.5%, another check-up study found that the overall prevalence of NAFLD as 48.3%.[23–25] Current histopathological data based on forensic autopsy series reveal that 43.3% of the population has steatotic liver disease, pointing to a prevalence that extends beyond clinical diagnosis rates.[26] This high prevalence is directly related to the dramatic upward trend in the frequency of obesity (36%) and T2DM (16.5%), which is also supported by epidemiological data (Table 4).

When the progressive course of the disease is examined, a significant proportion of MASLD cases in Türkiye carry the risk of hepatic inflammation and injury. An autopsy-based study confirmed the presence of MASH (steatohepatitis) in approximately 20.6% of individuals with steatosis.[26] Furthermore, MASLD prevalence is particularly higher in at-risk populations with existing cardiometabolic risk factors. Among adults with at least one cardiometabolic risk factor, the frequency of MASLD has been reported to be as high as 75.7%, while a high risk of advanced fibrosis, as defined by the FIB-4 score, has been identified in 12% of individuals.[27] Moreover, MASLD severity is known to increase with the cumulative burden of cardiometabolic risk factors, reaching its highest level in the presence of T2DM.[28] Another recent Turkish study reported a MASLD prevalence of 73.2% among patients with T2DM, with significant fibrosis identified in 14.1% of the cohort.[29] These data demonstrate that the burden of MASLD in our country extends beyond simple steatosis and represents a major public health concern, with the potential to progress to end-stage liver disease, including cirrhosis and hepatocellular carcinoma (HCC).

Natural Course and Risk Factors

Although MASLD is generally a slow-progressing disease, inflammation and progressive fibrosis develop in a small subset of patients

Table 4. Prevalence of steatotic liver disease and MASLD in Türkiye: summary of major epidemiological studies

Author (year)	Study type	Population/sample size	Diagnostic method	Prevalence (%)	Terminology used
Değertekin et al. (2021)[23]	Retrospective hospital-based study	6,567 check-up patients	US	48.3	NAFLD
Sezgin et al. (2023)[24]	Cross-sectional cohort study	2,797 individuals	US	60.1	SLD
Yilmaz et al. (2021)[25]	Multicenter, prospective cohort study	909 dyspeptic patients	US	45.5	MAFLD
Ergenc et al. (2024)[26]	Forensic autopsy study (cross-sectional)	62 autopsy cases (out of 1,797)	Histopathology	43.3	MASLD
Kirik et al. (2025)[27]	Cross-sectional multicenter study	14,371 adults with cardiometabolic risk factors	US	75.7	MASLD

US: Ultrasonography; SLD: Steatotic liver disease; NAFLD: Non-alcoholic fatty liver disease; MAFLD: Metabolic dysfunction-associated fatty liver disease; MASLD: Metabolic Dysfunction-associated steatotic liver disease.

Table 5. Modifiable and non-modifiable risk factors for MASLD and disease progression

Category	Risk factors	Description/clinical significance
Modifiable risk factors	Obesity/overweight	One of the strongest drivers of the disease; weight gain accelerates fibrosis progression.
	Insulin resistance, T2DM, prediabetes	Among the most important predictors of progression; increases the risk of HCC.
	Dyslipidemia	Atherogenic lipid profile increases hepatic steatosis.
	Hypertension	A component of metabolic syndrome; associated with fibrosis progression.
	Sedentary lifestyle	Lack of physical activity facilitates disease development.
	Unhealthy diet	Diets rich in fructose and saturated fats increase steatosis.
	Alcohol consumption (especially concomitant)	Exhibits a synergistic effect with metabolic factors.
	Smoking	Associated with HCC and fibrosis progression.
	Sarcopenia	Contributes to disease progression by increasing insulin resistance.
Non-modifiable risk factors	Genetic predisposition (PNPLA3, TM6SF2, MBOAT7, etc.)	Determinant in disease development and severity.
	Age (>50)	Risk of developing fibrosis and cirrhosis increases.
	Gender and hormonal status	Risk is higher in men and postmenopausal women.
	Ethnicity	Higher prevalence and severity in certain populations (e.g., Hispanic individuals).
	Family history	Reflects a combination of genetic and environmental factors.

T2DM: Type 2 diabetes mellitus; HCC: Hepatocellular carcinoma.

with MASLD. The rate of liver fibrosis progression is the most critical factor determining the prognosis of the disease. According to comprehensive paired-biopsy studies, the rate of fibrosis progression in patients with MASLD has been calculated at an average of one stage every 14 years.[30] However, this process is not linear; while some patients remain stable for a long time (non-progressors), others may exhibit a "fast-progressor" character. The risk factors for both the development and rapid progression of the disease are similar (Table 5).[31] In paired biopsy studies conducted in Türkiye, fibrosis progression was found to be significantly associated with baseline hypertension and elevated AST and ALT levels.[32]

The progression from simple steatosis to cirrhosis typically occurs over a period of 20–30 years. Population-based data show that approximately 3–5% of patients with MASLD progress to cirrhosis at the end of this process.[33] Once cirrhosis has developed, the annual risk of developing HCC is approximately 1–1.5%.[34] Notably, HCC associated with MASH can occur without the development of cirrhosis (non-cirrhotic HCC). In patients with MASLD, cardiovascular disease is the leading cause of death, followed by extrahepatic malignancies and liver-related complications.[33] Although the course of the disease varies on an individual basis, effective management of metabolic factors can slow down progression or allow for fibrosis regression.[35]

Recommendations

1. SLD should be used as a comprehensive umbrella term for all hepatic fat accumulation etiologies. Within this framework, MASLD (formerly NAFLD) represents the largest metabolic subgroup. Due to the high concordance rate (up to 99%) between NAFLD and MASLD, which ensures the continuity of existing scientific data while providing an affirmative and non-stigmatizing diagnosis, the updated nomenclature is preferred in clinical practice. [LoE: High; SoR: Strong]
2. Considering its high prevalence and disease burden in Türkiye, MASLD should be recognized as a major public health concern. Efforts should be made to increase both public and professional awareness, ensuring that MASLD is routinely considered in clinical practice by healthcare providers. [LoE: Moderate; SoR: Strong]
3. The presence of at least one cardiometabolic risk factor, such as obesity, T2DM, or hypertension, is the primary driver for MASLD diagnosis and serves as the most important critical predictor of disease progression. Consequently, all patients should undergo regular and systematic evaluations for all cardiometabolic risk factors. [LoE: High; SoR: Strong]

Screening and Diagnosis of MASLD

Although MASLD is a highly prevalent disorder affecting approximately 50% of the population in Türkiye, its diagnosis is not always straightforward.[25] This challenge can be attributed to limited physician awareness and delays in timely clinical action.[36] This section aims to outline a diagnostic pathway for physicians managing patients with MASLD in both primary and secondary care settings, incorporating non-invasive and invasive diagnostic strategies applicable to routine clinical practice in Türkiye.

Which Patients Should be Screened Primarily?

Given the high prevalence of MASLD, there is a need for cost-effective and patient-friendly screening strategies that can accurately identify individuals who require specialized care. These strategies should also minimize unnecessary healthcare utilization and expenditures. Screening is particularly recommended for individuals with concomitant comorbidities, as they are at greater risk of developing MASLD and its associated complications. Therefore, targeted screening of individuals at high risk for advanced fibrosis represents a justified and appropriate approach. MASLD is most commonly observed in individuals with metabolic comorbidities, including T2DM, obesity, hypertension, and hyperlipidemia.[12] T2DM is strongly associated with advanced fibrosis, the most important prognostic determinant of MASLD, affecting up to 17% of patients with MASLD and T2DM.[37] In addition to the high prevalence of advanced fibrosis in this group, individuals with T2DM exhibit the poorest survival outcomes compared with those with other metabolic risk factors, with a fourfold increase in overall mortality and a twentyfold increase in cardiovascular mortality.[28] These observations further support the rationale for targeted screening in this population. Indeed, screening high-risk individuals has been shown to be more cost-effective than no screening.[38,39] In particular, screening individuals with evidence of hepatic steatosis and a high cardiometabolic burden has been demonstrated to be both cost-effective and diagnostically efficient.[40,41]

As noted previously, the prevalence of MASLD among children with obesity or a high metabolic burden is comparable to that observed in adults and is associated with a lifelong disease burden.[18] Therefore, screening could be encouraged in these high-risk pediatric populations. Given the early onset of disease and its potentially prolonged course, affected individuals may require long-term follow-up throughout adulthood. Notably, pediatric MASLD is associated with a significantly higher likelihood of requiring liver transplantation compared with the general population.[42] However, screening strategies in children differ from those used in adults and are primarily based on ultrasonography, measurement of transaminase levels, and assessment of metabolic risk factors.[43]

Recommendations

1. Patients with T2DM, obesity + ≥1 cardiometabolic risk factor, or signs of hepatic steatosis should be screened for advanced liver disease. [LoE: Moderate; SoR: Strong]
2. Children with obesity, elevated transaminase levels, or conditions associated with a high metabolic burden should be screened for the presence of MASLD. These individuals should undergo regular long-term follow-up to monitor disease progression and liver-related outcomes. [LoE: Low; SoR: Strong]

Use of Non-Invasive Diagnostic Tests in Screening and Diagnosis

Although liver biopsy remains the reference standard for the diagnosis of MASLD, NITs have demonstrated strong performance in the initial risk stratification of the disease and enable more accurate identification of advanced disease in high-risk individuals.[44] Risk stratification for fibrosis can be performed using both blood-based biomarkers and imaging modalities. For the screening of high-risk individuals—such as those with T2DM, obesity with at least one additional cardiometabolic risk factor, or evidence of hepatic steatosis—the FIB-4 index is an appropriate and widely used first-line tool for risk stratification. Its reliance on routinely available clinical parameters and ease of calculation make it particularly well-suited for use in primary care settings. However, its performance may be limited in certain populations, including younger individuals, lean patients and those with severe obesity; therefore, results should be interpreted with caution in these groups.[45,46] Additionally, caution is required when interpreting these findings for children and pregnant women, as the performance is less reliable within these specific groups.[47,48]

A FIB-4 value <1.3 generally excludes a high risk of advanced fibrosis, whereas in individuals older than 65 years, a higher threshold of <2.0 is recommended for the same purpose. The utility of the FIB-4 index, including its diagnostic performance, has been validated across various clinical settings and comorbid conditions such as type 2 diabetes mellitus and obesity. Studies conducted in Turkish cohorts have demonstrated a high negative predictive value, supporting its effectiveness in

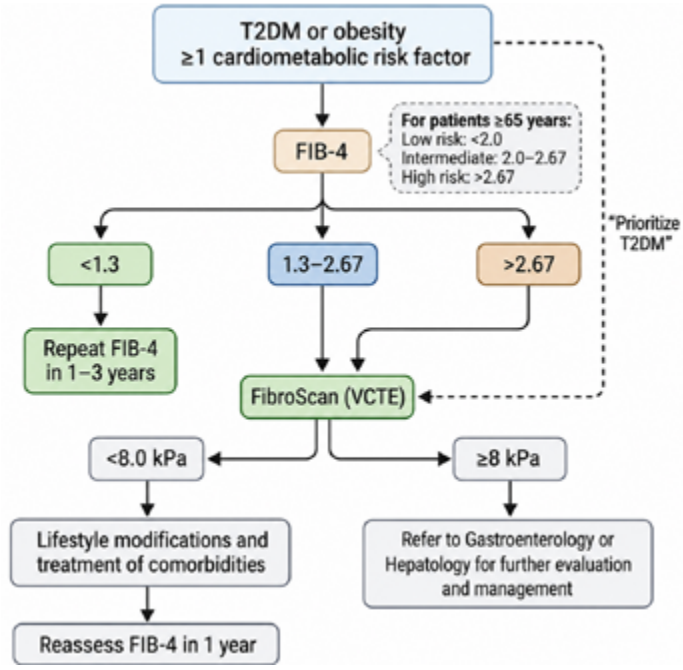


Figure 3. MASLD risk stratification and management algorithm.

MASLD: Metabolic dysfunction-associated steatotic liver disease; T2DM: Type 2 diabetes mellitus; VCTE: Vibration-controlled transient elastography; *: If available, MRE or ELF score can also be considered in the second step.

reliably excluding advanced fibrosis.[45,49,50] Although several alternative non-invasive scoring systems, such as the NAFLD Fibrosis Score (NFS), aspartate aminotransferase-to-platelet ratio index (APRI), and BARD score, are available, the FIB-4 index remains the most widely used for risk stratification. This preference is largely due to its ease of calculation and superior overall performance in identifying advanced fibrosis.[51]

For patients who are not classified as low-risk based on the initial FIB-4 assessment, further diagnostic work-up is required. Current recommendations support a two-step approach, in which individuals with a low probability of advanced fibrosis are first excluded, followed by a more detailed evaluation of those at an increased risk of advanced disease (Fig. 3). At this stage, a second-line assessment using either imaging-based modalities or more advanced blood-based algorithms with higher diagnostic accuracy is recommended. It should be noted that this algorithm is used in triage of the patients rather than evaluation for treatment. Suitable options include imaging techniques such as VCTE and magnetic resonance elastography (MRE), as well as blood-based tests such as the Enhanced Liver Fibrosis (ELF) test.[52–55] MRE has been shown to be particularly advantageous in individuals with obesity; however, owing to its limited availability, higher cost, and greater technical complexity, ultrasound-based techniques such as VCTE are more commonly utilized in clinical practice.[54,56] LSM is widely used as a non-invasive indicator of hepatic fibrosis. An LSM value <8 kPa generally rules out advanced fibrosis, whereas values >12 kPa are associated with a high likelihood of advanced fibrosis; higher values increase the likelihood of cirrhosis and should be interpreted in the appropriate clinical context.[57] With the use of the XL probe, VCTE has demonstrated acceptable performance in individuals with obesity. Conversely, measurement variability in patients with obesity remains a concern. To enhance reliability, performing repeat assessments at a one-week interval can be recommended for this population.[58,59] Moreover, as with other ultrasound-based techniques, accuracy is operator dependent.[60,61] Given the increased risk of advanced fibrosis in patients with T2DM, direct referral to hepatology for VCTE should be considered in this population.[62] This approach has been shown to rapidly reduce false-negative cases to near zero, albeit at the expense of an increased rate of false positives.[63] MRE may also be considered as a second-line assessment modality when available. MRI-based techniques offer advantages over ultrasound-based approaches due to lower operator dependency and reduced susceptibility to patient-related factors, including BMI.[64]

As mentioned previously, for the detection of hepatic steatosis, both blood-based indices, such as the Fatty Liver Index, and imaging modalities, including ultrasonography and FibroScan, can be utilized. MRI-PDFF is considered the reference standard; however, its use is largely confined to research settings and clinical trials.[65,66] Nevertheless, because hepatic steatosis is not the primary determinant of prognosis, screening strategies should not focus solely on its detection.

Role of Liver Biopsy

Although liver biopsy remains the reference standard, its routine use is not recommended because of its invasive nature, potential complications, and associated patient discomfort.[67,68] However, liver biopsy should be considered in selected clinical scenarios, including the following:

1. When the exclusion of concomitant or alternative etiologies is required
2. In the context of clinical trials
3. During bariatric surgery procedures
4. In cases of discordant results between NITs

Table 6 outlines the NITs utilized in the diagnosis and stratification of MASLD, as well as the indications for liver biopsy.

Recommendations

1. The FIB-4 index should be utilized as the first-line tool for risk stratification in patients with MASLD. [LoE: High; SoR: Strong]
2. Patients who are not classified as low risk in the initial step should undergo further evaluation, preferably with VCTE, or MRE if available. [LoE: High; SoR: Strong]
   a. Patients at higher clinical risk, including but not limited to those with type 2 diabetes mellitus, should be prioritized for second-line assessment using VCTE. [LoE: Moderate; SoR: Strong]
   b. Where available, VCTE may also be considered as a first-line risk assessment tool in high-risk populations. [LoE: Moderate; SoR: Conditional]
3. Liver biopsy is not routinely required in the diagnosis of MASLD and should be reserved for selected cases where clinically indicated. [LoE: Moderate; SoR: Strong]

Table 6. Use of NITs and liver biopsy in MASLD diagnosis

NIT	Utility	Setting	Cut-off	Advantages	Disadvantages
Ultrasonography	Detection of hepatic steatosis	Screening tool	Qualitative	Low cost, widely available, first-line screening	Low sensitivity for mild steatosis (<20%), operator-dependent, limited in severe obesity
MRI-PDFF	Detection of hepatic steatosis	Clinical trials	>5.5%	Highly accurate, quantifies fat across the whole liver, reference standard for research	High cost, limited availability, contraindicated in claustrophobia/implants
FIB-4	Estimation of advanced fibrosis	First line triaging of disease severity	<1.3 (Rule-out); >2.67 (Rule-in); <2.0 for age >65	Routine laboratory examination, well qualified for first line triaging	Age dependent, low performance in younger adults, lean and morbid obese patients, children and pregnant women
VCTE	Estimation of fibrosis status	Second step for triaging disease severity	<8.0 kPa (Rule-out F3); 12 kPa (Rule-in F3)	Point-of-care, validated extensively	Affected by BMI (requires XL probe), food intake, congestion, and operator experience
MRE	Estimation of fibrosis status	Second step for triaging disease severity, can be encouraged in obese individuals	F2: 3.14 kPa F3: 3.53 kPa F4: 4.45 kPa	Most accurate NIT for fibrosis staging, whole liver assessment, less affected by BMI/ascites	Very high cost, limited clinical availability, time-consuming
ELF	Estimation of fibrosis status	Second step for triaging disease severity	<7.7 (Rule-out F3); >9.8 (Rule-in F3)	Validated prognostic value for liver-related events	Proprietary test, costly, limited availability in routine clinical labs
Liver biopsy	Reference standard	Clinical trials, discordance in NITs, exclusion of alternative diagnoses	NA (Histological grading/staging)	Direct visualization of MASH activity, assesses co-pathologies, definitive staging.	Invasive, risk of complications (pain, bleeding), sampling error, inter-observer variability

NIT: Non-invasive test; MASLD: Metabolic dysfunction-associated steatotic liver disease; MASH: Metabolic dysfunction-associated steatohepatitis; FIB-4: Fibrosis-4 index; VCTE: Vibration-controlled transient elastography; MRI-PDFF: Magnetic resonance imaging proton density fat fraction; MRE: Magnetic resonance elastography; ELF: Enhanced liver fibrosis; NA: Not applicable.

Treatment of MASLD

The management of MASLD is primarily centered on weight reduction, encompassing lifestyle interventions, pharmacological therapies, and bariatric and endoscopic treatment options, all aimed at achieving meaningful and sustained weight loss. In recent years, clinical trials have led to the approval of therapies specifically targeting MASH, thereby expanding the therapeutic landscape.[69] This section outlines the current treatment approaches for MASLD.

Role of Lifestyle Modifications

Lifestyle modifications, including a healthy diet promoting weight loss and regular physical activity, represent both the initial and fundamental components of MASLD management for any patient group including children. Successful weight loss is defined as achieving a minimum 5% reduction from baseline weight at the sixth month and maintaining it for at least 12 months.[70] Therefore, an evaluation for therapy success can be recommended after six months of lifestyle interventions. A paired liver biopsy study demonstrated that a weight loss of ≥5% of body weight is associated with improvement in hepatic steatosis, 7–10% with resolution of inflammation, and ≥10% with improvement in fibrosis. Notably, nearly all patients who achieved ≥10% weight loss exhibited resolution of MASH, with approximately half also showing regression of fibrosis.[71] Consequently, lifestyle modifications targeting weight loss represent the cornerstone of MASLD management and should be implemented alongside any other therapeutic interventions. However, the long-term sustainability of lifestyle modifications is limited, as they are frequently associated with weight regain; in many cases, substantial or even complete weight regain can occur within slightly more than one year.[72,73] However, even when weight regain occurs, the beneficial effects of prior weight loss, particularly in terms of reductions in hepatic steatosis and improvements in insulin resistance, may persist.[74] Notwithstanding the benefits of weight loss in individuals with obesity, even lean patients with hepatic steatosis may benefit from modest weight reduction, particularly in terms of improvement in hepatic fat content.[75] Therefore, recommending a weight loss of at least 5% of body weight is beneficial for all patients, whereas for lean individuals, a 3–5% target is appropriate.

Lifestyle modifications should aim not only for weight loss (including a hypocaloric diet) but also extend beyond it; specific recommendations regarding dietary composition and types of physical activity should be provided to patients. The Mediterranean diet, characterized by a high intake of olive oil, vegetables, and seafood, and limited consumption of ultra-processed foods, has consistently demonstrated broad health benefits, including improvements in liver health.[76–78] The Mediterranean diet may improve MASLD even in the absence of weight loss. Evidence suggests that adherence to this dietary pattern can reduce hepatic steatosis and improve cardiometabolic health through mechanisms independent of weight reduction, including improvements in insulin sensitivity.[79] Although less extensively studied than the Mediterranean diet, a low-fat diet may also serve as an equally effective dietary pattern providing similar health benefits, particularly for individuals who find the Mediterranean diet less palatable.[77,80] Another commonly adopted dietary approach is intermittent fasting; however, its benefits are less consistently established compared to the Mediterranean diet.[81] Nevertheless, some studies, particularly those evaluating Ramadan fasting, have reported potential metabolic and hepatic benefits.[82] Avoiding sarcopenia is also an important aspect of management, particularly in patients with established cirrhosis or in the elderly. These patients should be prescribed a high-protein diet (1.0–1.5 g/kg/day), ideally combined with resistance training to preserve muscle mass and function.[83] A late-evening snack is another effective nutritional strategy that may help prevent sarcopenia by reducing overnight muscle catabolism.[84]

The consumption of ultra-processed foods has been associated not only with MASLD but also with the development of hepatocellular carcinoma.[85,86] Moreover, improvements in hepatic steatosis have been shown to correlate with the extent of reduction in ultra-processed food intake,[87] suggesting a dose–response relationship in which lower consumption is associated with greater benefits. In addition, the consumption of sugar-sweetened beverages has been associated with an approximately twofold increased risk of MASLD.[88] This effect is largely attributed to their high fructose content. Notably, fructose restriction, even within an isocaloric diet, has been associated with the resolution of hepatic steatosis.[89] As previously reported, there is no established safe threshold for alcohol consumption; therefore, abstinence should be recommended for patients with MASLD.[90] In contrast, regular coffee consumption—particularly an intake of more than two cups per day, ideally three to four cups—has been associated with beneficial effects on liver health.[91,92] Although evidence regarding the impact of brewing methods is limited, traditional preparation techniques, such as filtered coffee, French press, and Turkish coffee, are known to contain compounds with potential hepatoprotective properties.[91] Although direct evidence regarding their effects on liver health is limited, black and green tea may also exert hepatoprotective effects, potentially linked to their well-established cardiovascular benefits.[93,94]

Regular physical activity is an essential component of MASLD management. Notably, moderate- and vigorous-intensity exercise have been shown to confer similar benefits in reducing hepatic steatosis, as assessed by MRI-PDFF.[95] Current recommendations suggest engaging in moderate-to-vigorous physical activity for at least 150 minutes per week to achieve meaningful benefit. However, individuals who concentrate their activity into fewer sessions so-called "weekend warriors" may attain comparable benefits to those exercising more regularly.[96] Both aerobic exercise and resistance training have been shown to reduce hepatic steatosis. Therefore, resistance training may be particularly suitable for patients with limited cardiorespiratory capacity. However, combined exercise programs incorporating both aerobic and resistance components appear to provide synergistic benefits and are preferable when feasible.[97–99]

Recommendations

1. Lifestyle modifications aiming for a weight loss of at least 5% of body weight should be recommended for all patients with MASLD, with an optimal target of ≥10%. For lean individuals, a weight loss target of 3–5% of body weight should be aimed. [LoE: High; SoR: Strong]
2. The Mediterranean diet should be the preferred dietary approach. Consumption of ultra-processed foods and sugar-sweetened beverages should be minimized or avoided. [LoE: Moderate; SoR: Strong]
3. Coffee intake may be encouraged for patients without contraindications, provided that it is well tolerated. [LoE: Moderate; SoR: Conditional]
4. Physical activity combining aerobic exercise and resistance training should be encouraged and tailored to the patient's individual lifestyle and functional capacity. [LoE: High; SoR: Strong]
5. A high-protein diet and resistance training can be encouraged, particularly in elderly patients and those with MASH-related cirrhosis, to preserve skeletal muscle mass and prevent the development of sarcopenia. [LoE: Moderate; SoR: Strong]

Pharmacologic Treatment Options

We have now entered an era in which MASLD is no longer managed solely through lifestyle modification, owing to the recent approval of pharmacological therapies targeting the disease. This development has expanded therapeutic options and raised expectations for the approval of additional agents in the near future. Importantly, not only MASH-specific therapies but also treatments targeting associated comorbidities can contribute to disease improvement through indirect hepatic benefits. This section reviews the current treatment options and outlines future perspectives on the management of MASLD (Fig. 4, Table 7).

Liver-Targeted Therapies

Resmetirom is a liver-directed thyroid hormone receptor-β agonist that reduces hepatic steatosis and inhibits fibrogenesis. Owing to its high selectivity for the β receptor, it minimizes the off-target effects typically associated with thyroid hormones. It is currently the only liver-targeted therapy option[100] approved by both the European Medicines Agency (EMA) and Food and Drug Administration

Table 7. Therapeutic indications and contraindications of medications beneficial in MASLD

Medication	Indication	Cautions/contraindications
Resmetirom (NA in Türkiye)	MASH+F2-F3	Cirrhosis
GLP-1 receptor agonists	T2DM, obesity Can be safely used in MASH	History of medullary thyroid cancer, MEN 2, history of pancreatitis, Child B and C cirrhosis
SGLT2 inhibitors	T2DM, chronic heart and kidney disease	Child C cirrhosis
PPAR	MASH	Heart failure, osteoporosis, weight gain, oedema
Metformin	T2DM	Cirrhosis
Statins	Dyslipidemia	Decompensated cirrhosis, acute liver failure

GLP-1: Glucagon-like peptide-1; MASH: Metabolic dysfunction-associated steatohepatitis; MEN 2: Multiple endocrine neoplasia type 2; NA: Not available; PPAR: Peroxisome proliferator-activated receptor; SGLT2: Sodium-glucose cotransporter 2; T2DM: Type 2 diabetes mellitus.

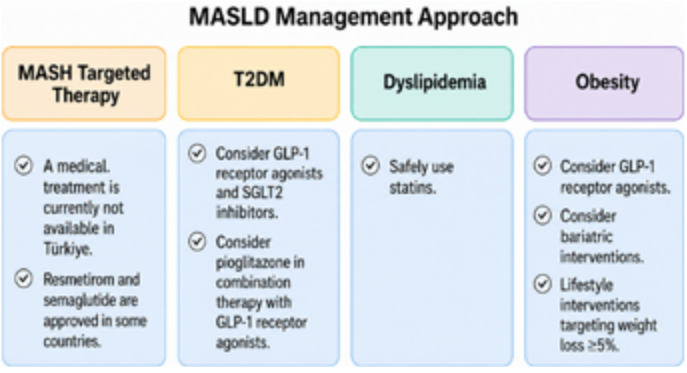


Figure 4. Pharmacotherapy in MASLD considering the comorbidities.

MASLD: Metabolic dysfunction-associated steatotic liver disease; T2DM: Type 2 diabetes mellitus; GLP-1: Glucagon-like peptide-1.

(FDA) for the treatment of noncirrhotic MASH with fibrosis F2 or F3. In the MAESTRO-NASH trial, the drug achieved MASH resolution in approximately 30% of patients and fibrosis improvement in approximately 25% of patients, both significantly higher than the placebo.[101] Following the positive results of this study, resmetirom has been approved in certain regions; however, it is not yet available in Türkiye. Given the FDA's accelerated-approval framework for noncirrhotic MASH with F2–F3 fibrosis, resmetirom's long-term clinical benefit remains to be confirmed in ongoing confirmatory outcome trials, the results of which are not yet available. Additionally, current approaches for determining treatment eligibility rely on NITs, which may have limitations in accurately identifying the most appropriate patients for therapy. Treatment eligibility is largely based on a VCTE-driven algorithm. Other diagnostic methods, such as MRE, may also be considered prior to initiating therapy. These diagnostic algorithms incorporate pharmacologic treatment decisions based on fibrosis assessment; for example, VCTE values above 10 kPa may support inclusion of patients with F2–F3 fibrosis, whereas values below 20 kPa may be used to help exclude cirrhosis (Fig. 5). However, validation in a Turkish MASLD cohort demonstrated significant limitations, with approximately 40% of patients being overprescribed and another 40% underdiagnosed, reflecting a very low level of agreement. Therefore, if the drug becomes available in our country, liver biopsy could be considered prior to treatment initiation in selected cases to ensure appropriate patient

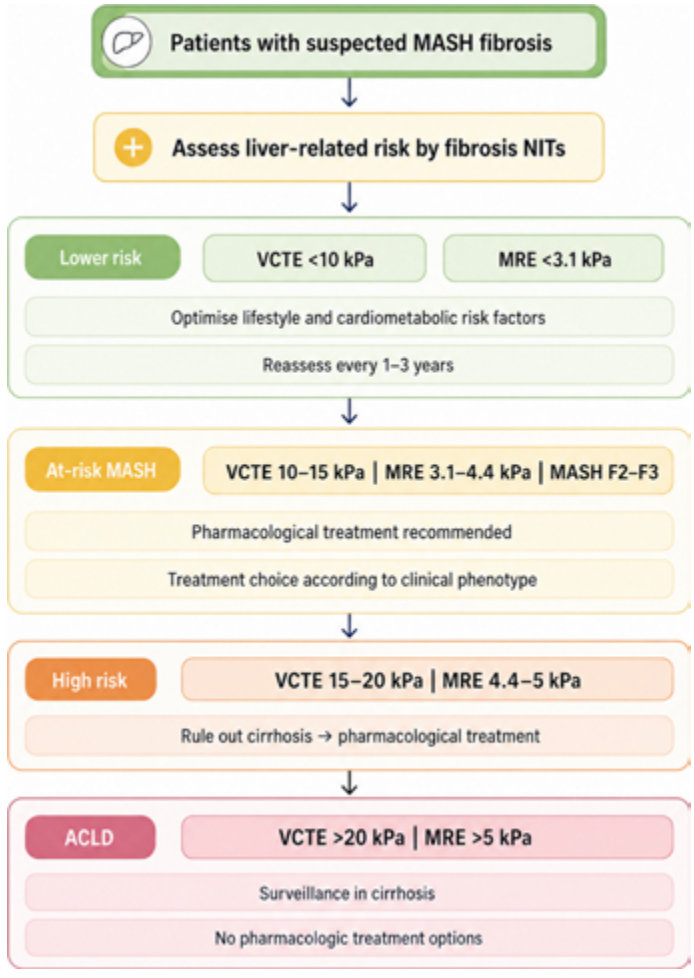


Figure 5. Algorithm for identifying adults with MASLD eligible for pharmacotherapy.

MASH: Metabolic dysfunction-associated steatohepatitis; VCTE: Vibration-controlled transient elastography; MRE: Magnetic resonance elastography; ACLD: advanced chronic liver disease.

selection and avoid unnecessary economic burden.[102] Furthermore, because resmetirom has only recently entered clinical practice, long-term real-world effectiveness, safety, and cost-effectiveness data remain limited, and further post-marketing studies are needed to better define optimal patient selection and treatment outcomes.

Antidiabetic Agents

Metformin is the most commonly prescribed first-line agent for the treatment of type 2 diabetes mellitus. Its principal hepatic benefit lies in reducing the risk of hepatocellular carcinoma by approximately 30%.[103] However, it does not appear to confer significant histological improvement in MASLD, including steatosis, inflammation, or fibrosis. In contrast, some evidence suggests a potential increase in lobular inflammation; therefore, metformin is not recommended as a direct treatment for MASLD.[104] Moreover, it should be avoided in decompensated cirrhosis due to a higher risk of lactic acidosis.[105]

SGLT2 inhibitors (empagliflozin, dapagliflozin) are antidiabetic agents that are preferentially used in patients with cardiovascular and renal disease, owing to their beneficial effects in reducing cardiovascular risk, slowing the progression of nephropathy, and promoting favorable metabolic and tissue-level changes.[106] SGLT2 inhibitors have also been shown to reduce hepatic fat content and lower transaminase levels, supporting their preferential use in patients with comorbid conditions such as cardiovascular or renal disease.[107,108] In addition, they demonstrated improvements in non-invasive markers of liver fibrosis.[109] Furthermore, their use has been associated with improved overall, cardiovascular, and liver-related outcomes in patients with MASLD and diabetes.[110]

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are antidiabetic agents that promote significant weight loss and reduce food intake by delaying gastric emptying and modulating central satiety pathways, in addition to their glucose-lowering effects.[111] Liraglutide was initially evaluated in patients with MASH in the phase 2 LEAN clinical trial. The study met its primary endpoint, with 39% of patients achieving resolution of MASH without worsening of fibrosis. Although significant improvements in liver enzyme levels were not observed, the treatment was associated with weight loss. Furthermore, liraglutide demonstrated a favorable safety profile, with predominantly mild to moderate adverse events.[112] However, its overall efficacy in reducing hepatic steatosis remains uncertain, with conflicting evidence reported in the literature.[113] In contrast, semaglutide appears to have a more favorable profile for the treatment of MASLD than other GLP-1 receptor agonists. In the SWITCH-SEMA trial, switching from liraglutide or dulaglutide to semaglutide resulted in a significant improvement in the Fatty Liver Index.[114] Moreover, following the ESSENCE trial, semaglutide has been approved for the treatment of MASLD due to its significant efficacy in achieving key histological endpoints.[115] However, similar benefits have not been demonstrated in patients with MASH-related cirrhosis, thereby limiting its utility in advanced stages of the disease.[116]

Pioglitazone represents a potentially cost-effective option for the treatment of MASLD, particularly in light of the high costs associated with newer therapies such as GLP-1 receptor agonists. It acts as a peroxisome proliferator-activated receptor (PPAR)-γ agonist with partial PPAR-α activity, thereby improving insulin sensitivity and contributing to reductions in plasma triglyceride levels. Pioglitazone has been shown to exert beneficial effects in MASLD, including reductions in hepatic fat content and inflammation.[117] Accumulating evidence, supported by meta-analyses, indicates its efficacy in improving liver fibrosis.[118] However, its use should be approached with caution due to potential adverse effects, including weight gain, an increased risk of bone fractures, particularly in postmenopausal women and cardiovascular complications related to fluid retention.[119–121] On the other hand, considering their beneficial effects on liver health, combination therapy with other antidiabetic agents, such as GLP-1 receptor agonists or dual GLP-1/GIP agonists, should be considered, particularly in patients with more severe disease. This approach may help minimize weight gain while optimizing liver-related benefits. For these reasons, the use of pioglitazone in MASH settings has already been recommended in T2DM guidelines.[122] Moreover, pioglitazone has been reported to reduce major vascular events, including stroke, and to improve insulin resistance, which further supports its use in appropriate patients.[123] Saroglitazar, another dual PPAR-α/γ agonist currently approved in India, has also demonstrated efficacy in the treatment of MASLD, with a generally favorable safety profile and predominantly mild adverse effects.[124]

Lipid Lowering Agents

Although the safety of statins in patients with MASLD, with the exception of decompensated cirrhosis, has been well established, concerns regarding potential hepatotoxicity persist, leading to the undertreatment of many individuals.[125–127] Statin use can lead to mild elevations in liver transaminases in over 15% of patients; however, clinically significant increases—defined as ALT levels greater than three times the upper limit of normal—are rare, occurring in less than 1% of cases. Consequently, treatment discontinuation is typically not warranted unless this threshold is exceeded. Furthermore, routine serial monitoring of liver enzymes is not required during statin therapy.[128] Statins may exert dose-dependent beneficial effects on liver fibrosis; however, the current evidence remains insufficient to draw definitive conclusions.[129]

Antioxidants

In patients with MASH and advanced liver disease, case–control studies have suggested that long-term vitamin E use is associated with a reduced risk of mortality and liver-related mortality.[130] In addition, the largest randomized controlled trial to date demonstrated that vitamin E supplementation (800 IU daily for two years) in non-diabetic patients with MASH led to significant improvements in hepatic steatosis and overall disease activity, accompanied by reductions in liver enzyme levels.[131] However, the effects of vitamin E on liver outcomes remain inconsistent across studies. In addition, safety concerns have been raised, including potential associations with hemorrhagic stroke, increased all-cause mortality, and prostate cancer.[132–134] Therefore, we do not recommend use of vitamin E in MASLD treatment.

Future Therapies

The therapeutic landscape for metabolic dysfunction-associated steatohepatitis (MASH) is evolving rapidly, with recent advances in pharmacologic options. Specifically, the accelerated approval of resmetirom (Rezdiffra) and semaglutide (Wegovy) now provides clinical pathways for patients with non-cirrhotic MASH and moderate-to-advanced fibrosis (F2–F3).

Beyond these initial approvals, a diverse pipeline of novel therapeutic agents is currently undergoing rigorous evaluation in phase 2 and phase 3 clinical trials. These emerging candidates are designed to target the

complex, multifaceted pathophysiology of MASH, including insulin resistance, obesity, hepatic inflammation, and fibrogenesis. Of particular note are the incretin-based multi-agonists, which include dual GLP-1/GIP agonists (e.g., tirzepatide), dual GLP-1/glucagon receptor agonists (e.g., cotadutide, survodutide, efinopegdutide), and triple GLP-1/GIP/glucagon receptor agonists (e.g., retatrutide). Parallel research continues to explore pathways involving bile acid signaling and lipid metabolism, with promising candidates such as the pan-PPAR α/δ/γ agonist lanifibranor and various FGF21 analogs, including efruxifermin, pegozafermin, and efimosfermin alfa.[135–138]

Clinical data indicate that both FGF21 analogs and incretin-based multi-agonists demonstrate robust histologic and non-invasive responses within a 24–52 week treatment window, frequently outperforming the substantial placebo responses observed in prior MASH clinical trials.[135] These multi-faceted therapeutic approaches reflect an increased capacity to address the complex underlying mechanisms of disease pathogenesis.

Recommendations

1. Pharmacological therapy is not a substitute for lifestyle interventions and should only be used as an adjunct when clinically indicated. Lifestyle modifications should be actively encouraged in all patients receiving pharmacotherapy. [LoE: High; SoR: Strong]
2. Pharmacological therapy with a MASH indication should be targeted at patients with clinically significant fibrosis and should exclude patients with cirrhosis. Treatment eligibility should be based primarily on non-invasive assessment, with VCTE as the preferred modality where available. [LoE: High; SoR: Strong]
    a. Patients with VCTE liver stiffness values in the 10–15 kPa range may be considered a priority group for consideration of pharmacological therapy. [LoE: Moderate; SoR: Conditional]
    b. In patients with VCTE liver stiffness values in the 15–20 kPa range, pharmacological therapy may be considered only if cirrhosis has been confidently excluded through clinical assessment, laboratory parameters, and imaging findings. In cases of diagnostic uncertainty, liver biopsy should be considered. [LoE: Moderate; SoR: Conditional]
3. Patients with MASLD and T2DM should be considered for antidiabetic pharmacotherapies with potential hepatic benefits:
    a. Pioglitazone may be encouraged in patients with type 2 diabetes mellitus and coexisting MASLD, where clinically appropriate and as a combination therapy. [LoE: Moderate; SoR: Conditional]
    b. SGLT2 inhibitors should be considered in patients with MASLD and type 2 diabetes mellitus, particularly in the presence of established or high-risk cardiovascular and/or renal disease. [LoE: High; SoR: Strong]

c. GLP-1 receptor agonists should be considered in patients with MASLD and type 2 diabetes mellitus, particularly in patients with coexisting obesity and/or in whom weight reduction is the key therapeutic target. [LoE: High; SoR: Strong]

Treatment of MASLD: Surgical and Endoscopic Therapy

Obesity has emerged as a critical global health crisis. Obesity is a major risk factor for metabolic syndrome and MASLD. While the prevalence of obesity among patients with MASLD is 50%, this figure reaches as high as 80% in biopsy-proven steatohepatitis cases. Conversely, among patients with obesity, the prevalence of MASLD is reported to be 75%, while that of MASH is 34%.[139]

Lifestyle modifications are recommended as the first-line treatment for obesity in all individuals and should not be abandoned under any circumstances. However, the impact of these approaches on sustainable weight loss remains limited. Pharmacological and bariatric treatments are recommended for patients who fail to achieve weight loss or demonstrate suboptimal weight loss despite at least six months of effort. Bariatric treatments contribute to MASH resolution and fibrosis regression by reducing hepatic inflammation, mitochondrial dysfunction, and endoplasmic reticulum stress, while increasing insulin sensitivity and promoting beneficial gut bacteria.[140] This section highlights the role of endoscopic and surgical interventions in MASLD treatment.

The indications for endoscopic and surgical therapies are defined as follows:[141]

- BMI ≥30 kg/m^2 and the presence of at least one obesity-related comorbidity (T2DM, obstructive sleep apnea (OSA), hyperlipidemia, hypertension, MASH, gastroesophageal reflux disease, asthma, osteoarthritis, polyendocrine metabolic ovarian syndrome (PMOS)).
- BMI ≥35 kg/m^2 (independent of the presence of obesity-related comorbidities).
- Endoscopic treatments are indicated for patients who are not eligible for surgery or who decline surgical intervention.

The contraindications are as follows:[141]

- Untreated major depression or psychosis
- Bulimia nervosa, Anorexia Nervosa
- Drug and alcohol use disorders
- Severe cardiac disease and coagulopathy
- Large Hiatal Hernia (>5 cm), active ulcer disease, severe GERD

Several endoscopic and surgical therapy options are available, and the choice of treatment should be individualized through shared decision-making with the patient. The most commonly preferred methods are illustrated in Figure 6.

Endoscopic Treatment Options

Endoscopic Sleeve Gastroplasty (ESG)

ESG is based on the principle of reducing gastric volume by endoscopic access to the patient's stomach via the transesophageal route and performing full-thickness sutures progressing from the antrum

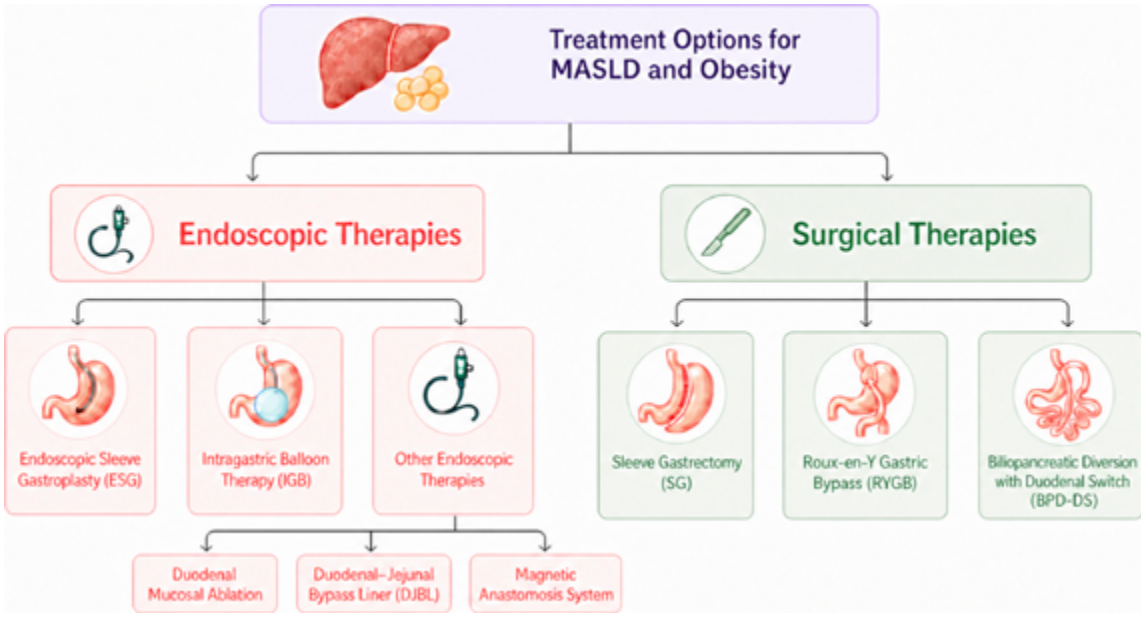


Figure 6. Endoscopic and surgical bariatric treatment options for MASLD and obesity.

toward the fundus. Weight loss following ESG appears sustainable in the long term. A recent meta-analysis demonstrated that at 6 months post-ESG, excess weight loss (EWL) was 48% and total body weight loss (TBWL) was 15.6%; at 60 months, EWL was 45.3% and TBWL was 15.9%.[142] In another meta-analysis evaluating the effects of ESG on patients with MASLD using non-invasive methods, ESG was associated with significant improvements in hepatic steatosis and fibrosis markers.[143]

Intragastric Balloon Therapy (IGB)

The working principle involves a balloon inflated with air or saline to a volume of at least 400 mL, which remains in the stomach for 6–12 months to promote early satiety and delay gastric emptying. The literature reports a TBWL ranging between 7.5% and 14% with this treatment. A meta-analysis of 442 patients found that IGB application resulted in a 79.2% improvement in steatosis and an 83.5% improvement in the MASLD activity score. Additionally, follow-up CT scans showed a reduction in liver volume in 93.9% of the patients. Furthermore, a biopsy-proven study observed an improvement of ≥2 points in the NAS score in 73% of patients and an improvement in fibrosis in 20%.[144]

Other Endoscopic Treatments

A method developed for treating metabolic diseases, such as type 2 DM and MASLD, involves the ablation of the duodenal mucosa between the Ampulla of Vater and the ligament of Treitz using thermal, radiofrequency, or steam therapy. The Duodenal-Jejunal Bypass Liner (DJBL) is designed to reduce nutrient absorption by placing a food-impermeable sleeve approximately 60 cm long into the duodenum. The Magnetic Anastomosis System aims to create a bypass by placing magnets in the duodenum and ileum to interact and form an anastomosis through tissue necrosis, thereby inducing weight loss via malabsorption.[145]

Surgical Methods

Sleeve Gastrectomy (SG)

SG is based on surgical excision of the gastric fundus and corpus to create a tubular gastric sleeve. This significantly reduces gastric volume; furthermore, neurohormonal modulation and changes in gastric emptying emerge as primary mechanisms for weight loss. A review of 3,542 patients found a one-year post-surgical TBWL of 29.5%. Literature evaluation indicates that during 1–3-year follow-ups post-SG, more than 50% of patients show histological and clinical improvement or resolution of MASLD.[146]

Roux-en-Y Gastric Bypass (RYGB)

RYGB is a highly effective and complex surgical method that aims to reduce food intake and nutrient absorption by creating a small gastric pouch and rerouting nutrients through a new path within the small intestine. Patients experience 60–70% EWL after RYGB, with a TBWL of 31.9% reported at the end of the first year. One review demonstrated a 53% reduction in steatohepatitis activity (NAS score) and a 26% reduction in liver fibrosis severity after RYGB. This protective effect persists during long-term follow-up.[147]

Biliopancreatic Diversion – Duodenal Switch (BPD-DS)

BPD-DS combines restrictive and malabsorptive mechanisms by delaying the mixing of bile and pancreatic enzymes with nutrients, resulting in superior long-term weight loss compared with other bariatric procedures. Excess weight loss approaches 80% at 2 years, while biopsy-based studies have reported MASH resolution in 70% of patients and fibrosis improvement in 32%. However, another study found fibrosis improvement in 27% of patients, whereas 40% experienced worsening, which was associated with low albumin levels, uncontrolled diarrhea, and menopausal status.[148–150]

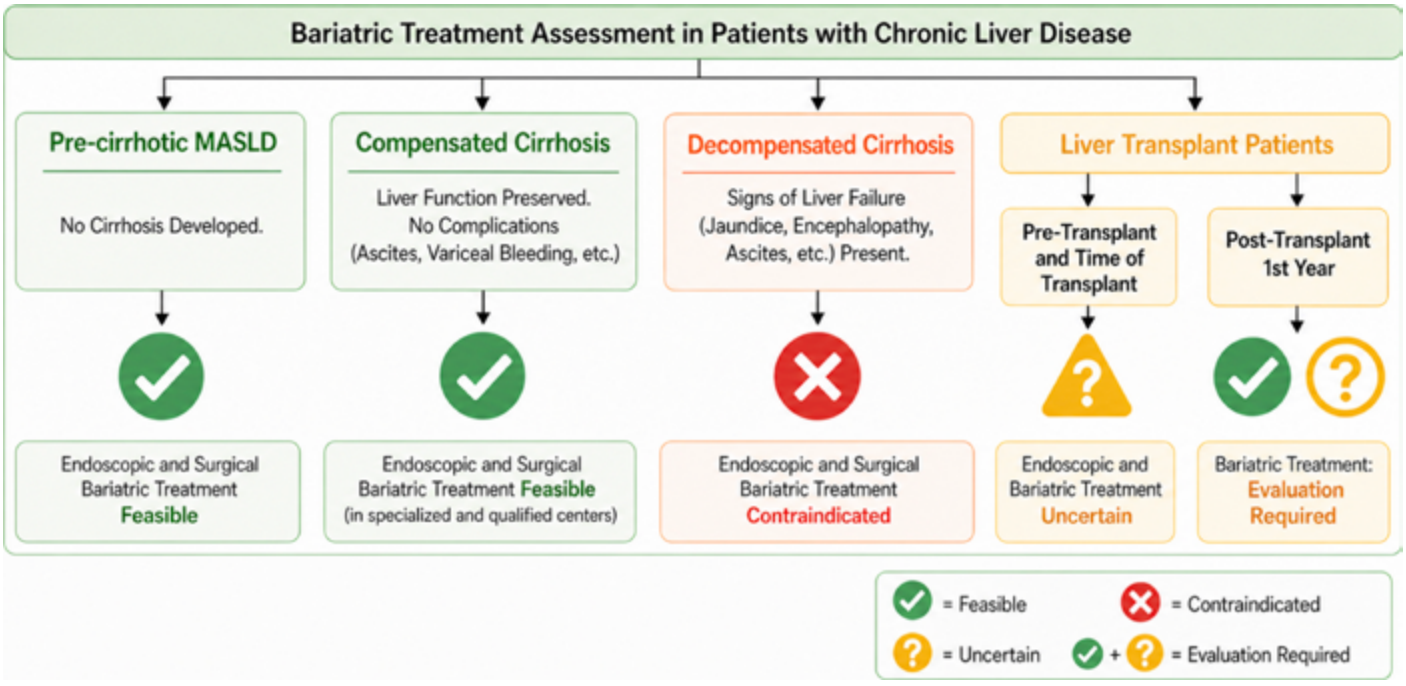


Figure 7. Bariatric treatment algorithm in patients with MASLD.

Bariatric Treatments in Special Populations

MASH Cirrhosis

Bariatric surgery may be preferred in patients with compensated advanced chronic liver disease (cACLD) or compensated cirrhosis (CC) secondary to MASH. However, the presence of clinically significant portal hypertension, indications, and type of surgery must be evaluated by an experienced multidisciplinary team in this specific patient population. In such cases, SG is preferred because of its lower complication rate and sustained long-term weight loss benefits.[151]

Although the perioperative risk is higher in patients with cACLD/CC than in those with pre-cirrhosis, beneficial long-term outcomes have been reported. A study matching 2,107 cirrhotic patients with non-bariatric cirrhotic patients showed that bariatric treatment led to a 37% reduction in all-cause mortality, a 76% reduction in liver-related mortality, a 47% reduction in the risk of decompensation, and a 60% reduction in the risk of transplantation. In the SPECCIAL study, conducted on a biopsy-proven patient group, the bariatric treatment group showed 50% less decompensation and 55% fewer Major Adverse Liver Outcomes (MALO) over a 15-year follow-up than the non-bariatric group.[151–153] Bariatric treatment is considered contraindicated in patients with decompensated cirrhosis unless performed in conjunction with liver transplantation.

Liver Transplant Patients

Bariatric treatment may be applied with careful evaluation in patients on the liver transplant waiting list with cACLD/CC.[154] Sleeve gastrectomy is the preferred approach and may be performed in combination with liver transplantation in selected cases in specialized centers.[151,154,155]

The recommendations are summarized in Figure 7.

Recommendations

1. Bariatric procedures are not a substitute for lifestyle interventions and should only be used as an adjunct when clinically indicated. Lifestyle modifications should be actively encouraged in all patients undergoing bariatric procedures. [LoE: Moderate; SoR: Strong]
2. Bariatric interventions should be performed in accordance with established obesity guideline indications. [LoE: Moderate; SoR: Strong]
3. Bariatric treatments are contraindicated in patients with decompensated cirrhosis. [LoE: Moderate; SoR: Strong]
4. Bariatric treatments are not recommended before or simultaneously with liver transplantation. It is advisable to wait until post-transplantation graft stabilization is achieved (>1 year). In selected cases, sleeve gastrectomy may be an option. [LoE: Low; SoR: Conditional]

Management of Metabolic Comorbidities and Cardiovascular Risk

MASLD is a multisystem disease rather than a condition limited solely to the liver.[156] Indeed, cardiovascular disease (CVD) represents the leading cause of mortality in individuals with MASLD, followed by extrahepatic malignancies. Overall, patients with MASLD have an approximately two-fold higher risk of fatal and non-fatal

Table 8. Checklist for baseline and longitudinal assessment of metabolic comorbidities and cardiovascular risk in MASLD

Time point	Assessment	Comments
At baseline	BMI and waist circumference	Record obesity and central adiposity
	Blood pressure	Measure systolic and diastolic blood pressure
	Fasting lipid profile	Total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides
	Lipoprotein(a)	Once-in-a-lifetime measurement
	Fasting plasma glucose and/or HbA1c	Consider OGTT if results are borderline or discordant
	Serum creatinine and eGFR	Preferably calculated using the CKD-EPI equation
	Urine albumin-to-creatinine ratio (UACR/ACR)	Baseline renal risk assessment
	Formal ASCVD risk estimation	Use a validated tool (e.g. SCORE2/SCORE2-OP in European/Turkish settings)
	Alcohol intake and tobacco use	Document and address at baseline
At every visit	BMI and waist circumference	Monitor change over time
	Blood pressure	Reassess and optimize control
	Alcohol intake and tobacco use	Reassess and reinforce counselling
Every 6–12 months	Fasting plasma glucose and/or HbA1c	Frequency according to baseline risk and diabetes status
	Fasting lipid profile	According to cardiovascular risk and lipid-lowering therapy
	Serum creatinine and eGFR	More frequent if diabetes, CKD, or higher renal risk
	ALT, AST, platelet count	Routine biochemical and fibrosis-related monitoring
Annually or risk-based	Urine albumin-to-creatinine ratio (UACR/ACR)	Especially in diabetes, hypertension, CKD risk, or advanced fibrosis
	ASCVD risk reassessment	Repeat if major risk factors change or at clinically appropriate intervals
	OSA screening	Use a validated questionnaire (e.g. Epworth Sleepiness Scale) in obesity and/or snoring
	Evaluation for PMOS/PCOS	In women with menstrual irregularities and/or hyperandrogenic features
	Sarcopenia screening	Consider SARC-F questionnaire, particularly in patients at higher clinical risk including cirrhosis and obesity treatments

ACR: Albumin-to-creatinine ratio; ALT: Alanine aminotransferase; ASCVD: Atherosclerotic cardiovascular disease; AST: Aspartate aminotransferase; BMI: Body mass index; CKD: Chronic kidney disease; CKD-EPI: Chronic kidney disease epidemiology collaboration; eGFR: Estimated glomerular filtration rate; HbA1c: Glycated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; OGTT: Oral glucose tolerance test; OSA: Obstructive sleep apnea; PMOS: Polyendocrine metabolic ovarian syndrome; PCOS: Polycystic ovary syndrome; SARC-F: Strength, assistance with walking, rise from a chair, climb stairs, and falls; SCORE2: Systematic coronary risk evaluation 2; UACR: Urine albumin-to-creatinine ratio.

cardiovascular events compared with the general population. Liver-related mortality becomes the dominant cause of death only in those who have progressed to advanced fibrosis or cirrhosis.[157] The MASLD nomenclature places metabolic dysfunction at the center of the diagnostic framework and extends beyond a liver-specific condition, reflecting a broader systemic metabolic disorder. Importantly, accumulating evidence demonstrates that the risk of severe liver outcomes increases in a stepwise manner with each additional metabolic trait, rather than being determined by the presence or absence of any single syndrome definition.[158] In the treatment of MASLD, not only the liver disease itself but also associated comorbidities should be considered and managed through a multidisciplinary approach to reduce both liver-related and overall morbidity and mortality. The baseline and follow-up comorbid parameters in MASLD management are summarized in Table 8. In this section, the management of MASLD is discussed in the context of concomitant comorbidities.

Type 2 Diabetes Mellitus

T2DM is one of the most important comorbidities in MASLD, given both its high prevalence and its significant impact on prognosis. In individuals with T2DM, MASLD is associated with an increased risk of MASH, cirrhosis, HCC, and liver-related mortality, as well as atherosclerotic cardiovascular disease and extrahepatic malignan-

cies. Conversely, individuals with MASLD have a two- to five-fold higher risk of developing incident T2DM compared with the general population.[159] Therefore, all individuals with MASLD should undergo baseline assessment for dysglycemia using HbA1c and/or fasting plasma glucose and vice versa. Moreover, patients with T2DM should be prioritized for risk stratification and further diagnostic evaluation. In case of discordant or borderline results, or when clinical suspicion persists, an Oral Glucose Tolerance Test (OGTT) should be performed. Subsequent monitoring should be risk-stratified according to baseline findings and overall cardiometabolic risk. Individuals with normal baseline results should undergo reassessment at least every three years, whereas those with prediabetes should be monitored annually. Management of T2DM in MASLD should aim to optimize glycemic control while mitigating the risk of progressive liver disease. Lifestyle intervention remains the cornerstone of therapy and should be universally implemented. This includes dietary modification, regular physical activity, and behavioral support, all of which improve glycemic control and reduce hepatic steatosis. Pharmacological treatment should be individualized, balancing glycemic efficacy, safety, and weight effects. Management should follow established diabetes care principles while also accounting for liver-related outcomes as noted previously.[160]

Obesity

Although reported associations between obesity and MASLD vary due to differences in definitions and populations, obesity remains a principal driver of disease. Prevalence increases markedly with rising BMI, reaching approximately 60–90% in obesity, 75–90% in severe obesity, and up to 95% in individuals with BMI >40 kg/m^2. Overall, overweight and obesity predominate in MASLD, affecting approximately 85–90% of patients, whereas the lean phenotype is relatively uncommon, accounting for around 10–15% of cases.[161,162] Visceral adiposity is particularly important in driving progression to MASH, advanced fibrosis, and HCC. Obesity is an independent determinant of morbidity and premature mortality, largely mediated through cardiovascular disease, but also contributing to T2DM, chronic kidney disease, and malignancy.[163]

All adults with MASLD and overweight or obesity should receive structured lifestyle intervention. The presence of MASH and/or clinically significant fibrosis (≥F2) should be regarded as a high-risk feature that justifies earlier escalation to effective weight-loss strategies. Weight loss targets in MASLD are closely linked to histological improvement. A reduction of at least 3–5% of body weight is associated with improvement in hepatic steatosis. Greater weight loss of 7–10% is typically required for resolution of steatohepatitis, while a reduction of 10% or more is associated with improvement or regression of liver fibrosis.

Hypertension

Hypertension is defined as a systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg, or current use of antihypertensive medication. It is a frequent and clinically relevant comorbidity in MASLD, and several studies report on a bidirectional association. The incidence of hypertension increases with advancing liver disease, rising from approximately 6.5 per 100 person-years in early MASLD to over 14 per 100 person-years in patients with cirrhosis, reflecting progressive cardiometabolic and vascular dysfunction.[164]

Hypertension is independently associated with fibrosis progression and adverse liver outcomes. The risk of severe liver events increases in a stepwise manner with the accumulation of metabolic traits. Patients with both hypertension and dyslipidemia have an approximately 1.8-fold higher risk of progression to cirrhosis or hepatocellular carcinoma, underscoring the synergistic effect of cardiometabolic risk factors on liver disease severity.[165]

Blood pressure assessment should be an integral part of MASLD care, and monitored regularly during follow-up, with treatment targets aligned to contemporary hypertension guidelines.

Treatment target for optimal blood pressure control is <140/90 mmHg. Pharmacological treatment of hypertension in MASLD should follow standard hypertension management principles, with attention to agents that may offer additional metabolic or hepatic benefits. Renin–angiotensin–aldosterone system (RAAS) blockers, including angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin receptor blockers (ARBs), are preferred first-line agents in the absence of contraindications. Beyond effective blood pressure control, RAAS blockade may attenuate hepatic fibrogenesis through anti-inflammatory and anti-fibrotic mechanisms. Among ARBs, telmisartan may be particularly attractive in selected patients because of its partial PPAR-γ agonistic activity, which has been associated with improvements in insulin sensitivity and reductions in hepatic fat content compared with other agents in this class.[166] Antihypertensive therapy should always be individualized based on blood pressure control, comorbidities, renal function, and tolerability. Furthermore, lifestyle modifications should complement pharmacotherapy for effective blood pressure management. In adults with hypertension, adopting a healthy dietary pattern, such as the Dietary Approaches to Stop Hypertension diet, and limiting daily sodium intake to less than 2,400 mg may help achieve target blood pressure levels.[167]

Dyslipidemia

Dyslipidemia is an important component of the metabolic dysfunction underlying MASLD and is incorporated into its diagnostic framework as a cardiometabolic risk factor. In adults with MASLD, dyslipidemia is defined by the presence of fasting plasma triglycerides ≥150 mg/dL, low HDL-cholesterol (<40 mg/dL in men or <50 mg/dL in women), or current use of lipid-lowering therapy. In addition, lipoprotein(a) represents an independent, genetically determined risk factor for atherosclerotic cardiovascular disease (ASCVD) and is increasingly recognized as relevant in this population.[168]

At the time of MASLD diagnosis and during regular follow-up, patients should undergo laboratory assessment of fasting plasma

triglycerides, total cholesterol, LDL-cholesterol, and HDL-cholesterol. A once-in-a-lifetime measurement of lipoprotein(a) is recommended, as elevated levels confer an independent and causal risk for Atherosclerotic Cardiovascular Disease (ASCVD) and may influence long-term cardiovascular risk stratification. The presence of dyslipidemia has been independently associated with progression to moderate-to-advanced liver fibrosis, particularly when combined with other metabolic risk factors.[169] Importantly, as MASLD advances to cirrhosis, serum lipid and lipoprotein levels may appear to "normalize" due to impaired hepatic synthesis. This apparent normalization should not be misinterpreted as risk reduction, as these patients often remain at high risk of coronary artery disease and adverse cardiovascular outcomes.

MASLD is not a contraindication to lipid-lowering therapy. Statins are safe across the entire spectrum of MASLD, including in patients with MASH and compensated cirrhosis, and do not increase the risk of hepatotoxicity when used appropriately. Statin use is associated with a lower risk of MASLD progression, MASH, liver fibrosis, and, in patients with cirrhosis, a reduced risk of hepatic decompensation and hepatocellular carcinoma.[170]

LDL-cholesterol treatment targets should be determined according to the patient's overall cardiovascular risk, in line with contemporary cardiovascular prevention guidelines. Routine discontinuation or dose adjustment of statins is not required in MASLD, and treatment should only be interrupted if transaminase levels exceed three times the upper limit of normal in the absence of alternative explanations. In patients with severe hypertriglyceridemia (≥500 mg/dL), treatment with fibrates should be considered to reduce the risk of pancreatitis, alongside dietary fat restriction and optimization of glycemic control.

Chronic Kidney Disease

Chronic kidney disease (CKD) is a common and clinically important extrahepatic comorbidity in MASLD. MASLD and CKD share multiple cardiometabolic risk factors, and accumulating evidence indicates that liver disease severity is directly linked to adverse renal outcomes. Individuals with MASLD have an approximately 1.4–1.5-fold higher risk of incident CKD (stage ≥3) compared with those without MASLD, independent of demographic factors and traditional CKD risk factors. MASLD is associated with an approximately two-fold higher risk of developing CKD over time.[171,172]

Clinicians should assess renal function using serum creatinine and estimated glomerular filtration rate, preferably calculated using the Chronic Kidney Disease Epidemiology Collaboration equation at diagnosis and follow-up. Albuminuria should be tested by spot urine albumin-to-creatinine ratio or, where appropriate, protein-to-creatinine ratio. Albuminuria provides important prognostic information and may precede detectable reductions in eGFR. Periodic monitoring of renal function should be intensified in patients with advanced liver fibrosis, given their higher risk of CKD progression. Individuals with type 2 diabetes or prediabetes warrant particular attention, as abnormal glucose metabolism markedly increases the risk of CKD through microvascular mechanisms and frequently coexists with progressive MASLD.

ACE inhibitors or ARBs are recommended in patients with albuminuria, as they provide renoprotective effects in addition to blood pressure control and may favorably influence fibrogenic pathways.[173] SGLT2 inhibitors are strongly recommended in patients with coexisting MASLD and type 2 diabetes, given their well-established renal protective effects and evidence for slowing CKD progression, alongside their metabolic benefits. Overall, early identification and proactive management of CKD are essential components of comprehensive MASLD care, as renal impairment substantially contributes to long-term morbidity and mortality in this population.

Atherosclerotic Cardiovascular Risk

CVD is the leading cause of death in individuals with MASLD, exceeding liver-related mortality in patients without advanced fibrosis. MASLD is strongly associated with ASCVD, as well as heart failure and cardiac arrhythmias, particularly atrial fibrillation. Overall, patients with MASLD have an approximately two-fold higher risk of fatal or non-fatal cardiovascular events compared with the general population, independent of traditional risk factors.[174]

The shift to MASLD places metabolic dysfunction at the core of disease pathophysiology and reinforces the need for proactive cardiovascular risk assessment and prevention. Traditional risk factors frequently cluster in MASLD, and reliance on liver-focused outcomes alone underestimates long-term prognosis. Cardiovascular risk assessment should therefore be integrated into routine MASLD care.

Cardiovascular Risk Assessment

All adults with MASLD should undergo formal cardiovascular risk assessment, irrespective of age, given the high background burden of cardiometabolic risk and the elevated lifetime risk of ASCVD in this population. Risk should be reassessed periodically, particularly when new metabolic risk factors develop.

For the Turkish population, cardiovascular risk assessment should be performed using the SCORE2 (Systematic COronary Risk Evaluation 2) risk estimation system developed by the European Society of Cardiology (ESC). SCORE2 estimates the 10-year risk of first fatal and non-fatal ASCVD events, specifically myocardial infarction and stroke, and is calibrated according to background regional cardiovascular risk. Türkiye is classified as a high-risk region within the ESC framework, and the corresponding SCORE2 charts should therefore be applied. SCORE2 is validated for adults aged 40 to 69 years, while SCORE2-OP (Older Persons) is designed for individuals aged 70 years and older. It is important to note that SCORE2 focuses on atherosclerotic outcomes and does not estimate the risk of heart failure, atrial fibrillation, or renal outcomes, nor does it incorporate albuminuria or non-traditional biomarkers.

American Heart Association Predicting Risk of Cardiovascular Disease Events (PREVENT) ASCVD risk calculator may be used in

selected settings. PREVENT can be applied from 30 years of age, provides both 10-year and 30-year risk estimates, and includes a broader range of cardiovascular outcomes, including heart failure.[175] PREVENT is derived from U.S. populations and is not regionally calibrated for Europe, therefore SCORE2 remains the preferred tool for routine cardiovascular risk assessment in Türkiye, in alignment with European prevention guidelines.[176]

Based on the estimated 10-year risk of ASCVD, patients are broadly classified as:

- Low to moderate risk: <5% (age-adjusted thresholds apply in younger individuals)
- High risk: ≥5% to <10% (includes many individuals with diabetes, CKD stage 3, or multiple metabolic risk factors)
- Very high risk ≥10% (includes patients with established ASCVD, diabetes with target-organ damage, severe CKD, or very high calculated risk)

In primary prevention, patients at moderate cardiovascular risk should generally aim for an LDL-cholesterol level below 100 mg/dL, while those at high risk should target LDL-cholesterol below 70 mg/dL with at least a 50% reduction from baseline. Individuals at very high risk, including those with established atherosclerotic cardiovascular disease, diabetes with target-organ damage, severe chronic kidney disease, or very high calculated risk, should aim for LDL-cholesterol below 55 mg/dL and a ≥50% reduction from baseline.

Obstructive Sleep Apnea (OSA)

OSA is a frequent extrahepatic comorbidity in MASLD, particularly among individuals with overweight or obesity. Compared with the general population, patients with MASLD have an approximately 2.2-fold higher risk of OSA, reflecting shared mechanisms such as insulin resistance, visceral adiposity, and intermittent hypoxia. OSA-related hypoxia has been associated with worsening metabolic dysfunction and more severe liver disease, including increased risk of steatohepatitis.[177]

Clinicians should maintain a high index of suspicion for OSA in patients with MASLD and should perform systematic clinical screening using targeted history and validated questionnaires, such as the Epworth Sleepiness Scale (and other recognized tools), focusing on symptoms of excessive daytime sleepiness, snoring, witnessed apneas, and nocturnal choking. Patients identified as being at high clinical risk should be referred for further diagnostic evaluation and management according to standard sleep-medicine practice.

Polyendocrine Metabolic Ovarian Syndrome (PMOS)

Polyendocrine metabolic ovarian syndrome (PMOS), previously known as polycystic ovary syndrome (PCOS), is a common multisystem endocrine and metabolic disorder affecting approximately one in eight women worldwide.[178] PMOS is characterized by hyperandrogenism, insulin resistance, and metabolic dysfunction, all of which promote hepatic fat accumulation and help explain its close association with MASLD. Women with PMOS have a markedly higher prevalence of MASLD and a more than twofold increased risk of developing type 2 diabetes. MASLD prevalence in PMOS ranges from about 34% to 70%, with a pooled estimate of around 43% in a large meta-analysis.[179] Emerging evidence suggests an association between PMOS and increased severity of steatohepatitis, although its impact on long-term fibrosis progression remains under investigation.[180] In women with MASLD, particularly those with features of hyperandrogenism or menstrual irregularities, PMOS should be considered and assessed as part of the broader metabolic evaluation.

Sarcopenia and Sarcopenic Obesity

Sarcopenia, defined by reduced skeletal muscle mass, strength, and function, and sarcopenic obesity, the coexistence of muscle loss with excess adiposity, are common in advanced MASLD, especially in cirrhosis. Compared with the general population, MASLD is associated with an approximately two-fold higher risk of sarcopenia.[181] Sarcopenia affects about 23.5% of patients with MASLD overall and increases markedly with cirrhosis, reaching approximately 41% and increasing further in advanced stages.[182] The majority of these patients have sarcopenic obesity.[183] Sarcopenia is associated with increased risk of fibrosis, hepatic decompensation, reduced physical function, and higher mortality.[184] In patients with MASH-related cirrhosis, nutritional and lifestyle interventions described under Role of Lifestyle Modifications should be adapted to preserve muscle mass.

Smoking and Alcohol

In addition to metabolic risk factors, alcohol consumption and tobacco use are important modifiers of disease course and cardiovascular risk in MASLD and should be routinely assessed. Notably, there is no established safe threshold for alcohol consumption in individuals with MASLD, and adverse liver and cardiometabolic effects may occur even at low or moderate levels of intake; the absence of criteria fulfilling overlap phenotypes such as MetALD does not imply safety. Tobacco smoking is independently associated with increased risks of cardiovascular disease, malignancy and all-cause mortality, and may further exacerbate both liver-related and extrahepatic outcomes.[185,186] Given their high prevalence in Türkiye and clinically significant impact,[187,188] alcohol use and smoking should be actively identified, counselled, and discouraged in all patients with MASLD as an integral component of comprehensive disease management. The ultimate goal should be complete smoking cessation and total abstinence from alcohol.

Recommendations

1. Body mass index (BMI) and waist circumference should be recorded at baseline and reassessed at each follow-up visit. [LoE: Moderate; SoR: Strong]
2. Systolic and diastolic blood pressure should be measured at baseline and monitored at every follow-up visit. [LoE: High; SoR: Strong]
3. A fasting lipid profile, including total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides, should be obtained at baseline and repeated at intervals determined by the patient's cardiovascular risk category and lipid-lowering treatment status. [LoE: High; SoR: Strong]
4. Lipoprotein(a) should be measured once in a lifetime to refine long-term ASCVD risk assessment. [LoE: Moderate; SoR: Strong]
5. Fasting plasma glucose and/or HbA1c should be measured at baseline and monitored periodically thereafter, with frequency tailored to baseline results and the individual risk profile. An OGTT should be considered when results are borderline or discordant, or when clinical suspicion persists. [LoE: High; SoR: Strong]
6. Assessment of insulin resistance using the homeostasis model assessment of insulin resistance (HOMA-IR) or OGTT-derived indices may be considered in patients without established diabetes or dysglycemia when clarification of metabolic dysfunction is clinically relevant. [LoE: Low; SoR: Conditional]
7. Renal risk should be assessed at baseline using serum creatinine with estimated glomerular filtration rate and urine albumin-to-creatinine ratio, and monitored thereafter at intervals guided by fibrosis stage, diabetes status, baseline renal function, and albuminuria. [LoE: Moderate; SoR: Strong]
8. Formal ASCVD risk estimation should be performed using an appropriate validated risk tool (for example, SCORE2/SCORE2-OP in European/Turkish settings), and updated when major risk factors change or at clinically appropriate intervals. [LoE: Moderate; SoR: Strong]
9. Smoking and alcohol intake should be routinely assessed and actively addressed as part of comprehensive risk management at baseline and during follow-up. Complete abstinence from both smoking and alcohol should be the goal. [LoE: Moderate; SoR: Strong]
10. In patients with obesity and/or symptoms suggestive of OSA (e.g., snoring), screening with a validated questionnaire such as the Epworth Sleepiness Scale should be considered, with referral for diagnostic evaluation when clinical risk is high. [LoE: Moderate; SoR: Conditional]
11. All women with menstrual irregularities may be referred for evaluation for PMOS, particularly when accompanied by features of hyperandrogenism or insulin resistance. [LoE: Low; SoR: Conditional]
12. Patients with cirrhosis should be screened for sarcopenia using a brief validated tool such as the SARC-F questionnaire, with further assessment and nutritional/physical intervention where indicated. [LoE: Moderate; SoR: Strong]

Cirrhosis, HCC Surveillance and Liver Transplantation in Patients with MASLD

MASH has increasingly become an indication for liver transplantation in Türkiye, in parallel with the rising prevalence of MASH-related cirrhosis.[189,190] Therefore, the management of MASH should be optimized. In this section, MASH-cirrhosis–related complications, HCC surveillance, and liver transplantation are discussed.

Diagnosis of Clinically Significant Portal Hypertension in MASLD-Related Cirrhosis

The risk of complications in patients with MASLD is determined by the presence, severity, and development of esophageal varices. Non-selective beta-blockers (NSBBs) can reduce variceal hemorrhage and prevent decompensation in individuals with clinically significant portal hypertension (CSPH), defined as a hepatic venous pressure gradient (HVPG) ≥10 mmHg. CSPH is the main driver of decompensation in patients with cACLD, and non-invasive markers can help predict this risk.[191] According to the Baveno VII criteria, CSPH may be ruled out when LSM is <15 kPa and the platelet count is ≥150×10^9/L. In adults with LSM ≥20 kPa and/or platelet count <150×10^9/L, upper gastrointestinal endoscopy should be performed to screen for varices. CSPH can be ruled in when the LSM ≥25 kPa; however, only in non-obese (BMI <30 kg/m^2) adults.[192] The ANTICIPATE-NASH model (based on the combination of LSM, PLT, and BMI) may help to predict CSPH in individuals with compensated MASH-related cirrhosis.[193,194]

Spleen stiffness measurement (SSM) using a 100 Hz specific transient elastography probe is an emerging non-invasive tool for assessing CSPH. In patients with Compensated Advanced Chronic Liver Disease (cACLD), SSM may improve risk stratification for CSPH and high-risk varices, particularly in individuals who fall into the indeterminate ("grey zone") category of the Baveno VII classification (LSM ≥20 kPa or platelet count ≤150×10^9/L). This limitation is especially relevant in patients with MASLD and obesity, in whom the diagnostic performance of liver stiffness–based rule-in thresholds is reduced.[192] In patients who are not candidates for NSBBs (propranolol or carvedilol) and who would otherwise require endoscopic screening according to the Baveno VI criteria, an SSM ≤40 kPa may identify individuals with a low probability of high-risk varices in whom screening endoscopy can be safely avoided. The newly implemented SSM by VCTE at 100 Hz, when combined with LSM, PLT, and BMI in a composite model known as 'non-invasive CSPH estimated risk' (NICER), demonstrated a greater ability to discriminate for identifying patients with CSPH compared to the ANTICIPATE-NASH model.[195] A recent multicenter cohort study, predominantly including patients with MASLD, suggested that although SSM is associated with CSPH, its ability to predict hepatic decompensation is limited when LSM and serum albumin levels are considered.[196]

Recommendations

1. LSM by VCTE ≤15 kPa together with a platelet count ≥150×10^9/L effectively rules out CSPH in patients with MASLD and may help avoid unnecessary endoscopic screening for varices. [LoE: High; SoR: Strong]
2. In patients with cACLD and an LSM ≥20 kPa and/or a platelet count ≤150×10^9/L, screening endoscopy for varices is recommended. In experienced centers, spleen stiffness measurement (SSM) ≤40 kPa may be used as an adjunctive tool to refine endoscopy decisions in these patients. [LoE: High (endoscopy)/Moderate (SSM); SoR: Strong, SSM adjunct: Conditional]
3. If CSPH is present, NSBBs should be considered unless contraindicated or not tolerated. [LoE: High; SoR: Strong]

Hepatocellular Carcinoma Surveillance in MASLD

The recommendation for HCC surveillance in patients with cirrhosis is supported by a strong clinical rationale as well as evidence from a landmark randomized controlled trial.[197] Approximately 80–90% of HCC cases arise in individuals with cirrhosis, and surveillance aims to detect HCC at an early stage when potentially curative treatments are more likely to be feasible and improve survival. There is a consensus among all international societies that patients with MASLD-cirrhosis should undergo HCC screening, as they appear to have an average HCC risk of 1–1.5% year.

The prevalence of MASLD-related cirrhosis and HCC is increasing in Türkiye. In a recent multicenter study from Türkiye with 4953 cirrhotic patients, the etiology of cirrhosis before and after 2010 was compared, and the proportion of MASLD-related cirrhosis increased significantly after 2010, rising from 12% to 25%. In addition, another recent multicenter study from Türkiye reported that the proportion of MASLD-related HCC increased from 6.6% to 13.4% after 2016, reflecting the growing contribution of MASLD to the HCC burden.[190,198,199]

A substantial proportion of MASLD-related HCC cases arise in the absence of cirrhosis. Nevertheless, the overall risk of HCC among patients with non-cirrhotic MASLD remains low and does not generally justify routine surveillance. Therefore, the main challenge is to accurately identify individuals with sufficiently elevated HCC risk among patients with MASLD who do not have cirrhosis. Population-based studies indicate that the incidence of HCC in non-cirrhotic MASLD is low, ranging from approximately 0.08 to 0.63 per 1,000 person-years.[34] In a meta-analysis of 18 studies including 470,404 patients with MASLD without cirrhosis, the incidence rate of HCC was 0.03 per 100 person-years.[200] Another systematic review and meta-analysis of 61 studies reported that nearly 40% of MASLD-related HCC cases occurred in patients without cirrhosis, compared with approximately 15% of HCC cases related to other etiologies. However, only 33% of patients with NAFLD-related HCC underwent surveillance prior to diagnosis.[201] In a cohort study of 1,773 adults with NAFLD, the incidence rate of HCC among patients with advanced fibrosis (F3) was 0.34 per 100 person-years, indicating an intermediate risk that is lower than that observed in cirrhosis but not negligible.[202] However, there is currently no consensus regarding the benefits of routine HCC surveillance in non-cirrhotic MASLD or MASH. Furthermore, staging advanced fibrosis (F3) using non-invasive methods can be challenging, which complicates risk stratification and makes surveillance decisions less favorable from a cost-effectiveness perspective. Therefore, screening for HCC is strongly recommended in patients with MASH-related cirrhosis. Routine HCC surveillance is not recommended in noncirrhotic patients with MASLD/MASH because of insufficient evidence and the low overall incidence of HCC. However, selected patients at higher estimated risk—including those with advanced fibrosis (F3), a family history of HCC, multiple cardiometabolic risk factors (particularly T2DM), or ongoing alcohol consumption—may be considered for individualized HCC surveillance after careful clinical risk assessment until more robust evidence becomes available.[203]

Current international society guidelines recommend ultrasound-based surveillance every 6 months, with or without alpha-fetoprotein measurement, in individuals with cirrhosis, regardless of the etiology. Evidence supporting HCC surveillance with ultrasound and alpha-fetoprotein (AFP) originates from a randomized controlled trial conducted in China.[197] Ultrasound LI-RADS was subsequently introduced to standardize ultrasound interpretation; however, studies including patients with cirrhosis and MASLD have reported high rates of visualization score C (severe limitations), indicating substantial technical limitations and highlighting the operator-dependent nature of ultrasound.[204] Therefore, alternative imaging modalities such as MRI have been explored. Prospective and observational studies have shown that full MRI provides higher sensitivity and positive predictive value for detecting early HCC and is associated with fewer false-positive results than ultrasound. However, the routine use of full MRI for surveillance is limited by its high cost, long examination time, and need for specialized expertise. Abbreviated MRI protocols have been proposed as potential alternatives; however, current evidence remains limited, as most studies are retrospective simulations or include populations that do not fully represent surveillance cohorts. Therefore, further prospective studies and ongoing clinical trials are needed to clarify the role of abbreviated MRI in HCC surveillance.[205]

AFP is currently the only biomarker with sufficient evidence to support its clinical use in HCC surveillance when combined with ultrasound. Two meta-analyses have shown that adding AFP to ultrasound increases the sensitivity for detecting early-stage HCC compared to ultrasound alone, although this improvement is accompanied by a decrease in specificity.[206,207]

Additional risk stratification approaches combining clinical variables, biomarkers, or fibrosis-based non-invasive tests have been explored, but these models remain insufficiently validated for routine clinical implementation. Biomarkers commonly used to improve the performance of AFP include des-gamma carboxyprothrombin (DCP) and lectin-bound AFP (AFP-L3). Several models combine demographic and clinical variables and serum biomarkers, such as the HCC risk

Table 9. Management of comorbidities in patients with MASLD before liver transplantation. Modified from [151, 224]

Condition	Recommendations
Diabetes mellitus	• Screen for impaired fasting glucose (IFG) or glucose tolerance (IGT) and/or T2DM (OGTT, HbA1c) • Achieve good glycemic control before LT • Weight-lowering (e.g., SGLT2 inhibitors or GLP-1 receptor agonists) or weight-neutral agents (e.g., metformin) should be preferred when liver and renal functions allow, with careful assessment of liver disease severity to guide the optimal therapeutic approach.
Nutritional status	• Assess nutritional status before LT • Assess alcohol consumption • Healthy diet, physical exercise and lifestyle modification (including weight reduction in individuals with obesity)
Cardiovascular disease	• Pre-liver transplantation cardiovascular risk stratification is mandatory in such cases. • A structured, multidisciplinary, diagnostic, cardiac workup should be performed. • LT candidates with cardiovascular risk should be managed with goal-directed medical management (e.g. statins, anti-platelet agents, beta blockers, RAAS blockers), based on the stage of cirrhosis and renal function
Kidney dysfunction	• Kidney function should be adequately monitored before LT • Comedications need to be adjusted dependent on kidney function
Malignancies	• Screening for pre-liver transplantation malignancies should follow the same protocols as those applied to patients without MASLD-related cirrhosis.

OGTT: Oral glucose tolerance test; HbA1c: Glycated hemoglobin; SGLT2: Sodium-glucose cotransporter-2; GLP1RA: Glucagon-like peptide-1 receptor agonist; LT: Liver transplantation; RAAS: Renin-angiotensin-aldosterone system; MASLD: Metabolic dysfunction-associated steatotic liver disease.

score, aMAP, and GALAD.[204,205,208,209] The GALAD score, which incorporates AFP, AFP-L3, DCP, age, and sex, is one of the most widely studied biomarker-based models for HCC detection. In a recent study from Türkiye, the GALAD score had sensitivities for any-stage (75.8%) and early-stage (57.8%) HCC, with 93.5% specificity, and demonstrated the best performance in non-viral hepatocellular carcinomas (AUC 0.872).[210] In a meta-analysis of more than 19,000 patients, GALAD demonstrated good diagnostic performance for early HCC. In patients with nonviral liver disease etiologies, the score showed a pooled sensitivity of 0.87 (95% CI 0.81–0.91), specificity of 0.91 (95% CI 0.85–0.95), and an AUC of 0.94 (95% CI 0.92–0.96). However, most of the included studies were retrospective case–control studies with potential selection bias, which may have overestimated the diagnostic performance of the GALAD score.[211,212]

Recommendations

1. HCC surveillance should be performed in all individuals with MASLD-related cirrhosis. [LoE: Moderate; SoR: Strong]
2. Routine HCC surveillance is not recommended in noncirrhotic adult patients with MASLD due to insufficient evidence and the low overall incidence of HCC in this population. [LoE: Moderate; SoR: Strong] However, selected cases such as patients with high metabolic risk, specifically patients with T2DM, may be considered for HCC screening even in the absence of clinical cirrhosis signs. [LoE: Low; SoR: Conditional]
3. Abdominal ultrasonography combined with serum AFP measurement every 6 months is recommended as the primary method for HCC surveillance. [LoE: Moderate; SoR: Strong] However, when feasible, additional laboratory- and imaging-based tools, such as the GALAD score and MRI, may be considered because of their higher diagnostic accuracy. [LoE: Moderate; SoR: Conditional]

Liver Transplantation in MASLD-Related Cirrhosis

MASLD-related cirrhosis has become one of the primary reasons for liver transplantation (LT) in two major transplant registries in the U.S. Scientific Registry of Transplant Recipients (SRTR) and the European Liver Transplant Registry (ELTR).[213] In Türkiye, the proportion of LTs for MASLD-related liver disease increased nearly eightfold from 2010–2014 to 2015–2020.[189]

Patients undergoing liver transplantation for MASLD are often older and have multiple cardiometabolic comorbidities that increase the risk of perioperative complications and long-term risks. Despite the higher burden of cardiometabolic comorbidities, post-transplant survival among patients with MASH appears comparable to other etiologies,[214] as shown in a recent study including a large cohort of LT recipients from both the United States and Europe.[213]

Patients with MASLD, particularly those with T2DM, have an increased risk of cardiovascular and renal complications after liver transplantation, with cardiovascular events occurring most frequently during the early post-transplant period.[215,216] However, recent large registry analyses from the SRTR and ELTR suggest that post-transplant mortality is mainly associated with recipient and donor characteristics (recipient age, MELD score, severe hepatic encephalopathy, donor age, and transplant center volume) rather than the underlying liver disease etiology.[213]

Pretransplant Management of Comorbidities in Patients with MASLD-Related Cirrhosis

In Türkiye, where the prevalence of obesity, T2DM, and MASLD-related cirrhosis is increasing, careful cardiovascular assessment of LT candidates is essential. Current evidence does not support a fundamentally different CVD screening algorithm for MASLD; rather, a stepwise, risk-adjusted, and multidisciplinary approach should be adopted, integrating clinical cardiovascular risk factors, age, functional status, and local cardiology expertise.[151,217,218] Risk stratification tools such as the cardiovascu-

lar risk in orthotopic liver transplantation (CAR-OLT) and coronary artery disease in liver transplantation (CAD-LT) scores may assist in identifying candidates at a higher risk of cardiovascular complications and guide further diagnostic evaluation.[219,220] Because stress-based testing may have limited diagnostic accuracy in advanced cirrhosis, coronary computed tomography angiography (CCTA) may be considered in selected high-risk candidates, while invasive coronary angiography should be reserved for those with positive signals on stress tests or CCTA or strong clinical suspicion of clinically significant CVD. If indicated, revascularization should be performed. Until locally validated data become available, transplant centers in Türkiye should implement standardized evaluation protocols based on international guidelines, available resources, and multidisciplinary expertise.[154]

Management of patients with MASLD prior to liver transplantation requires a comprehensive multidisciplinary approach targeting metabolic comorbidities, nutritional status, cardiovascular risk, renal function, and malignancy screening. Glycemic control should be carefully optimized, with insulin considered the safest option in Child-Pugh class C cirrhosis, while oral agents may be used in patients with Child-Pugh class A and B. Cardiometabolic risk factors, including diabetes, hypertension, and dyslipidemia, should be systematically assessed and treated, given their impact on peri- and post-transplant outcomes. Nutritional assessment and tailored lifestyle interventions are essential, as both obesity and sarcopenia adversely affect the outcomes of transplantation. In addition, renal function should be closely monitored and preserved, and appropriate screening for malignancy should be performed according to international guidelines. A summary of these recommendations is presented in Table 9.

Recommendations

1. Candidates with MASLD-related cirrhosis should undergo multidisciplinary pretransplant evaluation. [LoE: Moderate; SoR: Strong]
2. Pretransplant assessment should include systematic evaluation and optimization of cardiometabolic comorbidities, particularly coronary artery disease, type 2 diabetes, hypertension, dyslipidemia, obesity, sarcopenia, and chronic kidney disease. [LoE: Moderate; SoR: Strong]
3. CVD assessment in candidates with MASLD should follow a stepwise, risk-adjusted, multidisciplinary approach rather than a separate disease-specific algorithm. Risk scores such as CAR-OLT and CAD-LT may help identify candidates who warrant further cardiac investigation. [LoE: Moderate; SoR: Strong]
4. Because stress-based testing may have limited diagnostic performance in advanced cirrhosis, coronary computed tomography angiography may be considered in selected high-risk candidates, while invasive coronary angiography should be reserved for those with abnormal non-invasive findings or strong clinical suspicion of clinically significant coronary artery disease. [LoE: Moderate; SoR: Conditional]
5. Renal function should be closely monitored and preserved before transplantation, and simultaneous liver–kidney transplantation should be considered according to accepted criteria in eligible candidates. [LoE: Moderate; SoR: Strong]

Pretransplant Obesity and Management in Patients with MASLD-Related Cirrhosis

The impact of BMI on post-transplant outcomes remains controversial, and current evidence does not support specific BMI thresholds as contraindications to liver transplantation.[154,221–223] BMI alone inadequately reflects patient risk, as body composition—particularly sarcopenia and sarcopenic obesity—and overall nutritional status are more relevant determinants of outcomes.[224] Therefore, pretransplant management should focus on comprehensive nutritional assessment and optimization of modifiable risk factors. Pharmacological weight loss therapies, including GLP-1 receptor agonists, have not been sufficiently studied in transplant candidates and cannot currently be recommended. Endoscopic bariatric procedures are contraindicated in the presence of clinically significant portal hypertension, whereas bariatric surgery may be considered in carefully selected patients with compensated cirrhosis after failure of conservative measures, preferably in high-volume centers and with prior assessment of portal hypertension. Sleeve gastrectomy is the preferred approach and may be performed in combination with liver transplantation in selected cases.[154] In the setting of living donor liver transplantation, obesity alone does not appear to adversely affect graft or patient survival, although adequate graft-to-recipient weight ratio must be ensured, and sarcopenic obesity has been associated with impaired liver regeneration and worse outcomes.[223]

Recommendations

1. Body mass index alone should not be considered as a contraindication for liver transplantation. Risk stratification should incorporate body composition, sarcopenia or sarcopenic obesity, nutritional status, and overall frailty. [LoE: Moderate; SoR: Strong]
2. All candidates with MASLD-related cirrhosis should undergo formal nutritional and functional assessment, and tailored lifestyle and nutritional measures should be implemented whenever feasible. [LoE: Moderate; SoR: Strong]
3. Pharmacological weight-loss therapy cannot yet be routinely recommended in decompensated transplant candidates with MASLD-related cirrhosis because safety and efficacy data remain limited. [LoE: Low; SoR: Conditional]
4. Bariatric surgery may be considered only in carefully selected candidates with compensated cirrhosis, preferably in high-volume centers and after assessment for clinically significant portal hypertension; sleeve gastrectomy is the preferred approach. Endoscopic bariatric procedures should be avoided in clinically significant portal hypertension. [LoE: Low–Moderate; SoR: Conditional (for surgery)/Strong (against endoscopy in CSPH)]

Management of Cardiometabolic Risk Factors and Recurrence of MASLD After Liver Transplantation

In patients with LT due to MASLD who have a functioning graft, the primary causes of mortality are complications from cardiovascular disease and cancer. Management after LT in recipients with

Table 10. Management of cardiometabolic risk factors and recurrence of MASLD after liver transplantation. Modified from [224, 225]

Condition	Recommendations
Weight gain/obesity	• Dietary and lifestyle counselling should be implemented after LT, as rapid weight gain is common. • Obesity and related comorbidities should be actively treated because they contribute to cardiovascular risk, MASLD recurrence, and reduced long-term survival. • GLP-1 receptor agonists may be considered for weight control and obesity-related comorbidities, although transplant-specific data are limited. • Bariatric surgery may be considered in carefully selected recipients when other measures fail; sleeve gastrectomy is generally the preferred procedure.
Diabetes mellitus	• Good glycemic control should be pursued after LT to reduce cardiovascular and renal complications and possibly lower the risk of recurrent MASLD. • Long-term corticosteroid use should be avoided when possible, particularly beyond 3–6 months in recipients transplanted for MASH/MASLD. • Reduction of CNI exposure may be considered in selected recipients transplanted for MASH/MASLD, with or without adjunctive mycophenolate mofetil. • The choice of antihyperglycemic therapy should follow general clinical guidelines and account for renal function and drug interactions.
Hypertension	• Blood pressure should be regularly monitored and treated according to general clinical guidelines. • Optimal blood pressure control is strongly encouraged because it is associated with lower all-cause mortality and fewer cardiovascular events after LT. • Calcium channel blockers (Amlodipine or felodipine) are the first-line antihypertensive therapy. • In the presence of concurrent CAD, HF, CKD or stroke RAS blockers are the initial options. • Modulation of immunosuppressive therapy with the minimization of CNIs may be required.
Dyslipidemia	• Lipid disorders should be screened and treated according to general clinical guidelines. • Statins can be used after LT, including high-intensity statins when indicated, with careful titration and regular follow-up visits. • Attention should be paid to drug–drug interactions and adverse effects, although significant interactions with common immunosuppressive regimens appear to be limited.
Cardiovascular risk	• LT recipients for MASH/MASLD should be recognized as being at an increased long-term risk of cardiovascular events. • Management should focus on control of obesity, hypertension, T2DM, dyslipidemia, and other modifiable cardiovascular risk factors. • Routine follow-up should be individualized according to the overall cardiovascular risk rather than a fixed echocardiographic schedule for all recipients.
Kidney dysfunction	• Kidney function should be monitored longitudinally after LT. • Management should include optimization of T2DM and blood pressure control and consideration of immunosuppression minimization strategies when appropriate.

LT: Liver transplantation; MASLD: Metabolic dysfunction-associated steatotic liver disease; GLP-1: Glucagon-like peptide-1; MASH: Metabolic dysfunction-associated steatohepatitis; CNI: Calcineurin inhibitors; CAD: Coronary artery disease; HF: Heart failure; CKD: Chronic kidney disease; RAS: Renin-angiotensin system.

MASLD should focus on aggressive control of cardiometabolic risk factors, as rapid post-transplant weight gain, diabetes, hypertension, dyslipidemia, chronic kidney disease, and cardiovascular disease are common and substantially influence long-term outcomes.[224,225] Accordingly, post-transplant management should prioritize dietary and lifestyle measures, strict control of diabetes, hypertension, and dyslipidemia, careful monitoring of kidney and cardiovascular risk, and reduction of the metabolic burden of immunosuppression, particularly avoidance of prolonged corticosteroid exposure, and consideration of calcineurin inhibitor minimization where appropriate (Table 10).

Recurrent and *de novo* MASLD are frequent after LT, particularly in recipients with multiple metabolic risk factors. Recent data suggest that recurrent steatosis may occur in up to 80% of recipients by 5 years after LT, while recurrent MASH has been reported in 28–60% of cases; in a multicenter cohort of recipients transplanted for MASLD-related cirrhosis, 5-year recurrence rates of metabolic syndrome, steatosis, steatohepatitis, and advanced fibrosis were 86%, 80%, 60%, and 20%, respectively. In a recent study from Türkiye, post-transplant MASLD prevalence was 34%. *De novo* MASLD and *de novo* MASH also occur commonly after transplantation, although published studies remain limited by heterogeneous definitions, inconsistent adjudication of pre-transplant MASLD, and variable histologic follow-up. Despite the high recurrence rate, the impact of recurrent MASLD on graft survival appears modest, whereas the accompanying burden of cardiovascular and metabolic complications may be more clinically consequential. At present, no validated surveillance strategy exists for recurrent MASLD after liver transplantation; however, ultrasound and transient elastography with controlled attenuation parameter may be reasonable for follow-up, with liver biopsy reserved for uncertain cases or when alternative graft pathology is suspected.[225,226]

Recommendations

1. Recipients transplanted for MASLD should undergo systematic post-transplant assessment and management of cardiometabolic risk factors, including obesity, diabetes, hypertension, dyslipidemia, chronic kidney disease, and cardiovascular disease. [LoE: Moderate; SoR: Strong]
2. Dietary counselling, physical activity, weight control, and optimization of diabetes, blood pressure, and lipid management should form the cornerstone of post-transplant care in MASLD recipients. [LoE: Moderate; SoR: Strong]
3. Immunosuppressive regimens should be adjusted, when feasible, to reduce metabolic burden, particularly through avoidance of prolonged corticosteroid exposure and consideration of calcineurin inhibitor minimization in selected recipients. [LoE: Moderate; SoR: Conditional]
4. Recurrent and *de novo* MASLD are frequent after LT, particularly in recipients with multiple metabolic risk factors. In the absence of a validated surveillance strategy, screening for recurrent MASLD or *de novo* MASLD may include ultrasound and transient elastography with controlled attenuation parameter, while liver biopsy should be reserved for uncertain cases or when alternative graft pathology is suspected. [LoE: Low; SoR: Conditional]
5. Long-term follow-up should also include monitoring for cardiovascular disease, chronic kidney disease, and extrahepatic malignancy, which substantially influence post-transplant outcomes in this population. [LoE: Moderate; SoR: Strong]

Research Gaps, Evidence Limitations, and Future Recommendations

Although the evidence base for MASLD has expanded substantially in recent years, several important gaps remain. First, robust population-based epidemiological data from Türkiye, particularly in children, adolescents, and older adults, remain limited. Second, further validation of screening strategies, non-invasive diagnostic tools and algorithms for treatment selection in Turkish cohorts is required, especially in patients with obesity and type 2 diabetes mellitus. Third, long-term real-world outcome data for newly approved liver-directed therapies, as well as antidiabetic and anti-obesity pharmacotherapies in MASLD, remain insufficient. This is particularly relevant with respect to fibrosis regression, hepatic decompensation, hepatocellular carcinoma development, and overall survival.

Additional uncertainties persist regarding optimal risk stratification for hepatocellular carcinoma in non-cirrhotic MASLD, the management of recurrent disease after liver transplantation, and the cost-effectiveness of screening and treatment strategies within local healthcare systems.

Future studies should prioritize prospective multicenter cohorts in Türkiye to generate robust real-world data on MASLD and MASH. Key areas of focus should include implementation research, optimization of screening and risk stratification strategies, and long-term comparative effectiveness analyses of lifestyle, pharmacological, endoscopic, and surgical interventions.

TASL Practice Guidance for the Diagnosis and Management of MASLD

Consolidated Recommendations (1–52)

1. SLD should be used as a comprehensive umbrella term for all hepatic fat accumulation etiologies. Within this framework, MASLD (formerly NAFLD) represents the largest metabolic subgroup. Due to the high concordance rate (up to 99%) between NAFLD and MASLD, which ensures the continuity of existing scientific data while providing an affirmative and non-stigmatizing diagnosis, the updated nomenclature is preferred in clinical practice. *[LoE: High; SoR: Strong]*
2. Considering its high prevalence and disease burden in Türkiye, MASLD should be recognized as a major public health concern. Efforts should be made to increase both public and professional awareness, ensuring that MASLD is routinely considered in clinical practice by healthcare providers. *[LoE: Moderate; SoR: Strong]*
3. The presence of at least one cardiometabolic risk factor, such as obesity, T2DM, or hypertension, is the primary driver for MASLD diagnosis and serves as the most important critical predictor of disease progression. Consequently, all patients should undergo regular and systematic evaluations for all cardiometabolic risk factors. *[LoE: High; SoR: Strong]*
4. Patients with T2DM, obesity + ≥1 cardiometabolic risk factor, or signs of hepatic steatosis should be screened for advanced liver disease. *[LoE: Moderate; SoR: Strong]*
5. Children with obesity, elevated transaminase levels, or conditions associated with a high metabolic burden should be screened for the presence of MASLD. These individuals should undergo regular long-term follow-up to monitor disease progression and liver-related outcomes. *[LoE: Low; SoR: Strong]*
6. The FIB-4 index should be utilized as the first-line tool for risk stratification in patients with MASLD. *[LoE: High; SoR: Strong]*
7. Patients who are not classified as low risk in the initial step should undergo further evaluation, preferably with VCTE, or MRE if available. *[LoE: High; SoR: Strong]*
    a. Patients at higher clinical risk, including but not limited to those with type 2 diabetes mellitus, should be prioritized for second-line assessment using VCTE. *[LoE: Moderate; SoR: Strong]*
    b. Where available, VCTE may also be considered as a first-line risk assessment tool in high-risk populations. *[LoE: Moderate; SoR: Conditional]*
8. Liver biopsy is not routinely required in the diagnosis of MASLD and should be reserved for selected cases where clinically indicated. *[LoE: Moderate; SoR: Strong]*
9. Lifestyle modifications aiming for a weight loss of at least 5% of body weight should be recommended for all patients with MASLD, with an optimal target of ≥10%. For lean individuals, a weight loss target of 3–5% of body weight should be aimed. *[LoE: High; SoR: Strong]*
10. The Mediterranean diet should be the preferred dietary approach. Consumption of ultra-processed foods and sugar-sweetened beverages should be minimized or avoided. *[LoE: Moderate; SoR: Strong]*
11. Coffee intake may be encouraged for patients without contraindications, provided that it is well tolerated. *[LoE: Moderate; SoR: Conditional]*
12. Physical activity combining aerobic exercise and resistance training should be encouraged and tailored to the patient's individual lifestyle and functional capacity. *[LoE: High; SoR: Strong]*
13. A high-protein diet and resistance training can be encouraged, particularly in elderly patients and those with MASH-related cirrhosis, to preserve skeletal muscle mass and prevent the development of sarcopenia. *[LoE: Moderate; SoR: Strong]*
14. Pharmacological therapy is not a substitute for lifestyle interventions and should only be used as an adjunct when clinically indicated. Lifestyle modifications should be actively encouraged in all patients receiving pharmacotherapy. *[LoE: High; SoR: Strong]*
15. Pharmacological therapy with a MASH indication should be targeted at patients with clinically significant fibrosis and should exclude patients with cirrhosis. Treatment eligibility should be based primarily on non-invasive assessment, with VCTE as the preferred modality where available. *[LoE: High; SoR: Strong]*
    a. Patients with VCTE liver stiffness values in the 10–15 kPa range may be considered a priority group for consideration of pharmacological therapy. *[LoE: Moderate; SoR: Conditional]*
    b. In patients with VCTE liver stiffness values in the 15–20 kPa range, pharmacological therapy may be considered only if cirrhosis has been confidently excluded through clinical assessment, laboratory parameters, and imaging findings. In cases of diagnostic uncertainty, liver biopsy should be considered. *[LoE: Moderate; SoR: Conditional]*

16. Patients with MASLD and T2DM should be considered for antidiabetic pharmacotherapies with potential hepatic benefits.

- **a.** Pioglitazone may be encouraged in patients with type 2 diabetes mellitus and coexisting MASLD, where clinically appropriate and as a combination therapy. *[LoE: Moderate; SoR: Conditional]*
- **b.** SGLT2 inhibitors should be considered in patients with MASLD and type 2 diabetes mellitus, particularly in the presence of established or high-risk cardiovascular and/or renal disease. *[LoE: High; SoR: Strong]*
- **c.** GLP-1 receptor agonists should be considered in patients with MASLD and type 2 diabetes mellitus, particularly in patients with coexisting obesity and/or in whom weight reduction is the key therapeutic target. *[LoE: High; SoR: Strong]*

17. Bariatric procedures are not a substitute for lifestyle interventions and should only be used as an adjunct when clinically indicated. Lifestyle modifications should be actively encouraged in all patients undergoing bariatric procedures. *[LoE: Moderate; SoR: Strong]*

18. Bariatric interventions should be performed in accordance with established obesity guideline indications. *[LoE: Moderate; SoR: Strong]*

19. Bariatric treatments are contraindicated in patients with decompensated cirrhosis. *[LoE: Moderate; SoR: Strong]*

20. Bariatric treatments are not recommended before or simultaneously with liver transplantation. It is advisable to wait until post-transplantation graft stabilization is achieved (>1 year). In selected cases, sleeve gastrectomy may be an option. *[LoE: Low; SoR: Conditional]*

21. Body mass index (BMI) and waist circumference should be recorded at baseline and reassessed at each follow-up visit. *[LoE: Moderate; SoR: Strong]*

22. Systolic and diastolic blood pressure should be measured at baseline and monitored at every follow-up visit. *[LoE: High; SoR: Strong]*

23. A fasting lipid profile, including total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides, should be obtained at baseline and repeated at intervals determined by the patient's cardiovascular risk category and lipid-lowering treatment status. *[LoE: High; SoR: Strong]*

24. Lipoprotein(a) should be measured once in a lifetime to refine long-term ASCVD risk assessment. *[LoE: Moderate; SoR: Strong]*

25. Fasting plasma glucose and/or HbA1c should be measured at baseline and monitored periodically thereafter, with frequency tailored to baseline results and the individual risk profile. An OGTT should be considered when results are borderline or discordant, or when clinical suspicion persists. *[LoE: High; SoR: Strong]*

26. Assessment of insulin resistance using the homeostasis model assessment of insulin resistance (HOMA-IR) or OGTT-derived indices may be considered in patients without established diabetes or dysglycemia when clarification of metabolic dysfunction is clinically relevant. *[LoE: Low; SoR: Conditional]*

27. Renal risk should be assessed at baseline using serum creatinine with estimated glomerular filtration rate and urine albumin-to-creatinine ratio, and monitored thereafter at intervals guided by fibrosis stage, diabetes status, baseline renal function, and albuminuria. *[LoE: Moderate; SoR: Strong]*

28. Formal ASCVD risk estimation should be performed using an appropriate validated risk tool (for example, SCORE2/SCORE2-OP in European/Turkish settings), and updated when major risk factors change or at clinically appropriate intervals. *[LoE: Moderate; SoR: Strong]*

29. Smoking and alcohol intake should be routinely assessed and actively addressed as part of comprehensive risk management at baseline and during follow-up. Complete abstinence from both smoking and alcohol should be the goal. *[LoE: Moderate; SoR: Strong]*

30. In patients with obesity and/or symptoms suggestive of OSA (e.g., snoring), screening with a validated questionnaire such as the Epworth Sleepiness Scale should be considered, with referral for diagnostic evaluation when clinical risk is high. *[LoE: Moderate; SoR: Conditional]*

31. All women with menstrual irregularities may be referred for evaluation for PMOS, particularly when accompanied by features of hyperandrogenism or insulin resistance. *[LoE: Low; SoR: Conditional]*

32. Patients with cirrhosis should be screened for sarcopenia using a brief validated tool such as the SARC-F questionnaire, with further assessment and nutritional/physical intervention where indicated. *[LoE: Moderate; SoR: Strong]*

33. LSM by VCTE ≤15 kPa together with a platelet count ≥150×10^9/L effectively rules out CSPH in patients with MASLD and may help avoid unnecessary endoscopic screening for varices. *[LoE: High; SoR: Strong]*

34. In patients with cACLD and an LSM ≥20 kPa and/or a platelet count ≤150×10^9/L, screening endoscopy for varices is recommended. In experienced centers, spleen stiffness measurement (SSM) ≤40 kPa may be used as an adjunctive tool to refine endoscopy decisions in these patients. *[LoE: High (endoscopy)/Moderate (SSM); SoR: Strong (endoscopy); Conditional (SSM adjunct)]*

35. If CSPH is present, NSBBs should be considered unless contraindicated or not tolerated. *[LoE: High; SoR: Strong]*

36. HCC surveillance should be performed in all individuals with MASLD-related cirrhosis. *[LoE: Moderate; SoR: Strong]*

37. Routine HCC surveillance is not recommended in noncirrhotic adult patients with MASLD due to insufficient evidence and the low overall incidence of HCC in this population. *[LoE: Moderate; SoR: Strong]* However, selected cases such as patients with high metabolic risk, specifically patients with T2DM, may be considered for HCC screening even in the absence of clinical cirrhosis signs. *[LoE: Low; SoR: Conditional]*

38. Abdominal ultrasonography combined with serum AFP measurement every 6 months is recommended as the primary method for HCC surveillance. *[LoE: Moderate; SoR: Strong]* However, when feasible, additional laboratory- and imaging-based tools, such as the GALAD score and MRI, may be considered because of their higher diagnostic accuracy. *[LoE: Moderate; SoR: Conditional]*

39. Candidates with MASLD-related cirrhosis should undergo multidisciplinary pretransplant evaluation. *[LoE: Moderate; SoR: Strong]*

40. Pretransplant assessment should include systematic evaluation and optimization of cardiometabolic comorbidities, particularly coronary artery disease, type 2 diabetes, hypertension, dyslipidemia, obesity, sarcopenia, and chronic kidney disease. *[LoE: Moderate; SoR: Strong]*

41. CVD assessment in candidates with MASLD should follow a stepwise, risk-adjusted, multidisciplinary approach rather than a separate disease-specific algorithm. Risk scores such as CAR-OLT and CAD-LT may help identify candidates who warrant further cardiac investigation. *[LoE: Moderate; SoR: Strong]*

42. Because stress-based testing may have limited diagnostic performance in advanced cirrhosis, coronary computed tomography angiography may be considered in selected high-risk candidates, while invasive coronary angiography should be reserved for those with abnormal non-invasive findings or strong clinical suspicion of clinically significant coronary artery disease. *[LoE: Moderate; SoR: Conditional]*

43. Renal function should be closely monitored and preserved before transplantation, and simultaneous liver–kidney transplantation should be considered according to accepted criteria in eligible candidates. *[LoE: Moderate; SoR: Strong]*

44. Body mass index alone should not be considered as a contraindication for liver transplantation. Risk stratification should incorporate body composition, sarcopenia or sarcopenic obesity, nutritional status, and overall frailty. *[LoE: Moderate; SoR: Strong]*

45. All candidates with MASLD-related cirrhosis should undergo formal nutritional and functional assessment, and tailored lifestyle and nutritional measures should be implemented whenever feasible. *[LoE: Moderate; SoR: Strong]*

46. Pharmacological weight-loss therapy cannot yet be routinely recommended in decompensated transplant candidates with MASLD-related cirrhosis because safety and efficacy data remain limited. *[LoE: Low; SoR: Conditional]*

47. Bariatric surgery may be considered only in carefully selected candidates with compensated cirrhosis, preferably in high-volume centers and after assessment for clinically significant portal hypertension; sleeve gastrectomy is the preferred approach. Endoscopic bariatric procedures should be avoided in clinically significant portal hypertension. *[LoE: Low–Moderate; SoR: Conditional (for surgery)/Strong (against endoscopy in CSPH)]*

48. Recipients transplanted for MASLD should undergo systematic post-transplant assessment and management of cardiometabolic risk factors, including obesity, diabetes, hypertension, dyslipidemia, chronic kidney disease, and cardiovascular disease. *[LoE: Moderate; SoR: Strong]*

49. Dietary counselling, physical activity, weight control, and optimization of diabetes, blood pressure, and lipid management should form the cornerstone of post-transplant care in MASLD recipients. *[LoE: Moderate; SoR: Strong]*

50. Immunosuppressive regimens should be adjusted, when feasible, to reduce metabolic burden, particularly through avoidance of prolonged corticosteroid exposure and consideration of calcineurin inhibitor minimization in selected recipients. *[LoE: Moderate; SoR: Conditional]*

51. Recurrent and de novo MASLD are frequent after LT, particularly in recipients with multiple metabolic risk factors. In the absence of a validated surveillance strategy, screening for recurrent MASLD or de novo MASLD may include ultrasound and transient elastography with controlled attenuation parameter, while liver biopsy should be reserved for uncertain cases or when alternative graft pathology is suspected. *[LoE: Low; SoR: Conditional]*

52. Long-term follow-up should also include monitoring for cardiovascular disease, chronic kidney disease, and extrahepatic malignancy, which substantially influence post-transplant outcomes in this population. *[LoE: Moderate; SoR: Strong]*

Ethics Committee Approval: Ethical approval was not required for this study as it is a literature review and does not involve primary data collection, human subjects, or animal testing.

Conflict of Interest: Yusuf Yilmaz has served as a consultant and/or advisory board member for Zydus, Echosens, and Novo Nordisk. All other authors declare that they have no conflicts of interest relevant to the content of this guidance.

Funding: All authors declare that there is no financial support for completing the study or writing the manuscript.

Use of AI for Writing Assistance: Paperpal was used solely for English language editing and grammatical revisions. A general-purpose artificial intelligence (GPAI) agent was used to assist with formatting the figures. The authors reviewed, edited, and verified all AI-assisted outputs and take full responsibility for the final content of the manuscript.

Author Contributions: Concept: YY, MZ; Design: YY; Supervision – YY, MZ; Findings: YY, GA, IE; Materials: EK, DTG, CK; Data Collection and/or Processing: EK, DTG, CK; Analysis and/or Interpretation: YY, GA, IE, MZ; Literature Review: GA, IE, EK, DTG, CK; Writing: YY, GA, IE, EK, DTG, CK; Critical Review: YY, MZ, GDU, NT, ZK, AU, SK, USA, BD, Rİ.

Peer-review: Externally peer-reviewed.

References

1. Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: A consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology 2020;158(7):1999-2014.e1. [CrossRef]
2. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79(6):1542-1556. [CrossRef]
3. Targher G, Tilg H, Byrne CD. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach. Lancet Gastroenterol Hepatol 2021;6(7):578-588. [CrossRef]
4. Hagström H, Vessby J, Ekstedt M, Shang Y. 99% of patients with NAFLD meet MASLD criteria and natural history is therefore identical. J Hepatol 2024;80(2):e76-e77. [CrossRef]
5. Akdas S, Yazihan N. From NAFLD to MASLD: Meta-analysis and systematic review of NAFLD patients in Turkiye in terms of metabolic profile and MASLD potential. Hepatol Forum 2024;5(3):126-138. [CrossRef]
6. Kanwal F, Neuschwander-Tetri BA, Loomba R, Rinella ME. Metabolic dysfunction-associated steatotic liver disease: Update and impact of new nomenclature on the American Association for the Study of Liver Diseases practice guidance on nonalcoholic fatty liver disease. Hepatology 2024;79(5):1212-1219. [CrossRef]
7. Wang SW, Hsieh TH, Cheng YM, Wang CC, Kao JH. Liver and atherosclerotic risks of patients with cryptogenic steatotic liver disease. Hepatol Int 2024;18(3):943-951. [CrossRef]
8. European Association for the Study of the Liver; European Association for the Study of Diabetes; European Association for the Study of Obesity. EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD): Executive Summary. Diabetologia 2024;67(11):2375-2392. [CrossRef]
9. Karaaslan H, Inan H, Turkmen AT, Altintas I, Uyar N, Eren MA. Comparison of triglyceride-glucose index and anthropometric obesity indices in predicting severe grades of hepatic steatosis in nonalcoholic fatty liver disease among non-diabetic obese individuals. Hepatol Forum 2024;5(3):113-119. [CrossRef]
10. Arslan AY, Celik S, Amin F, Caylak I, Kesapli I, Kilic IB, et al. Prevalence, determinants, and fibrosis risk stratification of metabolic-associated fatty liver disease in a Turkish primary care setting: A retrospective study. Hepatol Forum 2023;5(2):63-67. [CrossRef]
11. Guo Z, Wu D, Mao R, Yao Z, Wu Q, Lv W. Global burden of MAFLD, MAFLD related cirrhosis and MASH related liver cancer from 1990 to 2021. Sci Rep 2025;15(1):7083. [CrossRef]
12. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology 2023;77(4):1335-1347. [CrossRef]
13. Younossi ZM, Kalligeros M, Henry L. Epidemiology of metabolic dysfunction-associated steatotic liver disease. Clin Mol Hepatol 2025;31(Suppl):S32-S50. [CrossRef]
14. Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, et al. The prevalence and incidence of NAFLD worldwide: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2022;7(9):851-861. [CrossRef]
15. Terrault NA, Francoz C, Berenguer M, Charlton M, Heimbach J. Liver transplantation 2023: Status report, current and future challenges. Clin Gastroenterol Hepatol 2023;21:2150-2166. [CrossRef]
16. Kan C, Zhang K, Wang Y, Zhang X, Liu C, Ma Y, et al. Global burden and future trends of metabolic dysfunction-associated Steatotic liver disease: 1990-2021 to 2045. Ann Hepatol 2025;30(2):101898. [CrossRef]
17. Zelber-Sagi S, Ivancovsky-Wajcman D, Kugelmas C, Weinstein AA, Wong VWS, Castera L, et al. Lifespan approaches for the prevention and management of steatotic liver disease. Nat Rev Gastroenterol Hepatol 2026;23:526-548. [CrossRef]
18. Kaya E, Keklikkiran C, Toy M, Yilmaz Y. Prevalence of metabolic dysfunction-associated steatotic liver disease among obese, overweight, and at-risk children and adolescents in Türkiye: A meta-analysis. Hepatol Forum doi: 10.14744/hf.2026.88519 [Epub ahead of print].
19. Yüksel F, Türkkan D, Yüksel I, Kara S, Celik N, Samdancı E. Fatty liver disease in an autopsy series of children and adolescents. Hippokratia 2012;16(1):61-65.
20. World Health Organization. Age-standardized prevalence of obesity among adults (18+ years). Available at: https://data.who.int/indicators/i/C6262EC/BEFA58B. Accessed May 31, 2026.
21. Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, et al. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol 2013 Feb;28(2):169-180. [CrossRef]
22. Satman I, Yilmaz T, Sengül A, Salman S, Salman F, Uygur S, et al. Population-based study of diabetes and risk characteristics in Turkey: results of the Turkish diabetes epidemiology study (TURDEP). Diabetes Care 2002;25(9):1551-1556. [CrossRef]
23. Değertekin B, Tozun N, Demir F, Söylemez G, Parkan Ş, Gürtay E, et al. The Changing Prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) in Turkey in the Last Decade. Turk J Gastroenterol 2021;32(3):302-312. [CrossRef]
24. Sezgin O, Akpınar H, Özer B, Törüner M, Bal K, Bor S. The abdominal ultrasonography results of cappadocia cohort study of Turkey reveals high prevalence of fatty liver. Turk J Gastroenterol 2023;34(6):652-664. [CrossRef]

25. Yilmaz Y, Yilmaz N, Ates F, Karakaya F, Gokcan H, Kaya E, et al. The prevalence of metabolic-associated fatty liver disease in the Turkish population: A multicenter study. Hepatol Forum 2021;2(2):37-42. [CrossRef]
26. Ergenc I, Kara E, Yilmaz ME, Demirtas CO, Keklikkiran C, Das T, et al. Prevalence of metabolic dysfunction-associated steatotic liver disease and steatohepatitis in Türkiye: A forensic autopsy study. Heliyon 2024;10(15):e34915. [CrossRef]
27. Kirik A, Sumbul HE, Koca N, Paşalı Kilit T, Demiral Sezer S, Binnetoglu E, et al. Prevalence of MASLD and Fibrosis Risk in Turkish Adults with Cardiometabolic Risk Factors: A Nationwide Multicenter Study (DAHUDER MASLD Study). J Clin Med 2025;14(19):7098. [CrossRef]
28. Golabi P, Paik JM, Kumar A, Al Shabeeb R, Eberly KE, Cusi K, et al. Nonalcoholic fatty liver disease (NAFLD) and associated mortality in individuals with type 2 diabetes, pre-diabetes, metabolically unhealthy, and metabolically healthy individuals in the United States. Metabolism 2023;146:155642. [CrossRef]
29. Dogay Us G, Innocenti F, Koc OM, Yumuk VD, Gungor ZB, Koek GH. Prevalence of MASLD and fibrosis in Turkey: Results from a multicenter study of at-risk populations. PLoS One 2026;21(2):e0341214. [CrossRef]
30. Singh S, Allen AM, Wang Z, Prokop LJ, Murad MH, Loomba R. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. Clin Gastroenterol Hepatol 2015;13(4):643-54.e1-9; quiz e39-40. [CrossRef]
31. Liebe R, Esposito I, Bock HH, Vom Dahl S, Stindt J, Baumann U, et al. Diagnosis and management of secondary causes of steatohepatitis. J Hepatol 2021;74(6):1455-1471. [CrossRef]
32. Turan Gokce D, Ekelik M, Gumussoy M, Kiremitci S, Bodakci E, Yilmaz V, et al. Histological disease progression in patients with metabolic dysfunction-associated steatotic liver disease using paired liver biopsy. Eur J Gastroenterol Hepatol 2026;38(1):76-81. [CrossRef]
33. Hagström H, Shang Y, Hegmar H, Nasr P. Natural history and progression of metabolic dysfunction-associated steatotic liver disease. Lancet Gastroenterol Hepatol 2024;9(10):944-956. [CrossRef]
34. Ioannou GN. Epidemiology and risk-stratification of NAFLD-associated HCC. J Hepatol 2021;75(6):1476-1484. [CrossRef]
35. Vilar-Gomez E, Yates KP, Kleiner DE, Behling C, Cummings OW, Wilson LA, et al. Genetic and non-genetic drivers of histological progression and regression in MASLD. J Hepatol 2026;84(3):502-516. [CrossRef]
36. Alqahtani SA, Yilmaz Y, El-Kassas M, Alswat K, Mawardi M, Sanai FM, et al. Knowledge about metabolic dysfunction-associated steatotic liver disease among the medical professionals from countries in the MENA region. Ann Hepatol. 2025;30(1):101569. [CrossRef]
37. Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. J Hepatol 2019;71(4):793-801. [CrossRef]
38. Lazarus JV, Agirre-Garrido L, Díaz LA, Danpanichkul P, Kivuyo SL, Kondili LA, et al. Cost-Effectiveness of MASH Diagnosis and Management Approaches Among Those With Type 2 Diabetes. JAMA Netw Open 2025;8(11):e2542750. [CrossRef]
39. Noureddin M, Jones C, Alkhouri N, Gomez EV, Dieterich DT, Rinella ME, et al. Screening for nonalcoholic fatty liver disease in persons with Type 2 Diabetes in the United States Is cost-effective: a comprehensive cost-utility analysis. Gastroenterology 2020;159(5):1985-1987.e4. [CrossRef]
40. Park H, Yoon EL, Kim M, Kwon SH, Kim D, Cheung R, et al. Cost-effectiveness study of FIB-4 followed by transient elastography screening strategy for advanced hepatic fibrosis in a NAFLD at-risk population. Liver Int 2024;44(4):944-954. [CrossRef]
41. Vilar-Gomez E, Lou Z, Kong N, Vuppalanchi R, Imperiale TF, Chalasani N. Cost effectiveness of different strategies for detecting cirrhosis in patients with nonalcoholic fatty liver disease based on United States health care system. Clin Gastroenterol Hepatol 2020;18(10):2305-2314.e12. [CrossRef]
42. Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, Benson JT, Enders FB, Angulo P. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. Gut 2009;58(11):1538-1544. [CrossRef]
43. Panganiban J, Kehar M, Ibrahim SH, Hartmann P, Sood S, Hassan S, et al. Metabolic dysfunction-associated steatotic liver disease (MASLD) in children with obesity: An Obesity Medicine Association (OMA) and expert joint perspective 2025. Obes Pillars 2025;14:100164. [CrossRef]
44. Younossi ZM, de Avila L, Petta S, Hagström H, Kim SU, Nakajima A, et al. Diagnostic accuracy of non-invasive tests for metabolic dysfunction-associated steatotic liver disease across age, Type 2 Diabetes, and obesity subgroups: a multinational study. Clin Gastroenterol Hepatol 2026;S1542-3565(26)00044-3.
45. Eren F, Kaya E, Yilmaz Y. Accuracy of Fibrosis-4 index and non-alcoholic fatty liver disease fibrosis scores in metabolic (dysfunction) associated fatty liver disease according to body mass index: failure in the prediction of advanced fibrosis in lean and morbidly obese individuals. Eur J Gastroenterol Hepatol 2022;34(1):98-103. [CrossRef]
46. McPherson S, Hardy T, Dufour JF, Petta S, Romero-Gomez M, Allison M, et al. Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis. Am J Gastroenterol 2017;112(5):740-751. [CrossRef]
47. Watanabe S, Suzuki S, Tsutsumi N, Sukeda A, Yorozu T, Nishimata S, et al. Non-invasive biomarkers in pediatric MASLD: utility of gamma-glutamyltransferase for steatohepatitis and the FIB-4 index for fibrosis. BMC Pediatr 2025;26(1):154. [CrossRef]
48. Cicek S, Kapudere B, Parspancı YBK, Tavukcuoglu Z, Eyisoy OG, Ayaz R. Diagnostic utility of APRI, FIB-4, and FIB-5 in intrahepatic cholestasis of pregnancy: A retrospective case-control study. Int J Gynaecol Obstet 2026;174(1):253-263. [CrossRef]
49. Alkayyali T, Qutranji L, Kaya E, Bakir A, Yilmaz Y. Clinical utility of non-invasive scores in assessing advanced hepatic fibrosis in patients with type 2 diabetes mellitus: a study in biopsy-proven non-alcoholic fatty liver disease. Acta Diabetol 2020;57(5):613-618. [CrossRef]
50. Kaya E, Bakir A, Eren F, Yilmaz Y. The utility of non-invasive scores in non-alcoholic fatty liver disease patients with normal and elevated serum transaminases. Hepatol Forum 2020;1(1):8-13. [CrossRef]
51. Wu YL, Kumar R, Wang MF, Singh M, Huang JF, Zhu YY, et al. Validation of conventional non-invasive fibrosis scoring systems in patients with metabolic associated fatty liver disease. World J Gastroenterol 2021;27(34):5753-5763. [CrossRef]
52. Jafarov F, Kaya E, Bakir A, Eren F, Yilmaz Y. The diagnostic utility of fibrosis-4 or nonalcoholic fatty liver disease fibrosis score combined with liver stiffness measurement by fibroscan in assessment of advanced liver fibrosis: a biopsy-proven nonalcoholic fatty liver disease study. Eur J Gastroenterol Hepatol 2020;32(5):642-649. [CrossRef]

53. Singh S, Venkatesh SK, Loomba R, Wang Z, Sirlin C, Chen J, et al. Magnetic resonance elastography for staging liver fibrosis in non-alcoholic fatty liver disease: a diagnostic accuracy systematic review and individual participant data pooled analysis. Eur Radiol 2016;26(5):1431-1440. [CrossRef]
54. Hsu C, Caussy C, Imajo K, Chen J, Singh S, Kaulback K, et al. Magnetic resonance vs transient elastography analysis of patients with nonalcoholic fatty liver disease: a systematic review and pooled analysis of individual participants. Clin Gastroenterol Hepatol.2019;17(4):630-637.e8. [CrossRef]
55. Guha IN, Parkes J, Roderick P, Chattopadhyay D, Cross R, Harris S, et al. Non-invasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. Hepatology 2008;47(2):455-460. [CrossRef]
56. Chen J, Yin M, Talwalkar JA, Oudry J, Glaser KJ, Smyrk TC, et al Diagnostic performance of MR elastography and vibration-controlled transient elastography in the detection of hepatic fibrosis in patients with severe to morbid obesity. Radiology 2017;283(2):418-428. [CrossRef]
57. Kwok R, Tse YK, Wong GL, Ha Y, Lee AU, Ngu MC, et al. Systematic review with meta-analysis: non-invasive assessment of non-alcoholic fatty liver disease--the role of transient elastography and plasma cytokeratin-18 fragments. Aliment Pharmacol Ther 2014;39(3):254-269. [CrossRef]
58. Velji-Ibrahim J, Woodard J, Alden J, Abrams GA. FibroScan discordance with liver biopsy significantly overestimates advanced fibrosis and cirrhosis in MASLD subjects with class 3 obesity: implications for resmetirom eligibility. J Clin Gastroenterol 2026;60(2):175-181. [CrossRef]
59. Ali AH, Al Juboori A, Petroski GF, Diaz-Arias AA, Syed-Abdul MM, Wheeler AA, et al. The utility and diagnostic accuracy of transient elastography in adults with morbid obesity: a prospective study. J Clin Med 2022;11(5):1201. [CrossRef]
60. de Lédinghen V, Wong VW, Vergniol J, Wong GL, Foucher J, Chu SH, et al. Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan®. J Hepatol 2012;56(4):833-839. [CrossRef]
61. Avcu A, Kaya E, Yilmaz Y. Feasibility of fibroscan in assessment of hepatic steatosis and fibrosis in obese patients: report from a general internal medicine clinic. Turk J Gastroenterol 2021;32(5):466-472. [CrossRef]
62. de Lédinghen V, Vergniol J, Gonzalez C, Foucher J, Maury E, Chemineau L, et al. Screening for liver fibrosis by using FibroScan(®) and FibroTest in patients with diabetes. Dig Liver Dis 2012;44(5):413-418. [CrossRef]
63. Vidal-Trécan T, Julla JB, El Khoury T, Venteclef N, Riveline JP, Paradis V, et al. Effectiveness of six international guidelines using fibrosis-4 and fibroscan for risk stratification of metabolic dysfunction-associated steatotic liver disease in Type 2 Diabetes. Clin Gastroenterol Hepatol 2025;23(12):2176-2186.e2. [CrossRef]
64. Ndaa M, Pandya PK, Swensson J, Samala N, Ajaz S, Joshi D, et al. Reliable monitoring of patients with metabolic dysfunction-associated steatotic liver disease using imaging: a systematic literature review and meta-analysis on measurement repeatability. Endocr Pract 2026;32(2):258-267. [CrossRef]
65. Caussy C, Reeder SB, Sirlin CB, Loomba R. Non-invasive, quantitative assessment of liver fat by MRI-PDFF as an endpoint in NASH trials. Hepatology 2018;68(2):763-772. [CrossRef]
66. Gu Q, Cen L, Lai J, Zhang Z, Pan J, Zhao F, et al. A meta-analysis on the diagnostic performance of magnetic resonance imaging and transient elastography in nonalcoholic fatty liver disease. Eur J Clin Invest 2021;51(2):e13446. [CrossRef]
67. Younossi ZM, de Avila L, Petta S, Hagström H, Kim SU, Nakajima A, et al. Global performance of non-invasive tests in MASLD: Insights from the G-MASLD study. Hepatology 2026;84(1):161-174. [CrossRef]
68. Alharthi J, Eslam M. Biomarkers of metabolic (dysfunction)-associated fatty liver disease: an update. J Clin Transl Hepatol 2022;10(1):134-139. [CrossRef]
69. Tilg H, Petta S, Stefan N, Targher G. Metabolic dysfunction-associated steatotic liver disease in adults: a review. JAMA 2026;335(2):163-174. [CrossRef]
70. Ramage S, Farmer A, Eccles KA, McCargar L. Healthy strategies for successful weight loss and weight maintenance: a systematic review. Appl Physiol Nutr Metab 2014;39(1):1-20. [CrossRef]
71. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015;149(2):367-78.e5; quiz e14-5. [CrossRef]
72. Guveli H, Ozlu T, Ersoy Tasar B, Batuhan Kenger E, Kaya E. Sustainability of diet-based moderate calorie restriction among obese patients with metabolic-associated fatty liver disease. Hepatol Forum 2021;2(3):97-101.
73. Malespin MH, Barritt AS 4th, Watkins SE, Schoen C, Tincopa MA, Corbin KD, et al. Weight loss and weight regain in usual clinical practice: results from the TARGET-NASH observational cohort. Clin Gastroenterol Hepatol 2022;20(10):2393-2395.e4. [CrossRef]
74. Haufe S, Haas V, Utz W, Birkenfeld AL, Jeran S, Böhnke J, et al. Long-lasting improvements in liver fat and metabolism despite body weight regain after dietary weight loss. Diabetes Care 2013;36(11):3786-3792. [CrossRef]
75. Hamurcu Varol P, Kaya E, Alphan E, Yilmaz Y. Role of intensive dietary and lifestyle interventions in the treatment of lean nonalcoholic fatty liver disease patients. Eur J Gastroenterol Hepatol 2020;32(10):1352-1357. [CrossRef]
76. Aller R, Sigüenza R, Pina M, Laserna C, Antolín B, Burgueño B, et al. Insulin resistance is related with liver fibrosis in type 2 diabetic patients with non-alcoholic fatty liver disease proven biopsy and Mediterranean diet pattern as a protective factor. Endocrine 2020;68(3):557-563. [CrossRef]
77. Properzi C, O'Sullivan TA, Sherriff JL, Ching HL, Jeffrey GP, Buckley RF, et al. Ad libitum mediterranean and low-fat diets both significantly reduce hepatic steatosis: a randomized controlled trial. Hepatology 2018;68(5):1741-1754. [CrossRef]
78. Hassani Zadeh S, Mansoori A, Hosseinzadeh M. Relationship between dietary patterns and non-alcoholic fatty liver disease: A systematic review and meta-analysis. J Gastroenterol Hepatol 2021;36(6):1470-1478. [CrossRef]
79. Ryan MC, Itsiopoulos C, Thodis T, Ward G, Trost N, Hofferberth S, et al. The Mediterranean diet improves hepatic steatosis and insulin sensitivity in individuals with non-alcoholic fatty liver disease. J Hepatol 2013;59(1):138-143. [CrossRef]
80. Dogay Us G, Innocenti F, Koc OM, Alagoz AE, Yumuk VD, Gungor ZB, et al. Mediterranean and low-fat diets are equally effective in MASLD resolution at 12 weeks regardless of PNPLA3 genotype: A randomized controlled trial. Hepatol Commun 2025;9(12):e0856. [CrossRef]
81. Abuelazm MT, Mohamed I, Naeem A, Khlidj Y, Tanashat M, Katamesh BE, et al. Intermittent fasting regimens for metabolic dysfunction-associated steatotic liver disease: a systematic review and network meta-analysis of randomized controlled trials. Eur J Gastroenterol Hepatol 2024;36(4):371-381. [CrossRef]

82. Castillo MF, Salgado-Canales D, Arrese M, Barrera F, Mikhailidis DP. Effect of intermittent fasting on lipid profile, anthropometric and hepatic markers in Non-Alcoholic Fatty Liver Disease (NAFLD): A systematic review. Curr Vasc Pharmacol 2024;22(3):187-202. [CrossRef]
83. Liu CH, Zeng QM, Kim W, Kim SU, Younossi ZM, Targher G, et al. Sarcopenia and MASLD: novel insights and the future. Nat Rev Endocrinol 2026;22(3):139-152. [CrossRef]
84. Leoni L, Valoriani F, Barbieri R, Pambianco M, Vinciguerra M, Sicuro C, et al. Unlocking the power of late-evening snacks: practical ready-to-prescribe chart menu for patients with cirrhosis. Nutrients 2023;15(15):3471. [CrossRef]
85. Souza M, Lima LCV, Amaral MJM, Moura FS. Higher consumption of ultra-processed foods and long-term risk of metabolic dysfunction-associated steatotic liver disease and primary liver cancer: A meta-analysis of preliminary evidence. Clin Nutr ESPEN 2026;72:102819. [CrossRef]
86. Commins I, Clayton-Chubb D, Fitzpatrick JA, George ES, Schneider HG, Phyo AZZ, et al. Associations Between MASLD, ultra-processed food and a mediterranean dietary pattern in older adults. Nutrients 2025;17(9):1415. [CrossRef]
87. García S, Monserrat-Mesquida M, Ugarriza L, Casares M, Gómez C, Mateos D, et al. Ultra-Processed food consumption and metabolic-dysfunction-Associated Steatotic Liver Disease (MASLD): A longitudinal and sustainable analysis. Nutrients 2025;17(3):472. [CrossRef]
88. Wu Y, Tan Z, Zhen J, Liu C, Zhang J, Liao F, et al. Association between diet soft drink consumption and metabolic dysfunction-associated steatotic liver disease: findings from the NHANES. BMC Public Health 2023;23(1):2286. [CrossRef]
89. Simons N, Veeraiah P, Simons PIHG, Schaper NC, Kooi ME, Schrauwen-Hinderling VB, et al. Effects of fructose restriction on liver steatosis (FRUITLESS); a double-blind randomized controlled trial. Am J Clin Nutr 2021;113(2):391-400. [CrossRef]
90. GBD 2020 Alcohol Collaborators. Population-level risks of alcohol consumption by amount, geography, age, sex, and year: a systematic analysis for the Global Burden of Disease Study 2020. Lancet 2022;400(10347):185-235. [CrossRef]
91. Khalifa R, Al-Naamani K, Elbadry M, Zhang YY, Alswat K, El-Kassas M. Protective role of coffee in chronic liver disease: a focus on processing. J Viral Hepat 2025;32(10):e70072. [CrossRef]
92. Yesil A, Yilmaz Y. Review article: coffee consumption, the metabolic syndrome and non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2013;38(9):1038-1044. [CrossRef]
93. Yilmaz Y. Health-Promoting Effects of Black Tea: A Narrative Review of Clinical Trials. Int J Food Sci 2025;2025:8560718. [CrossRef]
94. Yilmaz Y. Green tea mitigates the hallmarks of aging and age-related multisystem deterioration. Aging Dis 2025;17(2):712-730.
95. Zhang HJ, He J, Pan LL, Ma ZM, Han CK, Chen CS, et al. Effects of moderate and vigorous exercise on nonalcoholic fatty liver disease: a randomized clinical trial. JAMA Intern Med 2016;176(8):1074-1082. [CrossRef]
96. Zelber-Sagi S, Paik JM, Ivancovsky-Wajcmen D, Henry L, Yilmaz Y, Alqahtani SA, et al. "Weekend Warrior" exercise pattern protects against MASLD and mortality comparable to regular exercise: national cohort study. Liver Int 2025;45(8):e70226. [CrossRef]
97. Yang HJ, Hong YP, Yoon TY, Ryoo JH, Choi JM, Oh CM. Independent and synergistic associations of aerobic physical activity and resistance exercise with nonalcoholic fatty liver disease. Gut Liver 2023;17(4):600-609. [CrossRef]
98. Medeiros DG, Ferreira LF, Lamp JDS, Telles da Rosa LH. The impact of resistance training in patients diagnosed with metabolic dysfunction-associated steatotic liver disease: a systematic review. Eur J Gastroenterol Hepatol 2025;37(2):129-136. [CrossRef]
99. Hashida R, Kawaguchi T, Bekki M, Omoto M, Matsuse H, Nago T, et al. Aerobic vs. resistance exercise in non-alcoholic fatty liver disease: A systematic review. J Hepatol 2017;66(1):142-152. [CrossRef]
100. Kaya E, Yilmaz Y, Alkhouri N. Clinical insights on resmetirom: clinical indications, patient selection, and monitoring response to therapy. J Clin Gastroenterol 2025;59(5):412-419. [CrossRef]
101. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, et al. A Phase 3, randomized, controlled trial of resmetirom in NASH with liver fibrosis. N Engl J Med 2024;390(6):497-509. [CrossRef]
102. Kaya E, Aksoy S, Oruc N, Tasdemir C, Cengiz BI, Keklikkiran C, et al. Non-invasive tests for resmetirom treatment fail to accurately define the target population: Evidence from a biopsy-proven MASLD cohort. Hepatol Forum 2025;6(3):111-115. [CrossRef]
103. Iranshahy M, Rezaee R, Karimi G. Hepatoprotective activity of metformin: A new mission for an old drug? Eur J Pharmacol 2019;850:1-7. [CrossRef]
104. Said A, Akhter A. Meta-analysis of randomized controlled trials of pharmacologic agents in non-alcoholic steatohepatitis. Ann Hepatol 2017;16(4):538-547. [CrossRef]
105. Yip TC, Chan RNC, Wong VW, Tse YK, Liang LY, Hui VW, et al. Association of metformin use on metabolic acidosis in diabetic patients with chronic hepatitis B-related cirrhosis and renal impairment. Health Sci Rep 2021;4(3):e352. [CrossRef]
106. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Furtado RHM, et al. Comparison of the effects of glucagon-like peptide receptor agonists and sodium-glucose cotransporter 2 inhibitors for prevention of major adverse cardiovascular and renal outcomes in type 2 diabetes mellitus. Circulation 2019;139(17):2022-2031. [CrossRef]
107. Pokharel A, Kc S, Thapa P, Karki N, Shrestha R, Jaishi B, et al. The Effect of Empagliflozin on Liver Fat in Type 2 Diabetes Mellitus Patients With Non-Alcoholic Fatty Liver Disease. Cureus. 2021 Jul 28;13(7):e16687. [CrossRef]
108. Latva-Rasku A, Honka MJ, Kullberg J, Mononen N, Lehtimäki T, Saltevo J, et al. The SGLT2 inhibitor dapagliflozin reduces liver fat but does not affect tissue insulin sensitivity: a randomized, double-blind, placebo-controlled study with 8-week treatment in type 2 diabetes patients. Diabetes Care 2019;42(5):931-937. [CrossRef]
109. Wong C, Yaow CYL, Ng CH, Chin YH, Low YF, Lim AYL, et al. Sodium-glucose co-transporter 2 inhibitors for non-alcoholic fatty liver disease in asian patients with type 2 diabetes: a meta-analysis. Front Endocrinol (Lausanne) 2021;11:609135. [CrossRef]
110. Suki M, Imam A, Amer J, Milgrom Y, Massarwa M, Hazou W, et al. SGLT2 Inhibitors in MASLD (Metabolic Dysfunction-Associated Steatotic Liver Disease) Associated with sustained hepatic benefits, besides the cardiometabolic. Pharmaceuticals (Basel) 2025;18(8):1118. [CrossRef]
111. Newsome PN, Ambery P. Incretins (GLP-1 receptor agonists and dual/triple agonists) and the liver. J Hepatol 2023;79(6):1557-1565. [CrossRef]
112. Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet 2016;387(10019):679-690. [CrossRef]
113. Ciardullo S, Muraca E, Vergani M, Invernizzi P, Perseghin G. Advancements in pharmacological treatment of NAFLD/MASLD: a focus on metabolic and liver-targeted interventions. Gastroenterol Rep (Oxf) 2024;12:goae029. [CrossRef]

114. Nomoto H, Takahashi Y, Takano Y, Yokoyama H, Tsuchida K, Nagai S, et al. Effect of switching to once-weekly semaglutide on non-alcoholic fatty liver disease: The SWITCH-SEMA 1 Subanalysis. Pharmaceutics 2023;15(8):2163. [CrossRef]
115. Sanyal AJ, Newsome PN, Kliers I, Østergaard LH, Long MT, Kjær MS, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. N Engl J Med 2025;392(21):2089-2099. [CrossRef]
116. Loomba R, Abdelmalek MF, Armstrong MJ, Jara M, Kjær MS, Krarup N, et al. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. Lancet Gastroenterol Hepatol 2023;8(6):511-522. [CrossRef]
117. Belfort R, Harrison SA, Brown K, Darland C, Finch J, Hardies J, et al. A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. N Engl J Med 2006;355(22):2297-2307. [CrossRef]
118. Musso G, Cassader M, Paschetta E, Gambino R. Pioglitazone for advanced fibrosis in nonalcoholic steatohepatitis: New evidence, new challenges. Hepatology 2017;65(3):1058-1061. [CrossRef]
119. Portillo-Sanchez P, Bril F, Lomonaco R, Barb D, Orsak B, Bruder JM, et al. Effect of pioglitazone on bone mineral density in patients with nonalcoholic steatohepatitis: A 36-month clinical trial. J Diabetes 2019;11(3):223-231. [CrossRef]
120. Bełtowski J, Rachańczyk J, Włodarczyk M. Thiazolidinedione-induced fluid retention: recent insights into the molecular mechanisms. PPAR Res 2013;2013:628628. [CrossRef]
121. Zhu ZN, Jiang YF, Ding T. Risk of fracture with thiazolidinediones: an updated meta-analysis of randomized clinical trials. Bone 2014;68:115-123. [CrossRef]
122. American Diabetes Association Professional Practice Committee for Diabetes*. Summary of revisions: standards of care in diabetes-2026. Diabetes Care 2026;49(1 Suppl 1):S6-S12.
123. Lee M, Saver JL, Liao HW, Lin CH, Ovbiagele B. Pioglitazone for secondary stroke prevention: a systematic review and meta-analysis. Stroke 2017;48(2):388-393. [CrossRef]
124. Sanyal A, Doshi S, Behl N, Gupta HK, Bhatia V, Kavitha A, et al. Saroglitazar 4 Mg in metabolic dysfunction-associated steatotic liver disease: 24-week results from phase 4 study. Liver Int 2026;46(4):e70558. [CrossRef]
125. Del Ben M, Baratta F, Polimeni L, Pastori D, Loffredo L, Averna M, et al. Under-prescription of statins in patients with non-alcoholic fatty liver disease. Nutr Metab Cardiovasc Dis 2017;27(2):161-167. [CrossRef]
126. Blais P, Lin M, Kramer JR, El-Serag HB, Kanwal F. Statins are underutilized in patients with nonalcoholic fatty liver disease and dyslipidemia. Dig Dis Sci 2016;61(6):1714-1720. [CrossRef]
127. Ekstedt M, Franzén LE, Mathiesen UL, Holmqvist M, Bodemar G, Kechagias S. Statins in non-alcoholic fatty liver disease and chronically elevated liver enzymes: a histopathological follow-up study. J Hepatol 2007;47(1):135-141. [CrossRef]
128. Bril F, Portillo Sanchez P, Lomonaco R, Orsak B, Hecht J, Tio F, et al. Liver safety of statins in prediabetes or t2dm and nonalcoholic steatohepatitis: *post hoc* analysis of a randomized trial. J Clin Endocrinol Metab 2017;102(8):2950-2961. [CrossRef]
129. Commins I, Clayton-Chubb D, Janko N, Majeed A, Kemp W, Roberts SK. Efficacy and safety of statins in masld and other chronic liver diseases. Med Sci (Basel) 2026;14(1):84. [CrossRef]
130. Vilar-Gomez E, Vuppalanchi R, Gawrieh S, Ghabril M, Saxena R, Cummings OW, et al. Vitamin E improves transplant-free survival and hepatic decompensation among patients with nonalcoholic steatohepatitis and advanced fibrosis. Hepatology 2020;71(2):495-509. [CrossRef]
131. Sanyal AJ, Chalasani N, Kowdley KV, McCullough A, Diehl AM, Bass NM, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010;362(18):1675-1685. [CrossRef]
132. Schürks M, Glynn RJ, Rist PM, Tzourio C, Kurth T. Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials. BMJ 2010;341:c5702. [CrossRef]
133. Miller ER 3rd, Pastor-Barriuso R, Dalal D, Riemersma RA, Appel LJ, Guallar E. Meta-analysis: high-dosage vitamin E supplementation may increase all-cause mortality. Ann Intern Med 2005;142(1):37-46. [CrossRef]
134. Klein EA, Thompson IM Jr, Tangen CM, Crowley JJ, Lucia MS, Goodman PJ, et al. Vitamin E and the risk of prostate cancer: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2011;306(14):1549-1556. [CrossRef]
135. Dunn W, Alkhouri N. Therapeutic development in MASH: From accelerated approval to cirrhosis trial innovation. Med 2026;7(6):101172. [CrossRef]
136. Loomba R, Hartman ML, Lawitz EJ, Vuppalanchi R, Boursier J, Bugianesi E, et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. N Engl J Med 2024;391(4):299-310. [CrossRef]
137. Sanyal AJ, Bedossa P, Fraessdorf M, Neff GW, Lawitz E, Bugianesi E, et al. A phase 2 randomized trial of survodutide in MASH and fibrosis. N Engl J Med 2024;391(4):311-319. [CrossRef]
138. Sanyal AJ, Kaplan LM, Frias JP, Brouwers B, Wu Q, Thomas MK, et al. Triple hormone receptor agonist retatrutide for metabolic dysfunction-associated steatotic liver disease: a randomized phase 2a trial. Nat Med 2024;30(7):2037-2048. [CrossRef]
139. Quek J, Chan KE, Wong ZY, Tan C, Tan B, Lim WH, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2023;8(1):20-30. [CrossRef]
140. Sierra L, Chatterjee A, Prado R, Khurana A, Patel R, Firkins S, et al. Impact of metabolic endoscopy on fibrosis regression in steatotic liver disease. World J Hepatol 2025;17(9):108144. [CrossRef]
141. Di Lorenzo N, Antoniou SA, Batterham RL, Busetto L, Godoroja D, Iossa A, et al. Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: update 2020 endorsed by IFSO-EC, EASO and ESPCOP. Surg Endosc 2020;34(6):2332-2358. [CrossRef]
142. Stier CK, Téoule P, Dayyeh BKA. Endoscopic sleeve gastroplasty (ESG): indications and results-a systematic review. Updates Surg 2025;77(7):1915-1921. [CrossRef]
143. Nunes BCM, de Moura DTH, Kum AST, de Oliveira GHP, Hirsch BS, Ribeiro IB, et al. Impact of endoscopic sleeve gastroplasty in non-alcoholic fatty liver disease: a systematic review and meta-analysis. Obes Surg 2023;33(9):2917-2926. [CrossRef]
144. Chandan S, Mohan BP, Khan SR, Facciorusso A, Ramai D, Kassab LL, et al. Efficacy and safety of Intragastric Balloon (IGB) in non-alcoholic fatty liver disease (NAFLD): a comprehensive review and meta-analysis. Obes Surg 2021;31(3):1271-1279. [CrossRef]
145. Mingrone G, van Baar AC, Devière J, Hopkins D, Moura E, Cercato C, et al. Safety and efficacy of hydrothermal duodenal mucosal resurfacing in patients with type 2 diabetes: the randomised, double-blind, sham-controlled, multicentre REVITA-2 feasibility trial. Gut 2022;71(2):254-264. [CrossRef]
146. Tasabehji D, Saleh S, Mokadem M. Impact of bariatric surgery and endoscopic therapies on liver health in metabolic dysfunction-associated steatotic liver disease: a review. J Clin Med 2025;14(12):4012. [CrossRef]

147. de Brito E Silva MB, Tustumi F, de Miranda Neto AA, Dantas ACB, Santo MA, Cecconello I. Gastric bypass compared with sleeve gastrectomy for nonalcoholic fatty liver disease: a systematic review and meta-analysis. Obes Surg 2021;31(6):2762-2772. [CrossRef]

148. Larrad-Jiménez A, Díaz-Guerra CS, de Cuadros Borrajo P, Lesmes IB, Esteban BM. Short-, mid- and long-term results of Larrad biliopancreatic diversion. Obes Surg 2007;17(2):202-210. [CrossRef]

149. Russo MF, Lembo E, Mari A, Angelini G, Verrastro O, Nanni G, et al. Insulin resistance is central to long-term reversal of histologic nonalcoholic steatohepatitis after metabolic surgery. J Clin Endocrinol Metab 2021;106(3):750-761. [CrossRef]

150. Kral JG, Thung SN, Biron S, Hould FS, Lebel S, Marceau S, et al. Effects of surgical treatment of the metabolic syndrome on liver fibrosis and cirrhosis. Surgery 2004;135(1):48-58. [CrossRef]

151. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol 2024;81(3):492-542.

152. Rouillard NA, Barnett SD, Zhang X, Kam L, Manikat R, Cheung R, et al. Bariatric surgery reduces long-term mortality in patients with metabolic dysfunction-associated steatotic liver disease and cirrhosis. Clin Mol Hepatol 2025;31(1):227-239. [CrossRef]

153. Aminian A, Aljabri A, Wang S, Bena J, Allende DS, Rosen H, et al. Long-term liver outcomes after metabolic surgery in compensated cirrhosis due to metabolic dysfunction-associated steatohepatitis. Nat Med 2025;31(3):988-995. [CrossRef]

154. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on liver transplantation. J Hepatol 2024;81(6):1040-1086. [CrossRef]

155. Moctezuma-Velazquez C, Márquez-Guillén E, Torre A. Obesity in the liver transplant setting. Nutrients 2019;11(11):2552. [CrossRef]

156. Kaya E, Yilmaz Y. Metabolic-associated Fatty Liver Disease (MAFLD): A Multi-systemic Disease Beyond the Liver. J Clin Transl Hepatol 2022;10(2):329-338. [CrossRef]

157. Younossi ZM, de Avila L, Petta S, Hagström H, Kim SU, Nakajima A, et al. Predictors of fibrosis, clinical events, and mortality in MASLD: Data from the Global-MASLD study. Hepatology 2026;84(1):204-215. [CrossRef]

158. Cuthbertson DJ, Kennedy OJ, Bilson J, Hydes TJ, Targher G, Glyn-Owen K, et al. Impact of metabolic dysfunction severity in steatotic liver disease and its interaction with liver fibrosis on all-cause mortality and multiple hepatic and extra-hepatic outcomes. Metabolism 2025;170:156306. [CrossRef]

159. Cusi K, Abdelmalek MF, Apovian CM, Balapattabi K, Bannuru RR, Barb D, et al. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) in people with diabetes: the need for screening and early intervention. a consensus report of the american diabetes association. Diabetes Care 2025;48(7):1057-1082. [CrossRef]

160. Konings LAM, Miguelañez-Matute L, Boeren AMP, van de Luitgaarden IAT, Dirksmeier F, de Knegt RJ, et al. Pharmacological treatment options for metabolic dysfunction-associated steatotic liver disease in patients with type 2 diabetes mellitus: A systematic review. Eur J Clin Invest 2025;55(4):e70003. [CrossRef]

161. Wong VW, Ekstedt M, Wong GL, Hagström H. Changing epidemiology, global trends and implications for outcomes of NAFLD. J Hepatol 2023;79(3):842-852. [CrossRef]

162. Francque SMA, Dirinck E. NAFLD prevalence and severity in overweight and obese populations. Lancet Gastroenterol Hepatol 2023;8(1):2-3. [CrossRef]

163. Eguchi Y, Mizuta T, Sumida Y, Ishibashi E, Kitajima Y, Isoda H, et al. The pathological role of visceral fat accumulation in steatosis, inflammation, and progression of nonalcoholic fatty liver disease. J Gastroenterol 2011;46(Suppl 1):70-78. [CrossRef]

164. Zhou XD, Lian LY, Chen QF, Kim SU, Cheuk-Fung Yip T, Petta S, et al. Effect of hypertension on long-term adverse clinical outcomes and liver fibrosis progression in MASLD. J Hepatol 2026;84(2):254-265. [CrossRef]

165. Kanwal F, Kramer JR, Li L, Dai J, Natarajan Y, Yu X, et al. Effect of metabolic traits on the risk of cirrhosis and hepatocellular cancer in nonalcoholic fatty liver disease. Hepatology 2020;71(3):808-819. [CrossRef]

166. Alam S, Kabir J, Mustafa G, Gupta U, Hasan SK, Alam AK. Effect of telmisartan on histological activity and fibrosis of non-alcoholic steatohepatitis: A 1-year randomized control trial. Saudi J Gastroenterol 2016;22(1):69-76. [CrossRef]

167. Writing Committee Members*; Jones DW, Ferdinand KC, Taler SJ, Johnson HM, Shimbo D, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the prevention, detection, evaluation and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Hypertension 2025;82(10):e212-e316.

168. Reyes-Soffer G, Ginsberg HN, Berglund L, Duell PB, Heffron SP, Kamstrup PR, et al. Lipoprotein(a): a genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol 2022;42(1):e48-e60. [CrossRef]

169. Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. Gut 2024;73(4):691-702. [CrossRef]

170. Schreiner AD, Zhang J, Petz CA, Moran WP, Koch DG, Marsden J, et al. Statin prescriptions and progression of advanced fibrosis risk in primary care patients with MASLD. BMJ Open Gastroenterol 2024;11(1):e001404. [CrossRef]

171. Bilson J, Mantovani A, Byrne CD, Targher G. Steatotic liver disease, MASLD and risk of chronic kidney disease. Diabetes Metab 2024;50(1):101506. [CrossRef]

172. Heo JH, Lee MY, Kim SH, Zheng MH, Byrne CD, Targher G, et al. Comparative associations of non-alcoholic fatty liver disease and metabolic dysfunction-associated steatotic liver disease with risk of incident chronic kidney disease: a cohort study. Hepatobiliary Surg Nutr 2024;13(5):801-813. [CrossRef]

173. Hagström H, Wong VW. The role of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in managing metabolic dysfunction-associated steatotic liver disease. Hepatology 2026;83(2):209-211. [CrossRef]

174. Sattar N, Dalakoti M, Alazawi W, Aroda VR. Cardiovascular risk in MASLD: What multiple lines of evidence reveal. Journal of Hepatology 2026;85(1):159-164. [CrossRef]

175. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, et al. Development and validation of the American Heart Association's PREVENT equations. Circulation 2024;149(6):430-449. [CrossRef]

176. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. Eur Heart J 2021;42(25):2439-2454. [CrossRef]

177. Feng J, Chen W, Zhang Z, Zhou F, Liu Y, Qiu Z, et al. Obstructive sleep apnea is associated with greater MASH and significant fibrosis severity in patients with obesity: A prospective clinicopathological study. Diabetes Obes Metab 2026;28(3):1972-1983. [CrossRef]

178. Teede HJ, Khomami MB, Morman R, Laven JSE, Joham AE, Costello MF, et al. Polyendocrine metabolic ovarian syndrome, the new name for polycystic ovary syndrome: a multistep global consensus process. Lancet 2026;407(10545):2329-2339. [CrossRef]

179. Wang D, He B. Current perspectives on nonalcoholic fatty liver disease in women with polycystic ovary syndrome. Diabetes Metab Syndr Obes 2022;15:1281-1291. [CrossRef]

180. Sarkar M, Terrault N, Chan W, Cedars MI, Huddleston HG, Duwaerts CC, et al. Polycystic ovary syndrome (PCOS) is associated with NASH severity and advanced fibrosis. Liver Int 2020;40(2):355-359. [CrossRef]

181. Yilmaz Y, Allen AM, Boursier J, Arab JP. Association of metabolic dysfunction-associated steatotic liver disease with extrahepatic cancers and sarcopenia. Clin Liver Dis 2026;30(2):289-300. [CrossRef]

182. Li X, He J, Sun Q. The prevalence and effects of sarcopenia in patients with metabolic dysfunction-associated steatotic liver disease (MASLD): A systematic review and meta-analysis. Clin Nutr 2024;43(9):2005-2016. [CrossRef]

183. Nishikawa H, Kim SK, Yoshio S, Asai A. Metabolic dysfunction-associated steatotic liver disease and sarcopenia: review of literature. J Clin Med 2026;15(4):1661. [CrossRef]

184. Giri S, Anirvan P, Angadi S, Singh A, Lavekar A. Prevalence and outcome of sarcopenia in non-alcoholic fatty liver disease. World J Gastrointest Pathophysiol 2024;15(1):91100. [CrossRef]

185. Celik FB, Irgi T, Guvenc TS, Celik M, Yesildag F, Atici A, et al. Exposure to electronic cigarettes impairs vascular and microvascular function. Int J Cardiol 2025;441:133789. [CrossRef]

186. Enc FY, Ulasoglu C, Bakir A, Yilmaz Y. The interaction between current smoking and hemoglobin on the risk of advanced fibrosis in patients with biopsy-proven nonalcoholic fatty liver disease. Eur J Gastroenterol Hepatol 2020;32(5):597-600. [CrossRef]

187. Kostova D, Andes L, Erguder T, Yurekli A, Keskinkılıç B, Polat S, et al. Cigarette prices and smoking prevalence after a tobacco tax increase--Turkey, 2008 and 2012. MMWR Morb Mortal Wkly Rep 2014;63(21):457-461.

188. Ünübol H, Hızlı Sayar G. Prevalence and sociodemographic determinants of substance use in Turkey. Eur Addict Res 2021;27(6):447-456. [CrossRef]

189. Akarsu M, Dolu S, Harputluoglu M, Yilmaz S, Akyildiz M, Gencdal G, et al. Changing trends in the etiology of liver transplantation in Turkiye: A multicenter study. Hepatol Forum 2024;5(1):3-6. [CrossRef]

190. Üçbilek E, Yıldırım AE, Ellik Z, Turan İ, Haktanıyan B, Orucu B, et al. Changing trends in the etiology of cirrhosis in Türkiye: a multicenter nationwide study. Turk J Gastroenterol 2024;35(10):772-777. [CrossRef]

191. Pennisi G, Enea M, Viganò M, Schepis F, de Ledinghen V, Berzigotti A, et al. Oesophageal varices predict complications in compensated advanced non-alcoholic fatty liver disease. JHEP Rep 2023;5(9):100809. [CrossRef]

192. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol 2022;76(4):959-974. [CrossRef]

193. Pons M, Augustin S, Scheiner B, Guillaume M, Rosselli M, Rodrigues SG, et al. Non-invasive diagnosis of portal hypertension in patients with compensated advanced chronic liver disease. Am J Gastroenterol 2021;116(4):723-732. [CrossRef]

194. Pons M, Rivera-Esteban J, Ma MM, Davyduke T, Delamarre A, Hermabessière P, et al. Point-of-care non-invasive prediction of liver-related events in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2024;22(8):1637-1645.e9. [CrossRef]

195. Jachs M, Thöne P, Odriozola A, Turon F, Moga L, Téllez L, et al. Predicting hepatic decompensation using non-invasive tests in a contemporary multicentre cohort of patients with cACLD. J Hepatol 2026;84(4):738-748. [CrossRef]

196. Jachs M, Odriozola A, Turon F, Moga L, Téllez L, Fischer P, et al. Spleen stiffness measurement by vibration-controlled transient elastography at 100 Hz for non-invasive predicted diagnosis of clinically significant portal hypertension in patients with compensated advanced chronic liver disease: a modelling study. Lancet Gastroenterol Hepatol 2024;9(12):1111-1120. [CrossRef]

197. Zhang BH, Yang BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. J Cancer Res Clin Oncol 2004;130(7):417-422. [CrossRef]

198. Takeuchi Y, Tateishi R, Obi S, Otsuka M, Mochizuki H, Jazag A, et al. Temporal trends and regional variations in hepatocellular carcinoma etiology: a multinational study across Asia. Hepatol Int 2026;20(2):373-383. [CrossRef]

199. Guzelbulut F, Karaogullarindan U, Akkiz H, Altintas E, Demirtas CO, Bahadir O, et al. Characteristics of patients with hepatocellular carcinoma: A multicenter study. Hepatol Forum 2022;3(3):71-76. [CrossRef]

200. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatocellular carcinoma. J Hepatol 2025;82(2):315-374.

201. Eslam M, Fan JG, Yu ML, Wong VW, Cua IH, Liu CJ, et al. The Asian Pacific association for the study of the liver clinical practice guidelines for the diagnosis and management of metabolic dysfunction-associated fatty liver disease. Hepatol Int 2025;19(2):261-301. [CrossRef]

202. Ioannou GN, Green P, Kerr KF, Berry K. Models estimating risk of hepatocellular carcinoma in patients with alcohol or NAFLD-related cirrhosis for risk stratification. J Hepatol 2019;71(3):523-533. [CrossRef]

203. Younossi ZM, Zelber-Sagi S, Lazarus JV, Wong VW, Yilmaz Y, Duseja A, et al. Global consensus recommendations for metabolic dysfunction-associated steatotic liver disease and steatohepatitis. Gastroenterology 2025;169(5):1017-1032.e2. [CrossRef]

204. Kang JH, Kim NH, Kim DH, Choi Y, Choi JI. Ultrasound LI-RADS visualization scores on surveillance ultrasound for hepatocellular carcinoma: a systematic review with meta-analysis. Ultrasound Med Biol 2023;49(10):2205-2212. [CrossRef]

205. Tzartzeva K, Obi J, Rich NE, Parikh ND, Marrero JA, Yopp A, et al. Surveillance imaging and alpha fetoprotein for early detection of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. Gastroenterology. 2018;154(6):1706-1718.e1. [CrossRef]

206. Orci LA, Sanduzzi-Zamparelli M, Caballol B, Sapena V, Colucci N, Torres F, et al. Incidence of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression. Clin Gastroenterol Hepatol 2022;20(2):283-292.e10. [CrossRef]

207. Tan DJH, Ng CH, Lin SY, Pan XH, Tay P, Lim WH, et al. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. Lancet Oncol 2022;23(4):521-530. [CrossRef]

208. Sanyal AJ, Van Natta ML, Clark J, Neuschwander-Tetri BA, Diehl A, Dasarathy S, et al. Prospective study of outcomes in adults with nonalcoholic fatty liver Disease. N Engl J Med 2021;385(17):1559-1569. [CrossRef]

209. Singal AG, Haaland B, Parikh ND, Ozbay AB, Kirshner C, Chakankar S, et al. Comparison of a multitarget blood test to ultrasound and alpha-fetoprotein for hepatocellular carcinoma surveillance: Results of a network meta-analysis. Hepatol Commun 2022;6(10):2925-2936. [CrossRef]

210. Demirtas CO, Akin S, Yilmaz Karadag D, Yilmaz T, Ciftci U, Huseynov J, et al. Enhancing hepatocellular carcinoma surveillance: comparative evaluation of AFP, AFP-L3, DCP and composite models in a biobank-based case-control study. Cancers (Basel) 2025;17(14):2390. [CrossRef]

211. Best J, Bechmann LP, Sowa JP, Sydor S, Dechêne A, Pflanz K, et al. GALAD score detects early hepatocellular carcinoma in an international cohort of patients with nonalcoholic steatohepatitis. Clin Gastroenterol Hepatol 2020;18(3):728-735.e4. [CrossRef]

212. Guan MC, Zhang SY, Ding Q, Li N, Fu TT, Zhang GX, et al. The performance of galad score for diagnosing hepatocellular carcinoma in patients with chronic liver diseases: a systematic review and meta-analysis. J Clin Med 2023;12(3):949. [CrossRef]

213. Younossi ZM, Germani G, Wong R, Stepanova M, Nader F, Karam V, et al. Steatotic liver disease is the dominant indication for liver transplantation in both Europe and the United States: Trends and outcomes in the past 2 decades. Liver Transpl 2026;32(4):549-557. [CrossRef]

214. Haldar D, Kern B, Hodson J, Armstrong MJ, Adam R, Berlakovich G, et al. Outcomes of liver transplantation for non-alcoholic steatohepatitis: A European Liver Transplant Registry study. J Hepatol 2019;71(2):313-322. [CrossRef]

215. Vanwagner LB, Bhave M, Te HS, Feinglass J, Alvarez L, Rinella ME. Patients transplanted for nonalcoholic steatohepatitis are at increased risk for postoperative cardiovascular events. Hepatology 2012;56(5):1741-1750. [CrossRef]

216. Lee DU, Han J, Lee KJ, Kwon J, Fan GH, Jung D, et al. The clinical implications of pre-liver transplant diabetes on post-liver transplant outcomes in patients with NASH: analysis of the UNOS database. Hepatol Int 2022;16(6):1448-1457. [CrossRef]

217. Tsochatzis E, Coilly A, Nadalin S, Levistky J, Tokat Y, Ghobrial M, et al. International liver transplantation consensus statement on end-stage liver disease due to nonalcoholic steatohepatitis and liver transplantation. Transplantation 2019;103(1):45-56. [CrossRef]

218. Dove L, Chadha RM, Lai JC, DiMartini A, Liapakis A, Parikh ND, et al. AASLD AST Practice guideline on adult liver transplantation: candidate evaluation. Hepatology 2026;83(6):1609-1645. [CrossRef]

219. VanWagner LB, Ning H, Whitsett M, Levitsky J, Uttal S, Wilkins JT, et al. A point-based prediction model for cardiovascular risk in orthotopic liver transplantation: The CAR-OLT score. Hepatology 2017;66(6):1968-1979. [CrossRef]

220. Rachwan RJ, Kutkut I, Timsina LR, Bou Chaaya RG, El-Am EA, Sabra M, et al. CAD-LT score effectively predicts risk of significant coronary artery disease in liver transplant candidates. J Hepatol 2021;75(1):142-149. [CrossRef]

221. Gunay Y, Guler N, Dayangac M, Taskesen F, Yaprak O, Emek E, et al. Living donor liver transplantation for obese patients: challenges and outcomes. Liver Transpl 2014;20(3):311-322. [CrossRef]

222. Haugen CE, McAdams-DeMarco M, Verna EC, Rahimi RS, Kappus MR, et al. Association between liver transplant wait-list mortality and frailty based on body mass index. JAMA Surg 2019;154(12):1103-1109. [CrossRef]

223. Ali Deeb A, Settmacher U, Fritsch J, Dondorf F, Rohland O, Rauchfuß F. Sarcopenic obesity may predict worse liver regeneration after right graft living donor liver transplantation. Liver Transpl 2024;30(4):412-420. [CrossRef]

224. Burra P, Becchetti C, Germani G. NAFLD and liver transplantation: Disease burden, current management and future challenges. JHEP Rep 2020;2(6):100192. [CrossRef]

225. Sharma P, Izzy M, Ghabril MS, Serper M, Clark VC, Ison MG, Hameed B, Volk M, Brown RS Jr, Humar A, Martin P. AASLD/AST practice guideline on adult liver transplantation: diagnosis and post-transplant management of non-graft-related complications. Liver Transpl 2025 Dec 17. doi:10.1097/LVT.0000000000000785. [Epub ahead of print]. [CrossRef]

226. Adali G, Bilgic NM, Kalaman AE, Ozturk O, Ozdil K. Prevalence and predictors of metabolic-associated fatty liver disease in liver transplant recipients: A cross-sectional prospective study. Hepatol Forum 2023;4(3):129-134. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 215–217 DOI: 10.14744/hf.2026.84986

INVITED EDITORIAL

Body composition in glucagon-like peptide-1 receptor agonist therapy: Absolute loss, relative changes, and outcomes

Sang Chen[1,2], Wen-Yue Liu[3], Giovanni Targher[4,5], Christopher D Byrne[6], Yusuf Yilmaz[7], Ming-Hua Zheng[1,2]

1: MAFLD Research Center, Department of Hepatology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
2: Key Laboratory of Diagnosis and Treatment for the Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China
3: Department of Endocrinology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China
4: Department of Medicine, University of Verona, Verona, Italy
5: Metabolic Diseases Research Unit, IRCCS Sacro Cuore - Don Calabria Hospital, Negrar di Valpolicella, Italy
6: Southampton National Institute for Health and Care Research Biomedical Research Centre, University Hospital Southampton and University of Southampton, Southampton General Hospital, Southampton, UK
7: Department of Gastroenterology, School of Medicine, Recep Tayyip Erdogan University, Rize, Türkiye

Obesity, as one of the most prevalent chronic diseases globally, has well-documented adverse health effects.[1] Originally developed for their insulin-regulating properties, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have gained widespread attention in both clinical and public domains due to their significant weight-loss effects. Against the backdrop of the increasing prevalence of obesity and metabolic dysfunction-associated steatotic liver disease, the widespread use of GLP-1 RAs has raised important clinical questions regarding their impact on body composition, particularly on non-adipose tissues. Excessive loss of skeletal muscle may impair metabolic health, reduce physical function, and increase the risk of sarcopenia, frailty, and falls. Existing evidence on body composition changes during GLP-1 RA treatment presents certain complexities, with diverse indicators (such as lean body mass [LBM], fat-free mass [FFM], and skeletal muscle mass [SMM]) used to assess muscular impact. The clinical significance of these changes requires careful distinction between functional outcomes and structural alterations. This article compares the effects of different GLP-1 RAs on body composition during weight loss and analyzes key factors influencing these changes, aiming to optimize clinical strategies and identify future research directions.

Changes in Diverse Body Composition Indicators during GLP-1 RA Therapy

One of the key metrics for assessing muscular impact is LBM, defined as total body FFM minus total bone mineral content, also known as lean soft tissue mass. LBM typically decreases during weight loss induced by GLP-1 RAs, with the extent of reduction influenced by study design, specific agent, and treatment duration. Randomized controlled trials indicate that the use of tirzepatide or semaglutide can lead to an LBM reduction of 2.3–5.6 kg,[2–4] and real-world studies similarly observed decreases of 2.7 kg after liraglutide and 3.53 kg after semaglutide.[5,6] Nonetheless, weight loss is primarily driven by fat reduction, while the evidence for excessive depletion of LBM remains inconclusive. Other studies describe more modest LBM declines of about 1.1–1.3 kg (≈3.2% of lean soft tissue) with agents such as exenatide, semaglutide, and liraglutide.[7–9] Some studies even report well-preserved LBM, as exemplified by only a marginal decrease of 0.1 kg after 12 weeks of oral semaglutide treatment,[10] and no significant change following 52 weeks of exenatide therapy.[11] Moreover, despite potential reductions in limb LBM, the overall proportion of lean tissue may still increase.[12] In certain populations, such as hemodialysis patients, LBM showed a slight increasing trend after 6 months of semaglutide treatment.[13]

FFM is defined as the component of total body mass remaining after the subtraction of fat mass. Changes in FFM vary across studies, with its trend influenced by treatment duration, mode of intervention, and accompanying measures. Some studies have demonstrated an absolute increase in FFM, such as significant growth observed after 26 weeks of oral semaglutide treatment.[14] Conversely, other studies indicate varying degrees of reduction in FFM. For example, a decrease of approximately 1.15 kg after 52

How to cite this article: Chen S, Liu W-Y, Targher G, Byrne CD, Yilmaz Y, Zheng MH. Body composition in glucagon-like peptide-1 receptor agonist therapy: Absolute loss, relative changes, and outcomes. Hepatology Forum 2026; 7(3):215–217.

Received: March 17, 2026; **Revised:** May 03, 2026; **Accepted:** May 23, 2026; **Available Online:** July 21, 2026

Corresponding author: Ming-Hua Zheng; MAFLD Research Center, Department of Hepatology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China; Key Laboratory of Diagnosis and Treatment for the Development of Chronic Liver Disease in Zhejiang Province, Wenzhou, China; **E-mail:** zhengmh@wmu.edu.cn

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

weeks of GLP-1 RA therapy,[15] or a loss of 1.43 kg following 3 months of combined semaglutide treatment.[16] It is noteworthy that the relative reduction in FFM is generally smaller than that in fat mass.[17] Moreover, subcutaneous injection may lead to a more significant reduction compared to oral administration.[18] Meanwhile, while combined dietary education can enhance overall weight loss, it also results in greater loss of SMM compared to pharmacotherapy alone.[19] This highlights the necessity of prevention of muscle loss for maintaining FFM and SMM.

SMM serves as a more precise indicator for assessing muscle health. Available data show that the reduction in SMM is generally less pronounced than the overall decline in fat-free mass. For instance, following semaglutide treatment, SMM decreased by 0.88–0.99 kg, whereas the corresponding reduction in fat-free mass was 1.15–1.43 kg.[15,16] A similar trend was observed in a liraglutide study, where the decline in muscle mass (–3.6%) was significantly lower than the reduction in fat mass (–11.1%).[20] It is noteworthy that structural changes do not necessarily equate to functional impairment. Some studies have reported that despite a decrease in muscle mass, key functional measures such as handgrip strength can be preserved.[21] Other research has even documented concurrent increases in both SMM and FFM.[14] These findings suggest that although GLP-1 RA therapy may lead to a modest reduction in SMM, current studies have not consistently observed clinically significant functional impairment.

Potential Explanations for the Discrepant Effects of GLP-1 RAs on Body Composition

The observed heterogeneity in study results may be attributed to a combination of the following factors. First, differences in the baseline characteristics of the study populations may have a potential influence. While standardized study designs can effectively control for confounding factors, attention should also be paid to the representativeness of the sample and the generalizability of the findings. For example, enrolling more patients with conditions that may affect muscle metabolism, such as cardiovascular diseases or diabetic complications, could increase the risk of lean mass loss. Second, the degree of standardization in concomitant lifestyle interventions is also an important variable. Consistent dietary and exercise regimens are beneficial for the preservation of lean mass. Furthermore, differences in body composition assessment methods may introduce systematic errors. Although techniques such as dual-energy X-ray absorptiometry and magnetic resonance imaging are considered the "gold standard," bioelectrical impedance analysis is widely used due to its practicality and accessibility. However, the latter method is susceptible to physiological factors such as hydration status and body temperature, as well as measurement conditions, which may increase measurement variability and consequently affect the comparability of data across studies. Finally, due to significant heterogeneity in intervention measures and assessment methods across different studies, direct comparisons should be approached with caution.

Balancing Body Composition Changes and Metabolic Health in GLP-1 RA Therapy

To assess the clinical significance of body composition changes during GLP-1 RA-induced weight loss, we should not focus solely on the absolute value of LBM. While GLP-1 RA treatment leads to a reduction in LBM, current evidence does not consistently demonstrate significant impairment in muscle mass or function. Moreover, the overall metabolic benefits for most patients are likely to outweigh the risks associated with lean mass loss alone. It should be noted that current research on muscle function is relatively limited; therefore, future research should aim to fill this gap. Consequently, in vulnerable subpopulations with risk factors for sarcopenia, such as advanced age, frailty, sedentary lifestyle, or inadequate nutrition, the potential risks associated with GLP-1 RAs should not be overlooked. Systematic assessment of muscle function, along with increased monitoring frequency, should also be strengthened accordingly.

Therefore, in weight loss management, the focus of body composition monitoring should shift from merely tracking lean mass to preserving or improving muscle health, with greater emphasis on muscle strength and functional metrics to better balance metabolic gains against potential risks. According to current guidelines, for patients diagnosed with sarcopenia, it is recommended to establish a systematic monitoring protocol that includes at least an annual functional assessment (such as grip strength and gait speed testing) after diagnosis. Given the likelihood of long-term GLP-1 RA therapy, it is crucial to introduce more objective and comprehensive methods for assessing muscle health. These should encompass evaluations of muscle quantity, composition, function, mobility, and strength. Concurrently, individualized interventions centered on optimizing energy and protein intake alongside regular resistance training should be implemented, thereby minimizing the risk of therapy-related muscle loss.[22,23]

Conflicts of Interest: All other authors declare no conflicts of interest.

Financial Disclosure: Ming-Hua Zheng serves as a speaker for AstraZeneca, Hisky Medical Technologies, and Novo Nordisk; as a consultant for Boehringer Ingelheim and Eieling Technology; and has received consulting fees from Boehringer Ingelheim. Yusuf Yilmaz has received personal consultancy fees from Novo Nordisk and Zydus.

Use of Artificial Intelligence: The authors used an AI-assisted language editing tool (ChatGPT, OpenAI) to improve the clarity and grammar of the manuscript. The authors reviewed and edited the output and take full responsibility for the content of the publication.

Authors' Contributions: Concept: SC, M-HZ; Design: SC, M-HZ; Supervision: GT, CDB, YY, M-HZ; Findings: SC, W-YL; Materials: SC, W-YL; Data Collection and/or Processing: SC, W-YL; Analysis and/or Interpretation: SC, M-HZ; Literature Review: SC, W-YL; Writing: SC; Critical Review: SC, W-YL, GT, CDB, YY, M-HZ.

Peer-review: Externally peer-reviewed.

References

1. Willoughby D, Hewlings S, Kalman D. Body composition changes in weight loss: Strategies and supplementation for maintaining lean body mass, a brief review. Nutrients 2018;10(12):1876. [CrossRef]
2. McCrimmon RJ, Catarig AM, Frias JP, Lausvig NL, le Roux CW, Thielke D, et al. Effects of once-weekly semaglutide vs once-daily canagliflozin on body composition in type 2 diabetes: a substudy of the SUSTAIN 8 randomised controlled clinical trial. Diabetologia 2020;63(3):473-485. [CrossRef]
3. Wilding JPH, Batterham RL, Davies M, Van Gaal LF, Kandler K, Konakli K, et al; STEP 1 Study Group. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Diabetes Obes Metab 2022;24(8):1553-1564. [CrossRef]
4. Look M, Dunn JP, Kushner RF, Cao D, Harris C, Gibble TH, et al. Body composition changes during weight reduction with tirzepatide in the SURMOUNT-1 study of adults with obesity or overweight. Diabetes Obes Metab 2025;27(5):2720-2729. Erratum in: Diabetes Obes Metab 2025;27(11):6823. [CrossRef]
5. Santini S, Vionnet N, Pasquier J, Gonzalez-Rodriguez E, Fraga M, Pitteloud N, et al. Marked weight loss on liraglutide 3.0 mg: Real-life experience of a Swiss cohort with obesity. Obesity (Silver Spring) 2023;31(1):74-82. [CrossRef]
6. Pantanetti P, Cangelosi G, Alberti S, Di Marco S, Michetti G, Cerasoli G, et al. Changes in body weight and composition, metabolic parameters, and quality of life in patients with type 2 diabetes treated with subcutaneous semaglutide in real-world clinical practice. Front Endocrinol (Lausanne) 2024;15:1394506. [CrossRef]
7. Basolo A, Paolucci G, Piaggi P, Angeli V, Bechi Genzano S, Fierabracci P, et al. Effects of 6-month treatment with the GLP-1 receptor agonist liraglutide on 24-hour energy metabolism and body composition in adults with obesity. J Endocrinol Invest 2025;48(11):2735-2745. [CrossRef]
8. Blundell J, Finlayson G, Axelsen M, Flint A, Gibbons C, Kvist T, et al. Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference and body weight in subjects with obesity. Diabetes Obes Metab 2017;19(9):1242-1251. [CrossRef]
9. Johansen P, Hunt B, Iyer NN, Dang-Tan T, Pollock RF. A relative cost of control analysis of once-weekly semaglutide versus exenatide extended-release and dulaglutide for bringing patients to HbA1c and weight loss treatment targets in the USA. Adv Ther 2019;36(5):1190-1199. [CrossRef]
10. Gibbons C, Blundell J, Tetens Hoff S, Dahl K, Bauer R, Baekdal T. Effects of oral semaglutide on energy intake, food preference, appetite, control of eating and body weight in subjects with type 2 diabetes. Diabetes Obes Metab 2021;23(2):581-588. [CrossRef]
11. Bunck MC, Cornér A, Eliasson B, Heine RJ, Shaginian RM, Wu Y, et al. One-year treatment with exenatide vs. insulin glargine: effects on postprandial glycemia, lipid profiles, and oxidative stress. Atherosclerosis 2010;212(1):223-229. [CrossRef]
12. Yin TT, Bi Y, Li P, Shen SM, Wang WM, Jiang C, et al. Effects of exenatide versus insulin glargine on body composition in overweight and obese T2DM patients: a randomized controlled trial. Nutr Metab (Lond) 2018;15:67. [CrossRef]
13. Yugueros A, D'Marco L, Valero A, Vivó E, Martínez-Mas A, Calvé M, et al. Preliminary real-world experience with semaglutide in obese patients with Type 2 diabetes on chronic hemodialysis: A multicenter pilot study. Medicina (Kaunas) 2026;62(2):386. [CrossRef]
14. Volpe S, Lisco G, Fanelli M, Racaniello D, Colaianni V, Lavarra V, et al. Oral semaglutide improves body composition and preserves lean mass in patients with type 2 diabetes: a 26-week prospective real-life study. Front Endocrinol (Lausanne) 2023;14:1240263. [CrossRef]
15. Vozza A, Triggiani D, Fanelli M, Lisco G, Coletto D, Custodero C, et al. Predictive factors of body weight loss in patients with type 2 diabetes treated with GLP-1 receptor agonists: a 52-week prospective real-life study. Front Endocrinol (Lausanne) 2025;16:1674308. [CrossRef]
16. Chun E, Siojo A, Rivera D, Reyna K, Legere H, Joseph R, et al. Weight loss and body composition after compounded semaglutide treatment in a real world setting. Diabetes Obes Metab 2025;27(3):1536-1543. [CrossRef]
17. Wang Z, Wang L, Zhang X, Lowery BD, Shaffer LL, Chen Y, et al. Body composition changes after bariatric surgery or treatment with GLP-1 receptor agonists. JAMA Netw Open 2026;9(1):e2553323. [CrossRef]
18. Rodríguez Jiménez B, Rodríguez de Vera Gómez P, Belmonte Lomas S, Mesa Díaz ÁM, Caballero Mateos I, Galán I, et al. Transforming body composition with semaglutide in adults with obesity and type 2 diabetes mellitus. Front Endocrinol (Lausanne) 2024;15:1386542. [CrossRef]
19. Dearos Sanchis M, Voltas Arribas B, Carrasco-Querol N, Sauras Colón E, Sánchez Juan C. Impacto en la pérdida de peso y la composición corporal de una intervención de educación alimentaria asociada al tratamiento con liraglutida para el abordaje de la obesidad [Impact on weight loss and body composition of a food education intervention associated with Liraglutide treatment to address obesity]. Nutr Hosp 2024;41(3):585-593. [Spanish]. [CrossRef]
20. Park J, Kim JW, Lim S. Impact of liraglutide 3.0 mg on metabolic dysfunction-associated steatotic liver disease in individuals with obesity: A real-world study. Ann Nutr Metab 2025;81(6):328-337. [CrossRef]
21. Xiang J, Ding XY, Zhang W, Zhang J, Zhang YS, Li ZM, et al. Clinical effectiveness of semaglutide on weight loss, body composition, and muscle strength in Chinese adults. Eur Rev Med Pharmacol Sci 2023;27(20):9908-9915. [CrossRef]
22. Zanker J, Sim M, Anderson K, Balogun S, Brennan-Olsen SL, Dent E, et al. Consensus guidelines for sarcopenia prevention, diagnosis and management in Australia and New Zealand. J Cachexia Sarcopenia Muscle 2023;14(1):142-156. [CrossRef]
23. Linge JL, Birkenfeld AL, Neeland IJ. Muscle mass and glucagon-like peptide-1 receptor agonists: Adaptive or maladaptive response to weight loss? Circulation 2024;150(16):1288-1298. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 218–226 DOI: 10.14744/hf.2025.82371

SYSTEMATIC REVIEW

Duration of vasoconstrictors after endoscopic variceal ligation in acute variceal bleeding: A systematic review and network meta-analysis

Suprabhat Giri[1], Saurav Panda[2], Ankita Singh[3], Jijo Varghese[4], Sushrut Ingawale[5], Elliot B Tapper[6,7], Don C Rockey[8], Ashok Choudhury[9]

1: Department of Gastroenterology and Hepatology, Kalinga Institute of Medical Sciences, Bhubaneswar, India
2: Department of Gastroenterology and Hepatology, Mayo Clinic, Minnesota, USA
3: Department of Gastroenterology, Seth GS Medical College and KEM Hospital, Mumbai, India
4: Department of Gastroenterology, NS Hospital, Kollam, India
5: Division of Internal Medicine, Quinnipiac University Frank H. Netter MD School of Medicine, Bridgeport, USA
6: Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan, USA
7: Gastroenterology Section, VA Ann Arbor Healthcare System, Ann Arbor, Michigan, USA
8: Digestive Disease Research Center, Medical University of South Carolina, Charleston, USA
9: Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

Points to Note

- **Synthesis of Current Evidence:** Studies on vasoconstrictor duration after endoscopic variceal ligation (EVL) show no significant difference in rebleeding or mortality between short (≤72 hours) and standard durations (72–120 hours). Network meta-analysis suggests shorter treatment prevents rebleeding and mortality effectively.
- **Major Controversies:** The debate centers on the optimal duration for vasoconstrictor therapy, with concerns over adverse events from prolonged treatment.
- **Future Directions:** Future research should refine guidelines, reduce hospital stays, and identify patients needing extended therapy.

ABSTRACT

Background and Aim: Studies on the duration of vasoconstrictors after endoscopic variceal ligation (EVL) for acute variceal bleeding (AVB) have shown varying results. The present network meta-analysis compared the effectiveness of vasoconstrictors after EVL based on the therapy duration.

Materials and Methods: The electronic databases of MEDLINE, Embase, Cochrane Central Register of Controlled Trials, and Scopus were searched from inception to March 2024 for randomized studies comparing the duration of vasoconstrictors in AVB after EVL (Group 1: ≤24 hours, Group 2: >24 to ≤72 hours, Group 3: >72 to ≤120 hours). Rebleeding and mortality risk were analyzed using pairwise and network meta-analyses.

Results: Eleven studies (n=1,066) met the inclusion criteria. Rebleeding rates varied from 0–38% in Group 1, 2–12% in Group 2, and 0–26% in Group 3. There was no difference in the risk of rebleeding in Group 1 (risk ratio [RR]: 1.36, 95% confidence interval [CI]: 0.48–3.52) or Group 2 (RR: 1.34, 95% CI: 0.42–4.54), compared to Group 3. Similarly, there was no difference either in 5-day mortality risk among the groups (RR: 0.66, 95% CI: 0.09–2.52 and 1.08, 95% CI: 0.15–6.43 for Groups 1 and 2, respectively, vs. Group 3) or 30-day mortality risk (RR: 1.18, 95% CI: 0.51–2.51 and 0.98, 95% CI: 0.36–2.52 for Groups 1 and 2, respectively, vs. Group 3).

Conclusion: The current network meta-analysis provides no evidence to support the use of vasoconstrictors following EVL. These data suggest that vasoconstrictors can be stopped early after EVL, facilitating early discharge from the hospital.

Keywords: Banding, endoscopy, esophagogastroduodenoscopy, octreotide, terlipressin, varices.

How to cite this article: Giri S, Panda S, Singh A, Varghese J, Ingawale S, Tapper EB, et al. Duration of vasoconstrictors after endoscopic variceal ligation in acute variceal bleeding: A systematic review and network meta-analysis. Hepatology Forum 2026; 7(3):218–226.

Received: April 08, 2025; **Revised:** July 24, 2025; **Accepted:** August 05, 2025; **Available Online:** June 05, 2026

Corresponding author: Ashok Choudhury; Department of Hepatology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi, India; **E-mail:** doctor.ashokchoudhury@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

Acute variceal bleeding (AVB) associated with cirrhosis and portal hypertension is a devastating clinical complication associated with substantial morbidity and mortality.[1,2] Each bleeding episode is associated with a mortality risk of approximately 15–25%.[3,4] Best practice for management includes a combination of vasoconstrictor and endoscopic therapy,[5] which includes sclerotherapy or endoscopic variceal ligation (EVL). EVL is preferred and is more widely used due to lower rates of rebleeding and fewer endoscopic complications.[6,7] Traditionally, vasoconstrictor therapy has been continued for up to 5 days post-procedure to prevent rebleeding, and current guidelines suggest using vasoconstrictors for 3 to 5 days in AVB.[5]

There is considerable controversy surrounding the appropriate duration of use of vasoconstrictors in AVB. On the one hand, patients with high MELD scores or hepatic venous pressure gradient >20 mmHg, where early transjugular intrahepatic portosystemic shunt (TIPS) is recommended,[5] are at significant risk of rebleeding after primary hemostasis, thereby potentially justifying continued vasoconstrictor therapy (typically for at least five days or until TIPS or transplant is undertaken). On the other hand, the rationale for continuing vasoconstrictors post-endoscopic therapy is to reduce portal pressure and the risk of variceal rebleeding. However, previous data supporting this recommendation were developed when endoscopic sclerotherapy was the main treatment modality. Studies have shown the superiority of a combination of endoscopic sclerotherapy with vasoconstrictors over endoscopic sclerotherapy alone in preventing 5-day rebleeding rates,[8,9] but the same results have not been duplicated with EVL. Indeed, EVL alone has a primary hemostasis rate of some 95% and a low rebleeding rate.[7,10] Additionally, some vasoconstrictors, including octreotide, have a very rapid onset of tachyphylaxis,[11] raising pathophysiologically based questions about the role of prolonged vasoconstrictor therapy. Thus, guidelines may need to be reevaluated using data currently available from studies on EVL.

It is also notable that prolonged vasoconstrictor treatment not only lengthens hospital stay but may carry a significant risk of major adverse events (AE), including cardiac arrhythmias, pulmonary edema, respiratory failure, hyponatremia, and ischemic events.[12] One meta-analysis reported treatment-related AEs with terlipressin in 22% of cases, with serious AEs being 5%, with higher rates in those having hepatorenal syndrome and bilirubin >4.3 mg/dL.[12] Thus, the appropriate duration of vasoconstrictor treatment post-EVL requires further evaluation. Therefore, in this study, we aimed to help clarify this issue by analyzing the effect of treatment duration of vasoconstrictor therapy on the risk of rebleeding after AVB and mortality.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses (PRISMA-NMA) guideline was used to report the current meta-analysis.[13]

Information Sources and Search Strategy

The following databases were searched for relevant studies using the keywords: (Varices OR Variceal bleeding OR Variceal hemorrhage) and (Variceal ligation OR Band ligation OR Hemostasis) and (Vasoconstrictor OR Octreotide OR Somatostatin OR Terlipressin): MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus. Searches were from inception to March 2024. Additionally, the bibliography of all identified studies, guidelines, and reviews on the topic was searched for relevant trials.

Study Selection

Two reviewers independently screened titles and abstracts of retrieved search records for inclusion and exclusion criteria. Any differences were settled through discussion. Randomized controlled trials (RCTs) fulfilling the following PICO criteria were included: (a) Patients – Cirrhosis with AVB undergoing EVL; (b) Intervention – short duration of vasoconstrictors after EVL; (c) Comparison – standard duration of vasoconstrictors after EVL; (d) Outcomes – rebleeding and mortality. Single-arm studies, conference abstracts, and studies involving pediatric patients were excluded. Differences of opinion with regard to suitability for inclusion were settled through discussion.

Data Extraction

Two investigators extracted data independently, while a third reviewer resolved disagreement as to which data would be included. The following information was collected: study author and year, country, number of patients, demographic profiles of patients, clinical features of patients, endoscopic findings and treatment, dose and duration of vasoconstrictor, and outcomes including rebleeding and mortality.

Risk of Bias in Individual Studies and Confidence in Cumulative Evidence

Two independent reviewers evaluated the risk of bias using the Cochrane risk-of-bias tool for randomized trials (RoB 2).[14] The certainty of the evidence for all outcomes was assessed using the grading of recommendations assessment, development and evaluation (GRADE) approach for network meta-analysis.[15]

Statistical Analysis

A pair-wise meta-analysis was carried out using RevMan software (version 5.4.1, Cochrane Collaboration) and a random effects model. Dichotomous variables were assessed utilizing the Mantel-Haenszel test, and estimates were reported as risk ratio (RR) with their 95% confidence interval (CI). The study utilized Stata 17.0 software and MetaInsight (CRSU NMA web-based app) to conduct a network meta-analysis with a Bayesian random effects model.[16] For comparison in network meta-analysis, studies were divided into three groups based on the duration – very short/group 1 (≤24 hours), short/group 2 (>24 and ≤72 hours), and standard/group 3 (>72 to 120 hours). Global inconsistency was assessed using the Wald test.[17] Interventions were ranked relative to different outcomes using their surface under the cumulative ranking (SUCRA) score.[18] Publication bias was evaluated by analyzing the asymmetry of the funnel plot.[19]

Table 1. Baseline characteristics and study populations of the included studies

Author (year)	Country	Drug and dose	Duration	No. of patients	Age, years	Sex (male %)	Alcoholic cirrhosis (%)	Child-Pugh score (%)
Sung (1995)[20]	Hong Kong	Octreotide 100 µg bolus and 25 µg/h	0	47	56 (32-78)	76.6	31.9	A: 17%, B: 40.4%, C: 42.5%
			120 hours	47	58 (17-77)	65.9	36.2	A: 17%, B: 42.5%, C: 40.4%
Lee (1999)[21]	South Korea	Octreotide 100 µg bolus and 25 µg/h	0	30	50±10	93.3	50	7.93±2.10
			120 hours	24	47±9	91.7	62.5	8.58±1.74
Azam (2012)[22]	Pakistan	Terlipressin 2 mg bolus and 1 mg/6 h	24 hours	65	49.8±11.2	73.8	6.2	A: 10.8%, B: 46.2%, C: 43%
			72 hours	65	49.7±12.1	75.4	16.9	A: 10.8%, B: 63%, C: 26.2%
Lo (2013)[23]	Taiwan	Somatostatin 250-µg/h or terlipressin 1 mg/6 h	0	58	54.2±9.7	84.5	38	A: 25.9%, B: 41.4%, C: 32.7%
			120 hours	60	52.5±14.4	81.7	40	A: 30%, B: 53.3%, C: 16.7%
Chitapanarux (2015)[24]	Thailand	Somatostatin 250-µg IV bolus and 250-µg/h infusion	72 hours	50	45.1±12.4	92.0	62.0	A: 30%, B: 54%, C: 16%
			120 hours	45	49.5±11.0	92.1	42.2	A: 26.7%, B: 55.5%, C: 17.9%
Kumar (2015)[25]	India	Somatostatin 250-µg IV bolus and 250-µg/h infusion	0	30	42 (12-65)	80	33	A: 10%, B: 37%, C: 53%
			120 hours	31	45 (26-73)	77	39	A: 0%, B: 42%, C: 58%
Salim (2017)[26]	Pakistan	Terlipressin 2 mg bolus and 1 mg/6 h	12 hours	65	51.3±11.5	57	–	A: 0%, B: 55.4%, C: 44.6%
			72 hours	25	53.6±11.1		–	A: 0%, B: 52%, C: 48%
Zaman (2019)[27]	Pakistan	Terlipressin 2 mg bolus and 1 mg/6 h	24 hours	50	55.2±5.6	58	–	–
			72 hours	50			–	–
Poudel (2022)[28]	India	Terlipressin 2 mg bolus and 1 mg/4 h	0	25	48.3±12.0	80	68	–
			48 hours	25	48.1±10.2	80	68	–
			120 hours	24	48.0±11.6	87.5	83.3	–
Vaishnav (2024)[29]	India	Terlipressin 2 mg/4 h for the first 24 hours and 1 mg/6 h	24 hours	75	44 (36–51)	85.1	48.6	A: 28.4%, B: 55.4%, C: 16.2%
			72 hours	75	40 (37–48)	89.3	42.7	A: 22.7%, B: 64%, C: 13.3%
Lo (2024)[30]	Taiwan	Terlipressin 2 mg bolus and 1 mg/6 h	48 hours	52	55.2±11.1	86.5	42.3	A: 23.1%, B: 48.1%, C: 28.8%
			120 hours	48	58.9±12.3	81.2	47.9	A: 27.1%, B: 50%, C: 22.9%

Results

Baseline Characteristics of the Studies and Risk of Bias

The search strategy, as summarized in Methods, yielded 1,830 records, out of which 11 were included in the final analysis (Fig. 1). All studies were from Asia (Table 1).[20–30] The type and approach to dosing of vasoconstrictors varied: two studies used octreotide (100 µg bolus followed by 25 µg/h),[20,21] two used somatostatin (250-µg IV bolus followed by 250-µg/h infusion),[24,25] six studies used terlipressin (a bolus dose of 2 mg in five studies[22,26–28,30] or 2 mg/4 h for the first 24 hours in one study,[29] followed by 1 mg/6 h in five studies [22,26,27,29,30] or 1 mg/4 h in one study [28]), and one used either somatostatin or terlipressin.[23] The majority of patients included in the studies were males, and ethanol was the most common etiology of cirrhosis in most of the studies. The majority of the patients had Child-Pugh B or C cirrhosis classification. The definitions of rebleeding used in various studies are summarized in Supplementary Table 1. Risk of bias analysis using RoB 2 showed low evidence of bias in six studies,[22–25,29,30] some concern in four studies,[20,21,26,28] and a high risk of bias in one study[27] (Supplementary Fig. 1).

Pair-Wise Meta-Analysis

Five studies compared vasoconstrictor therapy that was stopped after EVL (0 hours) vs. vasoconstrictor therapy continued for 120

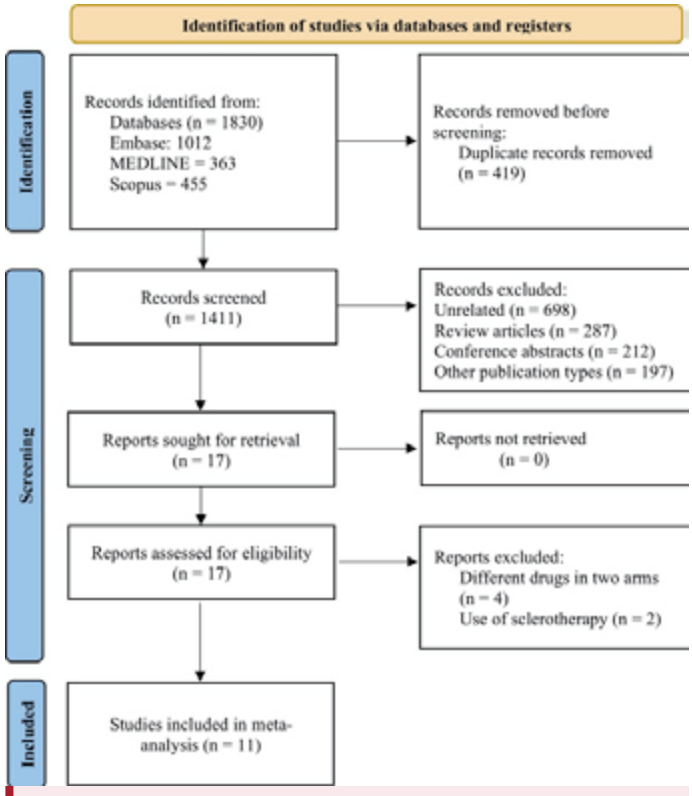


Figure 1. PRISMA flowchart for study identification, selection, and inclusion process. Shown is the process used to identify studies included in the analysis.

hours;[20,21,23,25,28] three compared 24 hours vs. 72 hours;[22,27,29] two compared 48 hours vs. 120 hours;[28,30] and one study each compared 12 hours vs. 72 hours[26] and 72 hours vs. 120 hours.[24] There was no difference in the risk of rebleeding at 5 days between the shorter duration (0–72 hours) and standard (72–120 hours) duration of vasoconstrictor therapy (RR 1.13, 95% CI: 0.67–1.91; I^2=16%) (Fig. 2). On subgroup analysis, there was no difference in the risk of rebleeding between vasoconstrictors for 0 vs. 120 hours (five studies) (RR 1.48, 95% CI: 0.55–3.97; I^2=53%) and 24 hours vs. 72 hours (three studies) (RR 0.84, 95% CI: 0.28–2.51; I^2 = 0%). Similarly, there was no difference in the risk of mortality between short-duration and standard-duration vasoconstrictors at 5 days (RR 0.91, 95% CI: 0.46–1.77; I^2=0%) (Supplementary Fig. 2) or 30 days (RR 1.05, 95% CI: 0.67–1.65; I^2=0%) (Supplementary Fig. 3). Subgroup analysis also showed no difference in mortality at 5 or 30 days.

Subgroup analysis based on the type of vasoconstrictor showed a higher risk of rebleeding with a short duration of octreotide (RR 4.45, 95% CI: 1.72–11.54; I^2=0%). However, there was no difference in the risk of rebleeding between short duration and standard duration for somatostatin and terlipressin (Supplementary Fig. 4). Comparison of AEs showed no difference between the shorter and standard duration in six studies,[21,22,24–26,30] while three studies showed a higher incidence of AEs with the standard duration of vasoconstrictors.[23,28,29] Comparative analysis could not be performed due to the non-uniform definition of AEs in the included studies.

Network Meta-Analysis

5-Day Rebleeding

All 11 studies reported on the rate of rebleeding at 5 days after EVL. There was no difference among vasoconstrictor groups (Group 1: ≤24 hours, Group 2: >24 to ≤72 hours, Group 3: >72 to ≤120 hours) on network estimate (Supplementary Table 2), with the very short duration and short duration having RR 1.36 (95% CI: 0.48–3.52) and RR 1.34 (95% CI: 0.42–4.54), respectively, compared to the standard duration group (Fig. 3). The SUCRA plot was generated from the ranking plot. Ranking based on SUCRAs accounts better for the uncertainty in the estimated treatment effects. Based on the SUCRA plot analysis for rebleeding, Group 3 was the best treatment for prevention of rebleeding at 5 days, with a SUCRA of 72.6, followed by Group 2 (40.5) and Group 1 (36.8) (Fig. 4) (certainty of evidence: very low).

5-Day Mortality

A total of 10 studies reported on mortality rates at 5 days after EVL. There was no difference among vasoconstrictor groups (as above) on network estimate (Supplementary Table 3), with the very short duration and short duration having RR 0.66 (95% CI: 0.09–2.52) and RR 1.08 (95% CI: 0.15–6.43), respectively, compared to the standard duration group (Fig. 3). Based on the SUCRA plot analysis for rebleeding, Group 1 was the best treatment for prevention of mortality at 5 days, with a SUCRA of 71.3, followed by Group 3 (41.1) and Group 2 (37.5) (Fig. 4). The certainty of evidence for the SUCRA ranking was moderate.

30-Day Mortality

A total of 10 studies reported data on the incidence of mortality at 30 days after EVL. There was no difference between the groups on network estimate (Supplementary Table 4), with the very short duration and short duration having RR 1.18 (95% CI: 0.51–2.51) and RR 0.98 (95% CI: 0.36–2.52), respectively, compared to the standard duration group (Fig. 3). Based on the SUCRA plot analysis for rebleeding, Group 2 was the best treatment for prevention of mortality at 30 days, with a SUCRA of 60.4, followed by Group 3 (57.9) and Group 1 (31.7) (Fig. 4). The certainty of evidence for the SUCRA ranking was moderate.

Publication Bias, Heterogeneity, Network Coherence, and Quality of Evidence

Funnel plot visual assessment did not show any evidence of significant publication bias (Supplementary Fig. 5). The estimated value of between-study variance for the network meta-analysis is 0.147 for the primary outcome, suggestive of no heterogeneity. The evaluation of inconsistency between the direct and indirect estimates for the primary outcome did not show any evidence of the same (Supplementary Table 5). The global test based on a random-effects design-by-treatment interaction model showed no evidence of inconsistency for any of the outcomes (p-value: 0.469 for the primary outcome). On analysis of individual durations (Supplementary Fig.

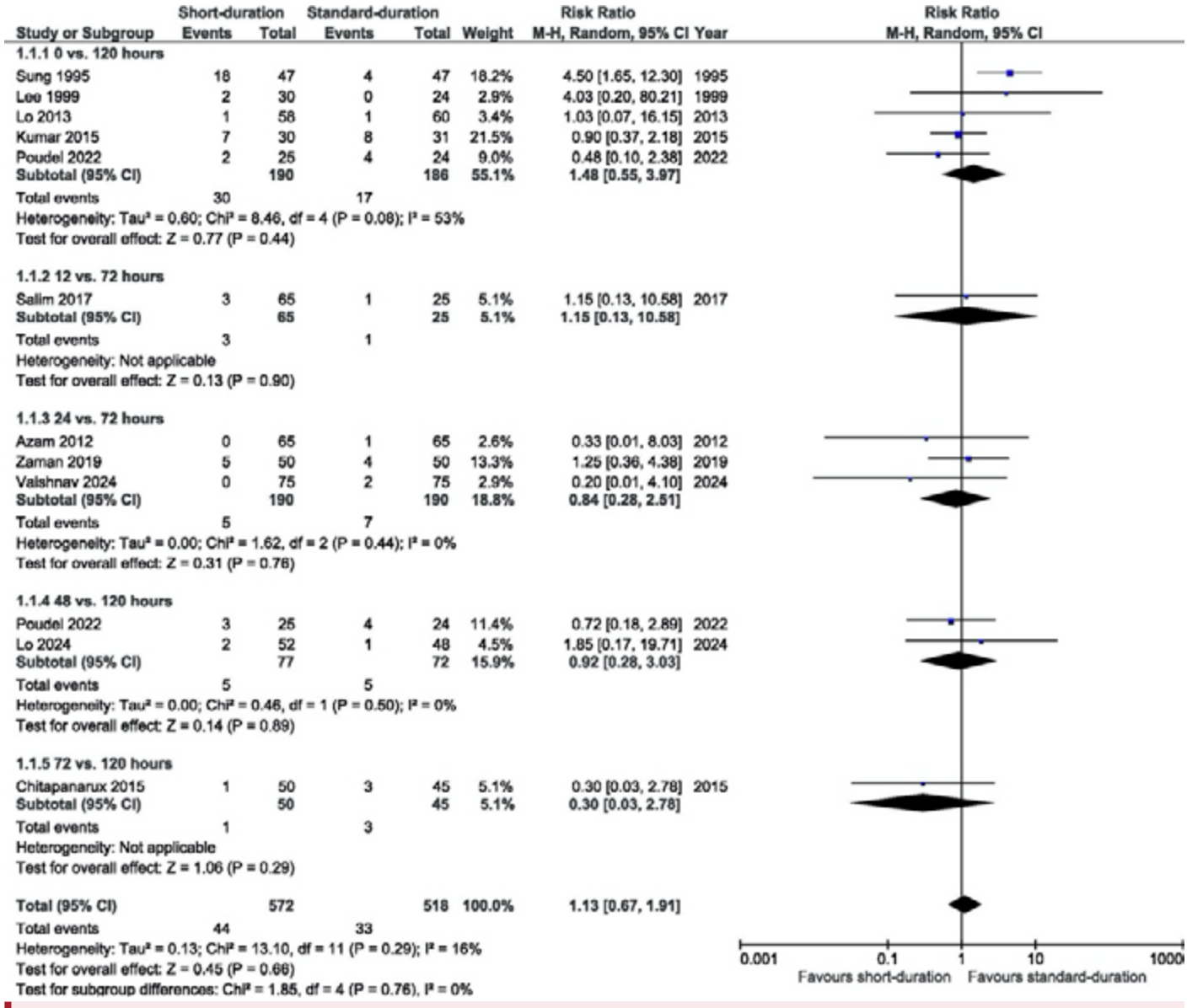


Figure 2. Forest plot comparing the risk of rebleeding at 5 days between short-duration vs. standard duration of vasoconstrictors with sub-group analysis.

6), there was no difference in the risk of rebleeding compared to 120 hours. SUCRA analysis showed that a duration of 24 hours was the best treatment for the prevention of rebleeding at 5 days (86.3), followed by 72 hours (67.6), 12 hours (55.9), 120 hours (41.8), 48 hours (27.5), and 0 hours (20.8) (Supplementary Fig. 7). Sensitivity analysis using leave-one-out analysis showed no difference in the effect. Table 2 displays the outcomes of treatment comparisons along with the quality of evidence.

Discussion

Current guidelines for the treatment of patients with AVB vary. The British guideline recommends giving terlipressin or somatostatin at presentation and continuing it for up to 5 days after successful hemostasis (the level of evidence reported in the guideline is 1a).[31] The most recent AASLD guideline recommends that treatment with vasoactive agents should then be stopped concurrently with the start of non-selective beta-blockers and not later than day 5.[32] The present network meta-analysis of 11 studies revealed no difference in the risk of rebleeding in patients who received vasoconstrictors for 0–24 hours (RR: 1.36, 95% CI: 0.48–3.52) and 24–72 hours (RR: 1.34, 95% CI: 0.42–4.54), compared to those receiving them for 72–120 hours. Similarly, there was no difference in mortality between the groups at either 5 or 30 days after EVL. Pair-wise analysis also did not show significant differences in various outcomes between short- and standard-duration vasoconstrictors. These findings are similar to the results of a recent individual patient data meta-analysis, which showed no difference in the rebleeding and mortality between the standard and shorter duration groups at 5 and 42 days.[33]

Table 2. Summary of findings table for the primary outcome comparing the duration of vasoconstrictors after endoscopic variceal ligation

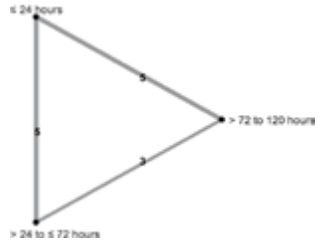
Population: Patients with cirrhosis and acute variceal bleeding undergoing endoscopic variceal ligation

Intervention: Very short (≤24 hours) and short (>24 and ≤72 hours) duration of vasoconstrictors

Comparator (reference): Standard duration (>72 to 120 hours) of vasoconstrictors

Primary outcome: Rebleeding within five days

Setting: Inpatient



Total studies: 11 RCTs **Total participants:** 1066	**Relative effect (95% CI)**	**Anticipated absolute effect**			**Certainty of evidence**	**Ranking (SUCRA)**	**Interpretation**
		Without intervention	**With intervention**	**Difference**			
Very short (≤24 hours) (5 RCTs; 363 patients)	1.36 (0.48-3.52)	75 per 1,000	102 per 1,000	27 more per 1,000 (39 fewer to 189 more)	●●○○ Low*¶	3 (36.8)	Probably inferior
Short (>24 to ≤72 hours) (3 RCTs; 244 patients)	1.34 (0.42-4.54)	75 per 1,000	100 per 1,000	25 more per 1,000 (44 fewer to 265 more)	●●○○ Low*¶	2 (40.5)	Probably inferior
Standard (>72 to 120 hours)	Reference comparator	Not estimable	Not estimable	Not estimable	Reference comparator	1 (72.6)	Reference comparator

Downgraded due to *Risk of bias ¶Imprecision.

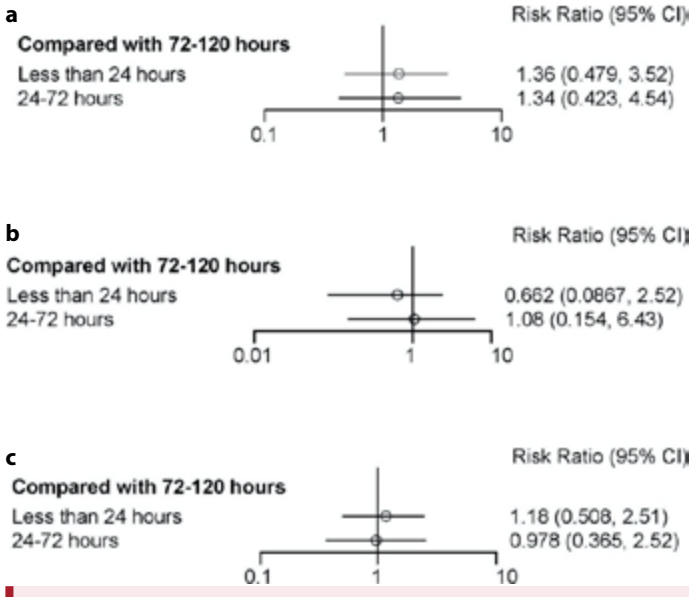


Figure 3. Bayesian Forest plots depicting the risk of different outcomes. **(a)** rebleeding, **(b)** mortality at 5 days, and **(c)** mortality at 30 days in different groups is shown [the duration of vasoconstrictor therapy is as follows: group 1 (≤24 hours) and group 2 (>24 and ≤72 hours)] and control group [group 3 (>72 to 120 hours)].

Bacterial infections are frequently associated with AVB in patients with cirrhosis. One study reported that bacterial infection was a significant and independent predictor of failure to achieve acute hemostasis in patients with cirrhosis and AVB.[34] Another study found that most infections occurred within the first 5 days of admission, with half occurring within the first 48 hours. Bacterial infection was associated with a higher requirement for blood transfusion and a higher incidence of rebleeding (43.5% vs. 9.8% in those without infection).[35] A previous meta-analysis reported a higher pooled incidence of bacteremia after sclerotherapy compared to EVL (17% vs. 6%). Again, the frequency of bacteremia after emergency sclerotherapy was significantly higher than after elective sclerotherapy (22% vs. 14%).[36] This could be responsible for the higher incidence of rebleeding after sclerotherapy in AVB, requiring continuation of vasoconstrictors, but not in patients undergoing EVL.

A previous study reported AEs in 50% of patients receiving terlipressin for variceal bleeding, the most common being electrolyte disturbances and hyponatremia. Other AEs included abdominal pain and cardiac dysrhythmia, requiring discontinuation of the drug. However, most of these AEs were either self-limited or improved after drug discontinuation.[37] One RCT included in the present analysis, using terlipressin, reported a significantly higher incidence of AE in the treatment group, with the most common AE being diarrhea, followed by hypokalemia and bradycardia.[28] The reported AEs with octreotide include gastrointestinal abnormalities, bradycardia, hypoglycemia, and hyperglycemia.[38] Thus, vasoconstrictors are associated with multiple different AEs, which not only limit their effectiveness but have the potential to cause harm. With the epidemiology shifting towards an increasing prevalence of metabolic dysfunction-associated steatotic liver disease-related cirrhosis,[39–41] more patients with variceal bleeding are likely to have cardiometabolic comorbidities, increasing the risk of AEs with vasoconstrictors, especially terlipressin.[42] We speculate that reducing the duration of vasoconstrictors will reduce the incidence of associated AEs and reduce cost. However, comparative analysis of the AEs could not be performed due to the absence of a uniform definition of AEs, requiring further studies.

It should be noted that in the studies included in this meta-analysis, patients in whom AVB could not be controlled endoscopically were excluded. Thus, it is possible that prolonged vasoconstrictor therapy, particularly terlipressin, could play a role in these patients. Multiple

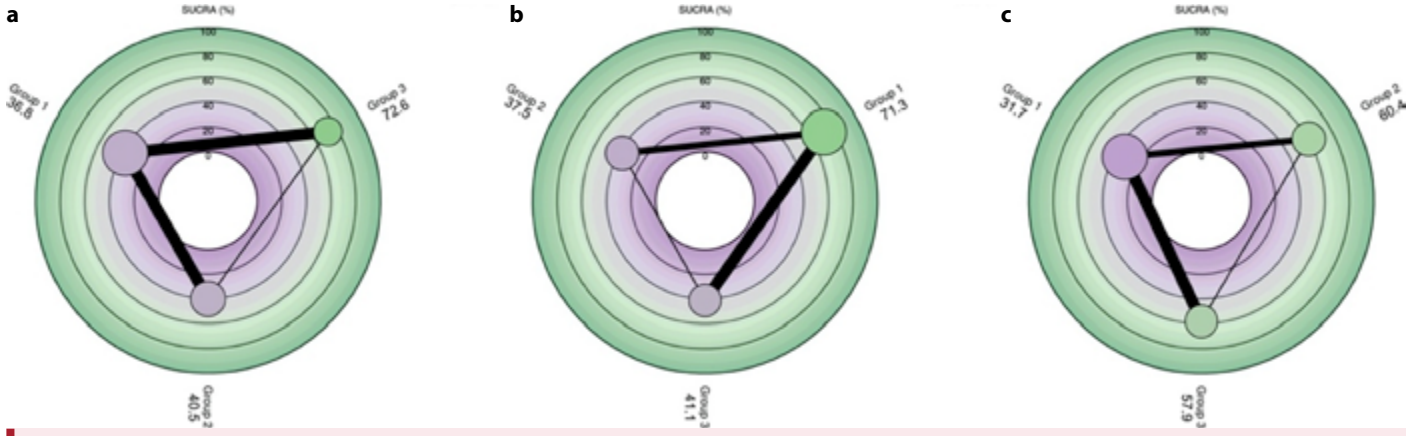


Figure 4. Radial surface under the cumulative ranking analysis (SUCRA) and network plots. Shown are plots for **(a)** rebleeding, **(b)** mortality at 5 days, and **(c)** mortality at 30 days. The number beside the groups indicates SUCRA values, where the groups represent different vasoconstrictor therapy durations. The duration of vasoconstrictor therapy is as follows: Group 1 (≤24 hours), group 2 (>24 and ≤72 hours), and group 3 (>72 to 120 hours). (The node size is in relation to the number of participants analyzed, while the lines connecting nodes indicate the network plot. The treatments are ranked radially based on their ranking score varying from 0-100.)

risk factors can contribute to the failure to control bleeding.[43] One study reported, in a predictive model of failure to control bleeding after sclerotherapy for AVB, that active bleeding at endoscopy was the strongest predictor of failure to control bleeding, as well as 30-day mortality.[44] Another study analyzed risk factors for failure to control bleeding after EVL for AVB and found that portal vein thrombosis and Child-Pugh C status with active bleeding on endoscopy were independent predictors of failure of emergency EVL.[45] Similarly, active bleeding on endoscopy, hypovolemic shock at presentation, and previous history of EVL (scars leading to insufficient suction) were found to be independent risk factors for failure to control bleeding after EVL.[46] Thus, patients at risk for failure to control bleeding may be best served by the continuation of vasoconstrictors, though further studies are required in this small subgroup of patients.

The strength of the present analysis is that it included only RCTs. Also, we conducted both pair-wise as well as network meta-analyses to increase the robustness of the results. Despite this, there are limitations that should be kept in mind. First, there was a significant variation in the duration of vasoconstrictors administered, which forced us to define the duration of therapy as "short" vs. "standard." Second, there were differences in the type of vasoconstrictor used in various studies, along with variation in the dosage and timing (Table 1). Although this is a concern, it should be noted that a previous meta-analysis reported no difference between the vasoconstrictors (terlipressin vs. somatostatin vs. octreotide) in terms of rebleeding after initial hemostasis for AVB.[47] Third, there was variation in the proportion of patients with Child-Pugh B or C status among studies. However, given that patients in all of the studies included were randomized, it is unlikely that there were imbalances within individual studies. Fourth, all of the studies included were from Asian medical centers, which, in theory, could limit generalizability to Western medical centers. It is notable, however, that a recent, small, multicenter U.S. study found no difference in rebleeding or mortality in trials of 24 vs. 72 hours of octreotide, suggesting that the data here are more widely generalizable.[48] Fifth, there was some heterogeneity in the definition of rebleeding, which could impact the validity of pooled estimates (Supplementary Table 1). Sixth, since the studies included in this meta-analysis did not report on hospital length of stay, we could not comment on this outcome. Nonetheless, we speculate that shorter treatment duration with vasoconstrictors in patients with AVB is likely to reduce hospital length of stay, consistent with a recent study that found that patients receiving 24 hours of octreotide therapy in AVB had shorter hospital length of stay than patients receiving 72 hours of octreotide therapy.[48] Seventh, many SUCRA rankings are based on low to moderate certainty of evidence, requiring cautious interpretation of the results. Lastly, a cost-effectiveness analysis could not be performed due to the unavailability of data regarding the same in the included studies.

Conclusion

In conclusion, the present network meta-analysis showed that rebleeding and mortality were similar for short or longer durations of vasoconstrictor therapy in patients with cirrhosis and AVB. The study further emphasized that there is a lack of quality evidence to support the prolonged use of vasoconstrictors after EVL. Given these data, clinical practice should evolve to discontinuing vasoconstrictors early after EVL, facilitating early discharge from the hospital and reducing the cost and burden on healthcare facilities. The most appropriate time for early discontinuation requires further study, and additional studies are required to identify the subset of patients at risk for failure to control bleeding who might benefit from the continuation of vasoconstrictors.

Online Appendix Link: https://file.paplino.com/hepatologyforum/files/1785250650-appendix-en.pdf

Conflict of Interest: There are no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: The authors declare that they have not used any AI tools or technologies to prepare this manuscript.

Author Contributions: Concept: SG, AC; Design: SG, SI, AC; Supervision: SG, EBT, DCR, AC; Materials: SG, SP, AS, JV, SI; Data Collection and/or Processing: SG, SP, AS, JV, SI; Analysis and/or Interpretation: SG, AS; Literature Search: SG, SP, AS, JV, SI; Writing: SG, AS; Critical Reviews: SG, SP, AS, JV, SI, EBT, DCR, AC.

Peer-review: Externally peer-reviewed.

References

1. Sharara AI, Rockey DC. Gastroesophageal variceal hemorrhage. N Engl J Med 2001;345(9):669-681. [CrossRef]
2. Garcia-Tsao G, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. N Engl J Med 2010;362(9):823-832. [CrossRef]
3. Augustin S, Altamirano J, González A, Dot J, Abu-Suboh M, Armengol JR, et al. Effectiveness of combined pharmacologic and ligation therapy in high-risk patients with acute esophageal variceal bleeding. Am J Gastroenterol 2011;106(10):1787-1795. [CrossRef]
4. Amitrano L, Guardascione MA, Manguso F, Bennato R, Bove A, DeNucci C, et al. The effectiveness of current acute variceal bleed treatments in unselected cirrhotic patients: refining short-term prognosis and risk factors. Am J Gastroenterol 2012;107(12):1872-1878. [CrossRef]
5. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C; Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol 2022;76(4):959-974. [CrossRef]
6. Dai C, Liu WX, Jiang M, Sun MJ. Endoscopic variceal ligation compared with endoscopic injection sclerotherapy for treatment of esophageal variceal hemorrhage: a meta-analysis. World J Gastroenterol 2015;21(9):2534-2541. [CrossRef]
7. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding. A meta-analysis. Ann Intern Med 1995;123(4):280-287. [CrossRef]
8. Bañares R, Albillos A, Rincón D, Alonso S, González M, Ruiz-del-Arbol L, et al. Endoscopic treatment versus endoscopic plus pharmacologic treatment for acute variceal bleeding: a meta-analysis. Hepatology 2002;35(3):609-615. [CrossRef]
9. Zuberi BF, Baloch Q. Comparison of endoscopic variceal sclerotherapy alone and in combination with octreotide in controlling acute variceal hemorrhage and early rebleeding in patients with low-risk cirrhosis. Am J Gastroenterol 2000;95(3):768-771. [CrossRef]
10. Lo GH, Lai KH, Cheng JS, Lin CK, Huang JS, Hsu PI, et al. Emergency banding ligation versus sclerotherapy for the control of active bleeding from esophageal varices. Hepatology 1997;25(5):1101-1104. [CrossRef]
11. Escorsell A, Bandi JC, Andreu V, Moitinho E, García-Pagán JC, Bosch J, et al. Desensitization to the effects of intravenous octreotide in cirrhotic patients with portal hypertension. Gastroenterology 2001;120(1):161-169. [CrossRef]
12. Shang Y, Wang C, Lu H, Chai L, Xu W, Bernardi M, et al. Incidence and type of adverse events in patients with cirrhosis receiving terlipressin: A systematic review and meta-analysis. Hepatol Commun 2024;8(5):e0526. [CrossRef]
13. Hutton B, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 2015;162(11):777-784. [CrossRef]
14. Higgins JP, Altman DG, Gotzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomized trials. BMJ 2011;343(7829):d5928. [CrossRef]
15. Puhan MA, Schünemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al; GRADE Working Group. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. BMJ 2014;349:g5630. [CrossRef]
16. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004;23(20):3105-3124. [CrossRef]
17. Higgins JP, Thompson SG, Spiegelhalter DJ. A re-evaluation of random-effects meta-analysis. J R Stat Soc Ser A Stat Soc 2009;172(1):137-159. [CrossRef]
18. Nevill CR, Cooper NJ, Sutton AJ. A multifaceted graphical display, including treatment ranking, was developed to aid interpretation of network meta-analysis. J Clin Epidemiol 2023;157(5):83-91. [CrossRef]
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629-634. [CrossRef]
20. Sung JJY, Lai CW, Lee YT, Leung VKS, Li MKK, Chung SCS, et al. Prospective randomised study of effect of octreotide on rebleeding from oesophageal varices after endoscopic ligation. Lancet 1995;346(8987):1666-1669. [CrossRef]
21. Lee GH, Cho SW, Kim HJ, Ko KH, Ko YY, Ko JH, et al. Endoscopic variceal ligation plus octreotide versus variceal ligation alone for the prevention of early rebleeding from esophageal varices. Korean J Hepatol 1999;5(4):299-305.
22. Azam Z, Hamid S, Jafri W, Salih M, Abbas Z, Abid S, et al. Short course adjuvant terlipressin in acute variceal bleeding: A randomized double blind dummy controlled trial. J Hepatol 2012;56(4):819-824. [CrossRef]
23. Lo GH, Perng DS, Chang CY, Tai CM, Wang HM, Lin HC. Controlled trial of ligation plus vasoconstrictor versus proton pump inhibitor in the control of acute esophageal variceal bleeding. J Gastroenterol Hepatol 2013;28(4):684-689. [CrossRef]
24. Chitapanarux T, Ritdamrongthum P, Leerapun A, Pisespongsa P, Thongsawat S. Three-day versus five-day somatostatin infusion combination with endoscopic variceal ligation in the prevention of early rebleeding following acute variceal hemorrhage: A randomized controlled trial. Hepatol Res 2015;45(13):1276-1282. [CrossRef]
25. Kumar A, Jha SK, Mittal VV, Sharma P, Sharma BC, Sarin SK. Addition of somatostatin after successful endoscopic variceal ligation does not prevent early rebleeding in comparison to placebo: A double blind randomized controlled trial. J Clin Exp Hepatol 2015;5(3):204-212. [CrossRef]
26. Salim A, Malik K, Haq IU, Butt AK, Alam A. Comparison of 12-hour with 72-hour terlipressin therapy for bleeding esophageal varices. J Coll Physicians Surg Pak 2017;27(5):334-337.
27. Zaman M, Zaidi AR, Hyder A, Kumar M, Amin J, Malik K. Frequency of rebleeding between short course terlipressin different courses (24 hours) and usual course (72 hours) terlipressin in adult cirrhotic patients presenting with acute variceal rebleeding. Med Forum Mon 2019;30(8):130-133.
28. Poudel RC, Dhibar DP, Sharma N, Sharma V, Taneja S, Prakash A. Rational for continuing terlipressin after endoscopic variceal ligation in acute variceal haemorrhage needs further evidence: A pilot study. Arq Gastroenterol 2022;59(1):89-96. [CrossRef]

29. Vaishnav M, Biswas S, Shenoy A, Pathak P, Anand A, Swaroop S, et al. Comparison of 1-day versus 3-day intravenous terlipressin in cirrhosis patients with variceal bleeding: A pilot randomised controlled trial. Aliment Pharmacol Ther 2024;59(5):645-655. [CrossRef]
30. Lo GH, Yeh JH, Tseng CH, Chen TH, Tai CM, Wang WL, et al. A noninferiority trial comparing 2 days vs 5 days of terlipressin and ceftriaxone in terms of 5-day rebleeding for patients with acute gastroesophageal variceal hemorrhage. Am J Gastroenterol 2024;119(8):e63-e74. [CrossRef]
31. Tripathi D, Stanley AJ, Hayes PC, Patch D, Millson C, Mehrzad H, et al. Guidelines - UK guidelines on the management of variceal haemorrhage in cirrhotic patients. Clinical Services and Standards Committee of the British Society of Gastroenterology. Gut 2015;64(11):1680-1704. [CrossRef]
32. Kaplan DE, Ripoll C, Thiele M, Fortune BE, Simonetto DA, Garcia-Tsao G, et al. Practice Guidelines - AASLD practice guidance on risk stratification and management of portal hypertension and varices in cirrhosis. Hepatology 2024;79(5):1180-1211. [CrossRef]
33. Biswas S, Lo GH, Mehta S, Elhence A, Wong YJ, Vaishnav M, et al. Abbreviated duration of vasoactive agents has similar outcomes as standard duration of therapy in patients with liver cirrhosis and variceal bleeding: An individual patient data meta-analysis. Dig Dis Sci 2025;70(5):1201-1214. [CrossRef]
34. Goulis J, Armonis A, Patch D, Sabin C, Greenslade L, Burroughs AK. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. Hepatology 1998;27(5):1207-1212. [CrossRef]
35. Bernard B, Cadranel JF, Valla D, Escolano S, Jarlier V, Opolon P. Prognostic significance of bacterial infection in bleeding cirrhotic patients: A prospective study. Gastroenterology 1995;108(6):1828-1834. [CrossRef]
36. Jia Y, Dwivedi A, Elhanafi S, Ortiz A, Othman M, Zuckerman M. Low risk of bacteremia after endoscopic variceal therapy for esophageal varices: A systematic review and meta-analysis. Endosc Int Open 2015;3(4):E409-E417. [CrossRef]
37. Zhang J, Zhou X, Zhao H, Deng J, Qi X. Adverse events of terlipressin in liver cirrhosis with acute gastrointestinal bleeding: A clinical pharmacist's real-world observational study. Dig Med Res 2018;1(1):2. [CrossRef]
38. Debnath D, Cheriyath P. Octreotide. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
39. Swaroop S, Vaishnav M, Arora U, Biswas S, Aggarwal A, Sarkar S, et al. Etiological spectrum of cirrhosis in India: A systematic review and meta-analysis. J Clin Exp Hepatol 2024;14(8):101291. [CrossRef]
40. Giri S, Ingawale S, Khatana G, Gore P, Praharaj DL, Wong VW, et al. Metabolic cause of cirrhosis is the emerging etiology for primary liver cancer in the Asia-Oceania region: Analysis of Global Burden of Disease (GBD) Study 2021. J Gastroenterol Hepatol 2025;40(6):1188-1201. [CrossRef]
41. Huang DQ, Terrault NA, Tacke F, Gluud LL, Arrese M, Bugianesi E, et al. Global epidemiology of cirrhosis - aetiology, trends and predictions. Nat Rev Gastroenterol Hepatol 2023;20(6):388-398. [CrossRef]
42. Krag A, Bendtsen F, Mortensen C, Henriksen JH, Møller S. Effects of a single terlipressin administration on cardiac function and perfusion in cirrhosis. Eur J Gastroenterol Hepatol 2010;22(9):1085-1092. [CrossRef]
43. Giri S, Sundaram S, Jearth V, Bhrugumalla S. Predictors of early bleeding after endoscopic variceal ligation for esophageal varices: A systematic review and meta-analysis. Clin Exp Hepatol 2022;8(3):267-277. [CrossRef]
44. Ben-Ari Z, Cardin F, McCormick AP, Wannamethee G, Burroughs AK. A predictive model for failure to control bleeding during acute variceal haemorrhage. J Hepatol 1999;31(3):443-450. [CrossRef]
45. Liu K, Zhang R, Shi C, Wu B, Liu S, Tian H, et al. Risk factors for emergency endoscopic variceal ligation treatment failure of acute variceal bleeding. Scand J Gastroenterol 2022;57(12):1509-1516. [CrossRef]
46. Kim DH, Cho E, Jun CH, Son DJ, Lee MJ, Park CH, et al. Risk factors and on-site rescue treatments for endoscopic variceal ligation failure. Korean J Gastroenterol 2018;72(4):188-196. [CrossRef]
47. Wang C, Han J, Xiao L, Jin CE, Li DJ, Yang Z. Efficacy of vasopressin/terlipressin and somatostatin/octreotide for the prevention of early variceal rebleeding after the initial control of bleeding: A systematic review and meta-analysis. Hepatol Int 2015;9(1):120-129. [CrossRef]
48. Allam J, De Melo S, Feagins LA, Agrawal D, Malespin M, Shuja A, et al. Comparison of 24 vs 72-hour octreotide infusion in acute esophageal variceal hemorrhage - a multi-center, randomized clinical trial. Am J Med Sci 2024;368(3):267-275. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 227–235 DOI: 10.14744/hf.2026.65328

SYSTEMATIC REVIEW

Large language models in hepatology: A systematic review

Thanathip Suenghataiphorn[1], Narisara Tribuddharat[2], Pojsakorn Danpanichkul[3], Narathorn Kulthamrongsri[4]

1: Department of Internal Medicine, Griffin Hospital, Derby, CT, United States
2: St. Elizabeth Medical, Boston, MA, United States
3: Department of Internal Medicine, Texas Tech University Health Science Center, Lubbock, TX, United States
4: University of Hawaii, Honolulu, HI, United States

Points to Note

- **Synthesis of Current Evidence:** Generative AI and Large Language Models are being integrated into hepatology. Evidence is fragmented, with limited clinical evaluations. A shift is occurring from basic retrieval to advanced uses like data classification and radiological interpretation.
- **Major Controversies:** Concerns about inaccuracies, transparency, and biases in LLM outputs. Clinical safety of generative AI tools in hepatology is uncertain.
- **Future Directions:** Research should focus on data privacy, dataset quality, and clinical validation. Real-world studies are needed for safe integration.

ABSTRACT

Background and Aim: The rapid advancement of generative artificial intelligence (AI), particularly large language models (LLMs), has opened new frontiers in healthcare, with emerging implications for hepatology. This systematic review synthesizes the current state of research on the application of LLMs in hepatology, focusing on their capabilities in real-world clinical settings, limitations, and future directions.

Materials and Methods: Electronic databases, including MEDLINE, EMBASE, and OVID as a search platform, were used to identify eligible studies from inception to January 2025. Eligible studies investigated the clinical utility and performance of LLMs in hepatology, with a clear comparison to a defined ground truth. Key findings were extracted and synthesized narratively. The ROBINS-I tool was used to assess the risk of bias in each study.

Results: Twenty-one studies were included in this review. Our analysis reveals that LLMs demonstrate promising capabilities in processing textual and visual data related to various liver diseases, including hepatocellular carcinoma, cirrhosis, and non-alcoholic fatty liver disease. LLMs effectively assisted with radiological image interpretation, provided clinical decision support, and generated patient education materials. However, the accuracy of these models was highly variable, depending on the specific task and the complexity of the clinical scenario. Limitations, such as the generation of inaccurate or misleading information ("hallucinations"), dependence on training data quality, and ethical considerations, were identified across multiple studies.

Conclusion: Generative AI demonstrates feasibility across various hepatology applications, but study heterogeneity and significant challenges remain regarding accuracy, reliability, and safety. Future integration necessitates further research into training methods, data quality, ethical considerations, and real-world validation against standardized benchmarks.

Keywords: Generative AI, hepatology, large language models, liver, systematic review.

How to cite this article: Suenghataiphorn T, Tribuddharat N, Danpanichkul P, Kulthamrongsri N. Large language models in hepatology: A systematic review. Hepatology Forum 2026; 7(3):227–235.

Received: November 24, 2024; **Revised:** September 22, 2025; **Accepted:** January 19, 2026; **Available Online:** April 07, 2026

Corresponding author: Thanathip Suenghataiphorn; Department of Internal Medicine, Griffin Hospital, Derby, CT; 130 Division St, Derby, CT, United States; **E-mail:** thanathip.sue@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

The healthcare sector is undergoing a significant transformation, driven by the rapid advancement and integration of cutting-edge technologies.[1] Among these, artificial intelligence (AI) stands out, particularly through the development and application of large language models (LLMs).[2] Large language models are typically built on a transformer architecture, which allows them to process vast amounts of text data, identify complex patterns, and generate human-like text by predicting subsequent words in a sequence. Unlike traditional machine learning models that often require structured data, LLMs can work with unstructured narrative text, making them uniquely suited for tasks in the medical domain. These sophisticated systems, capable of processing and generating human-quality text and complex data, are poised to revolutionize numerous medical fields by enhancing diagnostic methodologies, refining treatment protocols, and elevating patient care standards.

Hepatology, a critical field focused on the diagnosis and treatment of liver diseases, presents unique opportunities for the integration of these technologies.[3] The field faces numerous challenges, including inter-observer variability in diagnostics, labor-intensive documentation, the need for personalized treatment strategies, and the constant need for clinicians to stay abreast of the latest research and guidelines.[4] LLMs offer the potential to address these challenges through their automation and processing capabilities. While traditional machine learning models in hepatology have addressed some limitations of human analysis,[5] LLMs, with their ability to process massive datasets, are expected to address a wider range of clinical unmet needs, as seen in other diseases.[6] These include enhancing diagnostic support, especially in complex cases like hepatocellular carcinoma (HCC) and metabolic dysfunction-associated steatotic liver disease (MASLD); automating the generation of clinical reports; tailoring patient education to individual needs; and potentially identifying novel research questions by processing vast amounts of literature.

Given the rapid proliferation of these tools, a comprehensive evaluation of the current literature is necessary to understand how LLMs are impacting hepatology. This systematic review seeks to examine the emerging applications of LLMs in this field, focusing on their real-world clinical utility. Specifically, this systematic review aims to understand the specific applications of LLMs in hepatology that have been investigated, the limitations and risks associated with using LLMs in hepatology, as well as the ethical considerations surrounding the use of LLMs in the hepatology field, particularly regarding data privacy, transparency, and bias. Through this exploration, we aim to contribute to the broader understanding of how AI and LLMs can be effectively and ethically integrated into healthcare, ultimately improving patient outcomes and advancing the field of hepatology.

Materials and Methods

Search Strategy & Eligibility

Two investigators (TS and NT) independently conducted searches in PubMed and Embase (via the Ovid platform) from inception through 20 January 2025, using the search strategy specified in Supplementary Table 1. The investigators (TS and NT) independently assessed the eligibility of the retrieved records. Any conflicts were resolved through further discussions involving a third investigator (PD). The protocol was designed based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA) checklist, as seen in Supplementary Table/Material 2.[7] The protocol was preregistered (PROSPERO: 643605). Studies were included if they satisfied the following criteria: (1) any type of studies that investigated the potential role of LLMs in the field of hepatology, (2) studies published in English, and (3) studies in full-text format. The exclusion criteria were: (1) studies that did not report on the direct application or role of LLMs in clinical hepatology (e.g., studies focusing solely on technical development without clinical application); (2) case reports, review papers, and editorials; (3) studies involving non-human subjects (e.g., animal or basic research); and (4) studies with insufficient data regarding the evaluation of LLMs in a hepatology context. Only publications conducted on human participants were included. The bibliographies of relevant papers were also reviewed to identify additional studies. No restrictions were applied regarding age, sex, or country of origin. The novelty of the current frontiers of application precluded a quantitative meta-analysis, which may provide misleading information due to its preliminary state.

Data Extraction

To ensure consistency and rigor, we implemented a standardized data collection protocol across all included studies. This protocol facilitated the systematic extraction of key variables pertinent to our research objectives. Extracted data included demographic information (first author's surname, country of study, year of publication), the primary AI/LLM model used, the study's topic and aims, evaluation criteria, the population or data source, the method of applying the LLM, the ground truth used for comparison, any other LLM models used in the study, and the main outcomes reported. A large language model (Gemini) was utilized solely to assist in summarizing long abstracts for readability; however, all inclusion and exclusion decisions were made manually by the human reviewers. No studies were excluded based on AI screening alone. Full-text review was subsequently performed manually by the same investigators.

Ethical Statement

This study is a systematic review based entirely on previously published, publicly available data. Therefore, it did not involve direct contact with human participants or animals, and formal ethical approval from an Institutional Review Board or Ethics Committee was not required for this specific analysis. We adhered rigorously to established systematic review methodologies to ensure transparency, objectivity, and accuracy in selecting, extracting, synthesizing, and reporting findings from the included studies. All source materials have been appropriately cited, upholding academic integrity throughout the research process.

Table 1A. LLM performance in information retrieval and patient education

First author	Citation	AI model	Study topic	Population / query source	Reference standard (comparator)	Outcome / expert rating
Cao	[9]	ChatGPT 3.5	Liver cancer screening	20 questions	Fellowship-trained Physicians	5/20 Reliable, 15/20 Unreliable
Endo	[10]	ChatGPT	Liver transplantation	29 questions	17 Experts in Transplant Surgery	76% rated "Very Good" or "Excellent"
Samaan	[11]	ChatGPT	Arabic General Hepatology	91 questions	Expert Transplant Hepatologist	72% correct response; 24% comprehensive
Yeo	[12]	ChatGPT 3.5	Cirrhosis & HCC	91 questions	Two Transplant Hepatologists	41-47% of responses deemed comprehensive
Cao	[14]	Multiple	HCC diagnosis/ management	20 questions	Six Fellowship-trained Physicians	No significant difference in accuracy between models
Colapietro	[15]	ChatGPT 4	Autoimmune Hepatitis	12 questions	11 Key Opinion Leaders	Median accuracy score 5/6; Safety 3/3
Daza	[16]	Multiple	Autoimmune liver disease	56 questions	10 Liver Specialists	Claude highest score (7.37/10); ChatGPT (7.17/10)
Ge	[13]	Liversa (RAG)	General Hepatology	20 questions	15 Board-Certified Hepatologists	No definitive superior AI model identified
Pradhan	[18]	Multiple	Cirrhosis Education	5 educational materials	8 Hepatologists & 14 Patients	All materials met 8th-grade reading ease goal
Pugliese	[19]	ChatGPT	MASLD	15 questions	13 MASLD Experts	Accuracy score 4.57/6 on Likert scale
Pugliese	[20]	ChatGPT	NAFLD	15 questions	10 Key Opinion Leaders	Accuracy score 4.84/6; Completeness 2.08/3
Malik	[21]	GPT-4 + RAG	Acute Liver Failure	16 questions	4 Independent Investigators	GPT-4 with RAG scored highest (4.70/5)
Zhang	[22]	Multiple	Steatotic Liver Disease	30 queries	3 Attending Physicians	GPT-4 provided 96.7% "appropriate" responses

Table 1B. LLM performance in diagnostics and image classification

First author	Citation	AI model	Task	Ground truth (objective)	Performance metrics
Zhang	[23]	ChatGPT-4	NAFLD histology ID	Biopsy (pathology database)	GPT-4 Accuracy: 87.5% vs. Bard: 38.3%
Zhang	[41]	ChatGPT-4	CT Abnormality detection	Radiopaedia cases	Accuracy: 54%; Sensitivity: 64%; Specificity: 30%
Wu	[26]	Multiple	LI-RADS categorization	Radiology reports	GPT-4 and Claude-2 superior for LI-RADS v2018
Wu	[27]	GPT-4	MASLD diagnosis	NHANES data (FLI/USFLI)	GPT-4 AUROC: 0.831 (comparable to Fatty Liver Index)

Table 1C. LLM utility in research and clinical data extraction

First author	Citation	AI model	Task	Comparator / method	Key outcome
Ge	[17]	GPT-3.5 Turbo	Data extraction (Imaging)	Manual chart review	Accuracy: 88.9% for extracting key data elements
Akabane	[24]	ChatGPT 4	Novel idea Generation	Expert panel grading	Ideas scored 67.6% for relevance/ impact
Far	[25]	GPT-4	Phenotyping (Cirrhosis)	Gold standard chart review	87.8%–98.8% accuracy for identifying cirrhosis
Geevarghese	[28]	GPT	Pathology data extraction	Manual curation / REGEX	High accuracy (84.1%–94.8%), comparable to REGEX

Data Synthesis

Due to the heterogeneity in the specified aims and methodologies of the included studies, a narrative synthesis approach was employed. This involved a qualitative synthesis of the findings, categorized by the specific applications of LLMs, their performance, limitations, and ethical considerations.

Methodological Quality Assessment

The quality of the included studies was assessed using the ROBINS-I tool,[8] which is designed for evaluating the risk of bias in non-randomized studies. This tool examines seven domains where bias can occur: confounding, participant selection, intervention classification, deviations from intended interventions, missing data, outcome measurement, and selective reporting of results. Each domain is rated as having a "low," "moderate," "serious," or "critical" risk of bias. The overall risk of bias for each study was determined by considering the highest risk rating across all domains. For instance, if a study had a "serious" risk in one domain and "moderate" or "low" in others, the overall risk was considered "serious." Two reviewers (TS and NT) independently assessed each study, and any disagreements were resolved through discussion or with the assistance of a third reviewer (PD).

Results

Our search strategy identified 1039 records. After removing 146 duplicates, we reviewed these studies by title and abstract, excluding 868 studies that did not meet the eligibility criteria related to study design or participants. Subsequently, we thoroughly reviewed 25 articles and excluded 4 for reporting a different topic/domain. Ultimately, 21 studies met the eligibility criteria for our systematic review.[9–28] Figure 1 illustrates our search methodology and selection process, and the characteristics and key findings of each included study are detailed in Table 1A–C.

The included studies investigated a variety of LLMs, including GPT-3.5, GPT-4, Claude-2, Google Bard, and fine-tuned models like Liversa (a RAG and GPT-3.5/4 customized model). These models were applied to a range of tasks within hepatology, broadly categorizable into three main areas: (1) information retrieval and question answering, (2) clinical data extraction and classification, and (3) novel idea generation.

Information Retrieval and Question Answering

Several studies evaluated the ability of LLMs to retrieve accurate and relevant information related to liver diseases, including liver cancer screening, liver transplantation, cirrhosis, autoimmune hepatitis, and steatotic liver disease.[10,12,14–16,19–22] These studies generally found that LLMs, particularly more recent models like GPT-4, could provide answers that were often comparable to those of fellowship-trained physicians or experts in hepatology. For instance, ChatGPT's responses to questions about liver transplantation were deemed "very good" or "excellent" in 76% of cases by a panel of transplant surgery experts.[10]

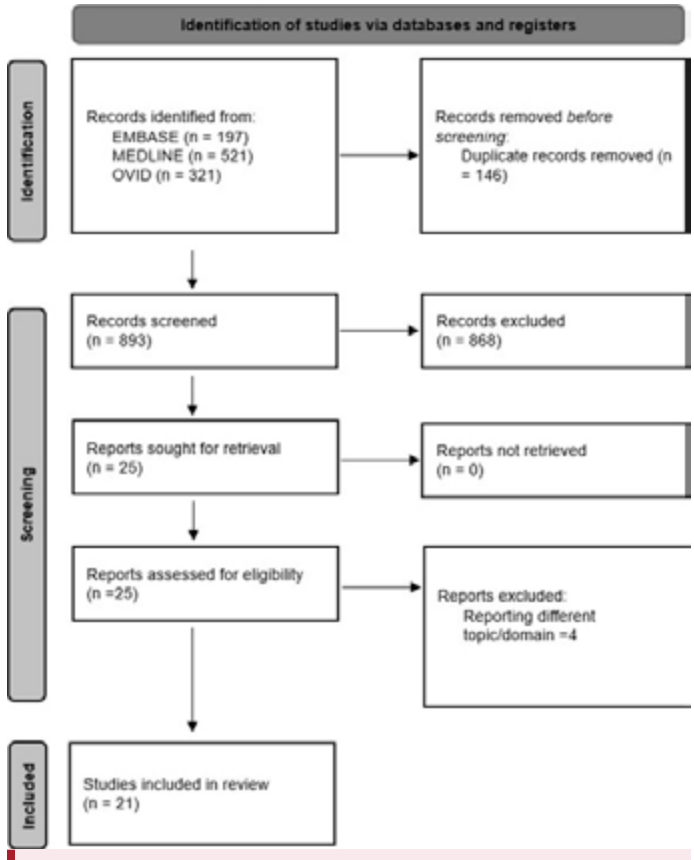


Figure 1. PRISMA diagram of the study.

Similarly, LLMs demonstrated the ability to provide comprehensive information on cirrhosis and HCC, although they sometimes struggled with specific decision-making cut-offs and treatment durations.[12] However, several studies also reported instances where LLMs provided incorrect, outdated, or incomplete information, particularly when dealing with nuanced clinical scenarios or questions requiring up-to-date knowledge of specific guidelines.[12,23]

Clinical Data Extraction and Classification

A subset of studies focused on the ability of LLMs to extract and classify clinical data from unstructured text sources, such as radiology reports, discharge summaries, and pathology reports.[13,18,25–28] These studies demonstrated that LLMs could achieve high accuracy in identifying and classifying various liver conditions, including cirrhosis, its complications, and different types of liver lesions. For example, one study reported that GPT-4 achieved 87.8%–98.8% accuracy in identifying cirrhosis and its complications from discharge summaries.[25] Another study found that LLMs could extract structured data elements from liver imaging reports with accuracy comparable to manual chart review.[13] Furthermore, LLMs showed promise in identifying metabolic dysfunction-associated steatotic liver disease (MASLD) from CT images and classifying liver imaging findings according to the Liver Imaging Reporting and Data System (LI-RADS).[26,27]

Table 2. Risk of bias evaluation (ROBINS-I assessment tool)

	Author	Citation	Pre-intervention/intervention bias			Post-Intervention Bias			
			Confounding	Participant selection	Classification	Deviations	Missing	Measurement	Result selection
1	Cao	[9]	Low	Low	Low	Low	Low	Low	Low
2	Endo	[10]	Low	Low	Low	Low	Low	Low	Low
3	Samaan	[11]	Low	Low	Low	Low	Low	Moderate	Low
4	Yeo	[12]	Low	Low	Low	Low	Low	Low	Low
5	Ge	[13]	Low	Low	Low	Low	Low	Low	Low
6	Cao	[14]	Low	Low	Low	Low	Low	Low	Low
7	Colapietro	[15]	Low	Low	Low	Low	Low	Moderate	Low
8	Daza	[16]	Low	Low	Low	Low	Low	Low	Low
9	Ge	[17]	Low	Low	Low	Low	Low	Low	Low
10	Pradhan	[18]	Low	Low	Low	Low	Low	Low	Low
11	Pugliese	[19]	Low	Low	Low	Low	Low	Low	Low
12	Pugliese	[20]	Low	Low	Low	Low	Low	Low	Low
13	Malik	[21]	Low	Low	Low	Low	Low	Low	Low
14	Zhang	[22]	Low	Low	Low	Low	Low	Low	Low
15	Akabane	[24]	Low	Low	Low	Low	Low	Low	Low
16	Zhang	[23]	Low	Low	Low	Low	Low	Low	Low
17	Zhang	[41]	Low	Low	Low	Low	Low	Moderate	Low
18	Far	[25]	Low	Low	Low	Low	Low	Low	Low
19	Wu	[26]	Low	Low	Low	Low	Low	Moderate	Low
20	Wu	[27]	Low	Low	Low	Low	Low	Low	Low
21	Geevarghese	[28]	Low	Low	Low	Low	Low	Low	Low

Novel Idea Generation

One study explored LLMs' capabilities to generate novel clinical research ideas in the field of liver transplantation.[24] While this application is still in its early stages, the study found that an LLM could generate research ideas that were considered relevant and potentially impactful by medical doctors specializing in liver transplantation, achieving an average score of 67.6% on a standardized evaluation scale.

Methodological Quality and Risk of Bias

The overall methodological quality of the included studies was variable. The risk of bias assessment for each study using the ROBINS-I tool is presented in Table 2. Based on the ROBINS-I assessment, the majority of studies had a low risk of bias across most domains (Table 2). However, several studies exhibited a moderate risk of bias in the domains of outcome measurement and selective reporting of results. This risk stemmed from the use of subjective evaluation methods, such as relying on unblinded expert opinions to grade the accuracy or comprehensiveness of LLM responses without predefined, validated scoring rubrics. This subjectivity introduces a significant concern for measurement bias, which may lead to an overestimation of the LLMs' true performance. Therefore, the favorable accuracy results reported in some studies should be interpreted with this limitation in mind.

Discussion

To date, this is the first systematic review to examine the rapidly evolving field of generative AI, particularly LLMs, and their specific applications within hepatology. Our analysis encompassed a range of studies evaluating the performance of LLMs in information retrieval, clinical data extraction and classification, and novel idea generation. The findings underscore the transformative potential of generative AI in hepatology while highlighting critical limitations and areas for future research that require careful consideration.

Capabilities of Generative AI in Hepatology

The earliest studies of generative AI in hepatology focused on retrieving information, from typical large language models[12] to more

specific fine-tuned models.[21] One of the primary capabilities of LLMs is their ability to process vast amounts of textual data, including research articles, clinical guidelines, and patient records. The included studies demonstrate that LLMs can answer questions related to liver disease diagnosis, management, and treatment with varying degrees of accuracy,[10,12,14–16,19–21,23] often utilizing subjective expert consensus as the primary evaluation metric. These findings align with studies in other medical fields that have shown the feasibility of LLMs to provide quick access to medical information and serve as valuable adjuncts to clinical decision-making.[29] However, our review also highlights that the accuracy of LLMs in hepatology is highly context-dependent and may be limited by the specificity and complexity of the clinical scenario.

The ability of LLMs to extract and classify clinical data from unstructured text sources has significant implications for streamlining clinical workflows and improving the efficiency of research.[13,18,25–28] By automating tasks such as chart review and data extraction from radiology reports, LLMs can potentially reduce the time and effort required for manual data processing, freeing up clinicians' time for direct patient care. In contrast to the subjective information retrieval studies, these investigations leveraged objective ground truth to demonstrate high performance. This capability could translate into meaningful clinical benefits; for instance, automated extraction of LI-RADS classifications from thousands of radiology reports could facilitate large-scale quality improvement initiatives or populate research registries in a fraction of the time required for manual review. This capability has been leveraged to develop tools for automated data extraction, which can significantly reduce the time and effort required for manual chart review, achieving high accuracy in extracting structured data elements from liver imaging reports, comparable to manual chart review. This application domain has been expanded to include imaging identification in more recent months.[23] This finding suggests that LLMs could effectively streamline the process of data collection for clinical research and quality improvement initiatives. Moreover, the application of LLMs to identify and classify liver conditions like cirrhosis and MASLD from various data sources could improve diagnostic accuracy and facilitate early detection.

The exploration of LLMs for novel idea generation, although preliminary, opens up exciting possibilities for accelerating research in hepatology.[24] The integration of LLMs into the research process can also accelerate the pace of discovery by automating the initial stages of literature review and data processing. By quickly sifting through large datasets and identifying key trends or gaps in the literature, LLMs can help researchers formulate focused and impactful research questions. This is particularly relevant in a rapidly evolving field like hepatology, where staying abreast of the latest findings is crucial but challenging due to the sheer volume of published research. The ability of an LLM to generate research ideas deemed relevant by clinical experts suggests that these models could serve as valuable tools for hypothesis generation and research prioritization.

Limitations of Generative AI in Hepatology

Despite the demonstrated capabilities of LLMs, several limitations have been identified. One major concern is the potential for LLMs to generate inaccurate or misleading information, often referred to as "hallucinations".[30] These inaccuracies can stem from biases in the training data,[31] limitations in the model's pattern-matching capabilities of complex medical concepts, and the lack of real-world clinical experience. Studies within this review have reported instances where LLMs provided incorrect or outdated information, particularly when dealing with specific clinical scenarios or nuanced questions.[22] Specific to hepatology, this "guideline drift" presents a significant safety risk. For instance, an LLM might reference outdated hepatocellular carcinoma (HCC) surveillance intervals from archived guidelines or fail to correctly apply updated formulae for MELD 3.0 or MELD-Na, leading to incorrect transplant listing prioritization. Furthermore, the "black box" nature of LLMs, where the decision-making process is often opaque, raises concerns about transparency and accountability.[32]

Beyond general LLM limitations, hepatology presents unique challenges that may create additional barriers to implementation. The field relies heavily on nuanced, multimodal data, including complex serological panels, dynamic imaging with specific criteria (e.g., LI-RADS for HCC), and detailed histopathology. An LLM trained on general medical text may struggle to interpret the specific significance of evolving liver function tests or differentiate subtle imaging features crucial for diagnosis and staging. Furthermore, treatment decisions in advanced liver disease, such as candidacy for transplantation, involve complex, multi-factorial assessments that include not only clinical data but also psychosocial factors and ethical considerations, which are currently beyond the scope of LLMs.

Moreover, the quality and scope of the training data significantly influence the performance of LLMs. These models are typically trained on vast datasets of text and code, which may not always reflect the most up-to-date or evidence-based medical knowledge, as seen in misinformation attacks.[33] This can lead to responses that are outdated, inaccurate, or incomplete. For instance, several studies in our review noted that LLMs struggled with questions related to recent guidelines or those requiring specific knowledge about local practices.[12]

Ethical Considerations and Safety Concerns

The use of LLMs in hepatology raises several ethical considerations and safety concerns. Ensuring data privacy and security is paramount, particularly when handling sensitive patient information. The use of PHI-compliant platforms, as demonstrated in one study,[25,34] is crucial to mitigate these risks. However, the potential for data breaches and unauthorized access to patient data remains a concern. Informed consent is another important ethical consideration, particularly regarding the use of patient data to train or improve LLMs.[35] The secondary use of patient data for training these models is a primary concern. While de-identification is a standard practice, robust governance is needed to ensure that patient privacy is protected in compliance with regulations like HIPAA and GDPR, and to manage patient consent for data use in AI development. Patients should be made aware of how their data might be used and have the opportunity to opt out.



Figure 2. Conceptual framework of retrieval-augmented generation (RAG) in hepatology. Unlike standard LLMs that rely on static training data, a RAG system retrieves current, verified information (e.g., clinical guidelines) to ground the model's response, thereby reducing hallucinations and ensuring adherence to up-to-date protocols.

Transparency about the limitations of LLMs is essential to ensure that patients and clinicians do not rely solely on these tools for making critical healthcare decisions. This is particularly relevant for models using Retrieval-Augmented Generation (RAG), which grounds responses in external knowledge bases. While RAG can improve accuracy, it also introduces a risk of retrieving and presenting information from biased, outdated, or low-quality sources, contributing to misinformation under a veneer of authority. Lastly, the issue of bias in LLMs is a significant concern.[36] LLMs can inherit biases present in their training data, leading to responses that perpetuate health disparities or reflect societal prejudices.[37] For example, if the training data overrepresents certain populations or diseases, the LLM may perform better for those groups, leading to inequitable outcomes. Addressing bias in LLMs requires careful curation of training data, ongoing monitoring for biased outputs, and the development of methods to mitigate bias during the training process.

Future Directions of Generative AI in Hepatology

The rapid evolution of generative AI presents unprecedented opportunities to advance the field of hepatology. Future research should prioritize enhancing the accuracy and reliability of these models by developing more robust training methods that incorporate high-quality, curated medical data specific to hepatology. To address the limitations of hallucinations and outdated training data, future hepatology-specific AI tools should employ Retrieval-Augmented Generation (RAG).[17] As illustrated in Figure 2, a RAG framework first retrieves relevant, up-to-date documents from a verified external knowledge base—such as the latest AASLD or EASL clinical practice guidelines or MELD 3.0 calculation protocols—before generating a response. This allows the model to "cite its sources" and ensures that recommendations are grounded in the most current evidence rather than static training data.[29,38,39]

Efforts should also be made to improve the clinical utility of LLMs by integrating them into clinical workflows in a seamless and user-friendly manner. To improve clinical utility, research should focus on practical integration into real-world hepatology workflows. For example, an LLM could be developed as an EMR-integrated tool that pre-screens outpatient notes to flag patients who meet criteria for HCC surveillance or automatically drafts a summary of recent lab trends and imaging findings for review at a multidisciplinary tumor board. Prospective trials are needed to measure the impact of such tools on clinician efficiency, diagnostic accuracy, and, ultimately, patient outcomes. However, this validation necessitates the establishment of open-source, de-identified liver disease benchmark datasets for objective testing, similar to MIMIC-III in critical care. Further exploration in several key areas will be vital for realizing the full potential of LLMs in hepatology. This includes expanding their multilingual and multimodal capabilities, enabling them to process diverse data types (e.g., imaging, genomics) and cater to a broader patient population.[38,40] Personalization and customization are also essential, with a focus on developing methods to tailor LLM responses to individual patient characteristics, preferences, and specific clinical contexts.

Limitations of This Review

This systematic review has several limitations. A key limitation of this review is inherited from the methodological quality of the included primary studies themselves. Although many studies demonstrated a low risk of bias regarding their internal protocols (Table 2), the reliance on subjective endpoints (e.g., Likert scales) inherently limits the strength of the evidence compared to patient-centered outcomes. The relatively small number of studies focusing specifically on LLMs in hepatology limits the generalizability of our findings. Additionally, the heterogeneity in study designs, LLM applications, and outcome measures made it challenging to perform a quantitative synthesis or meta-analysis. Furthermore, the rapid pace of advancements in generative AI means that new studies and developments may have emerged since the completion of our literature search.

Conclusion

Generative AI, particularly LLMs, demonstrates feasibility across a wide range of hepatology applications. These models can assist with a wide range of tasks, from processing medical images and generating clinical documentation to providing clinical decision support and patient education. However, significant challenges remain in ensuring the accuracy, reliability, and safety of these tools, particularly in the

context of real-world clinical application. Ongoing research, coupled with ethical considerations and regulatory frameworks, will be crucial to harness the full spectrum of generative AI and improve the care of patients with liver diseases. Multistakeholder collaboration will be crucial for the responsible development and deployment of generative AI, ensuring that these powerful tools are used to enhance patient care in an ethical and equitable manner. By addressing the limitations and building upon the capabilities of LLMs, we can pave the way for a new era of AI-enhanced hepatology practice that is both effective and equitable, ultimately leading to improved diagnostic accuracy, more personalized treatment strategies, and enhanced patient outcomes.

Online Appendix Link: https://file.paplino.com/hepatologyforum/files/1785315148-appendix-en.pdf

Ethics Committee Approval: This study is a systematic review based entirely on previously published, publicly available data. Therefore, it did not involve direct contact with human participants or animals, and formal ethical approval from an Institutional Review Board or Ethics Committee was not required for this specific analysis.

Conflict of Interest: The authors declare no conflicts of interest.

Financial Disclosure: No funding was sought for this study.

Use of AI for Writing Assistance: During the preparation of this work the author(s) used Gemini in order to summarize each original article. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Author Contributions: Concept: TS, NT; Design: TS, NT; Supervision: TS, PD; Data Collection and/or Processing: TS, NK; Analysis and/or Interpretation: TS, PD; Literature Review: TS, PD, NT; Writing: TS, NK; Critical Review: TS, PD.

Peer-review: Externally peer-reviewed.

References

1. Junaid SB, Imam AA, Balogun AO, De Silva LC, Surakat YA, Kumar G, et al. Recent advancements in emerging technologies for healthcare management systems: A survey. Healthcare (Basel) 2022;10(10):1940. [CrossRef]
2. Yang R, Tan TF, Lu W, Thirunavukarasu AJ, Ting DSW, Liu N. Large language models in health care: Development, applications, and challenges. Health Care Sci 2023;2(4):255-263. [CrossRef]
3. Friedman SL, Sanyal AJ. The future of hepatology. Hepatology 2023;78(2):637-648. [CrossRef]
4. Losurdo G, Gravina AG, Maroni L, Gabrieletto EM, Ianiro G, Ferrarese A; Young Investigator group of SIGE, the Italian Society of Gastroenterology. Future challenges in gastroenterology and hepatology, between innovations and unmet needs: A SIGE Young Editorial Board's perspective. Dig Liver Dis 2022;54(5):583-597. [CrossRef]
5. Schattenberg JM, Chalasani N, Alkhouri N. Artificial intelligence applications in hepatology. Clin Gastroenterol Hepatol 2023;21(8):2015-2025. [CrossRef]
6. Suenghataiphorn T, Tribuddharat N, Danpanichkul P, Kulthamrongsri N. Large language models in obesity: a systematic review. Int J Obes (Lond) 2026;50(3):479-491. [CrossRef]
7. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. [CrossRef]
8. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919. [CrossRef]
9. Cao JJ, Kwon DH, Ghaziani TT, Kwo P, Tse G, Kesselman A, Kamaya A, Tse JR. Accuracy of information provided by ChatGPT regarding liver cancer surveillance and diagnosis. AJR Am J Roentgenol 2023;221(4):556-559. [CrossRef]
10. Endo Y, Sasaki K, Moazzam Z, Lima HA, Schenk A, Limkemann A, et al. Quality of ChatGPT responses to questions related to liver transplantation. J Gastrointest Surg 2023;27(8):1716-1719. [CrossRef]
11. Samaan JS, Yeo YH, Ng WH, Ting PS, Trivedi H, Vipani A, et al. ChatGPT's ability to comprehend and answer cirrhosis related questions in Arabic. Arab J Gastroenterol 2023;24(3):145-148. [CrossRef]
12. Yeo YH, Samaan JS, Ng WH, Ting PS, Trivedi H, Vipani A, et al. Assessing the performance of ChatGPT in answering questions regarding cirrhosis and hepatocellular carcinoma. Clin Mol Hepatol 2023;29(3):721-732. [CrossRef]
13. Ge J, Li M, Delk MB, Lai JC. A comparison of a large language model vs manual chart review for the extraction of data elements from the electronic health record. Gastroenterology 2024;166(4):707-709.e3. [CrossRef]
14. Cao JJ, Kwon DH, Ghaziani TT, Kwo P, Tse G, Kesselman A, et al. Large language models' responses to liver cancer surveillance, diagnosis, and management questions: accuracy, reliability, readability. Abdom Radiol (NY) 2024;49(12):4286-4294. [CrossRef]
15. Colapietro F, Piovani D, Pugliese N, Aghemo A, Ronca V, Lleo A. Is ChatGPT-4 a reliable tool in autoimmune hepatitis? Am J Gastroenterol 2025;120(4):914-919. [CrossRef]
16. Daza J, Bezerra LS, Santamaría L, Rueda-Esteban R, Bantel H, Girala M, et al. Evaluation of four chatbots in autoimmune liver disease: A comparative analysis. Ann Hepatol 2025;30(1):101537. [CrossRef]
17. Ge J, Sun S, Owens J, Galvez V, Gologorskaya O, Lai JC, et al. Development of a liver disease-specific large language model chat interface using retrieval-augmented generation. medRxiv [Preprint]. 2023 Nov 10:2023.11.10.23298364. doi: 10.1101/2023.11.10.23298364. Update in: Hepatology 2024;80(5):1158-1168. [CrossRef]
18. Pradhan F, Fiedler A, Samson K, Olivera-Martinez M, Manatsathit W, Peeraphatdit T. Artificial intelligence compared with human-derived patient educational materials on cirrhosis. Hepatol Commun 2024;8(3):e0367. [CrossRef]
19. Pugliese N, Polverini D, Lombardi R, Pennisi G, Ravaioli F, Armandi A; Nafld Expert Chatbot Working Group. Evaluation of ChatGPT as a counselling tool for Italian-speaking MASLD patients: Assessment of accuracy, completeness and comprehensibility. J Pers Med 2024;14(6):568. [CrossRef]
20. Pugliese N, Wai-Sun Wong V, Schattenberg JM, Romero-Gomez M, Sebastiani G; NAFLD Expert Chatbot Working Group; Aghemo A. Accuracy, reliability, and comprehensibility of ChatGpt-generated medical responses for patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2024;22(4):886-889.e521. [CrossRef]

21. Malik S, Frey LJ, Gutman J, Mushtaq A, Warraich F, Qureshi K. Evaluating artificial intelligence-driven responses to acute liver failure queries: A comparative analysis across accuracy, clarity, and relevance. Am J Gastroenterol 2024;120(9):2081-2085. [CrossRef]
22. Zhang Y, Liu H, Sheng B, Tham YC, Ji H. Preliminary fatty liver disease grading using general-purpose online large language models: ChatGPT-4 or Bard? J Hepatol 2024;80(6):e279-e281. [CrossRef]
23. Zhang Y, Wu L, Mu Z, Ren L, Chen Y, Liu H, et al. Letter 2 regarding "Assessing the performance of ChatGPT in answering questions regarding cirrhosis and hepatocellular carcinoma". Clin Mol Hepatol 2024;30(1):113-117. [CrossRef]
24. Akabane M, Iwadoh K, Melcher ML, Sasaki K. Exploring the potential of ChatGPT in generating unknown clinical questions about liver transplantation: A feasibility study. Liver Transpl 2024;30(2):229-234. [CrossRef]
25. Far AT, Bastani A, Lee A, Gologorskaya O, Huang CY, Pletcher MJ, et al. Evaluating the positive predictive value of code-based identification of cirrhosis and its complications utilizing GPT-4. Hepatology 2025;81(6):1753-1763. [CrossRef]
26. Wu Q, Wu Q, Li H, Wang Y, Bai Y, Wu Y, et al. Evaluating large language models for automated reporting and data systems categorization: Cross-sectional study. JMIR Med Inform 2024;12:e5579927. [CrossRef]
27. Wu W, Guo Y, Li Q, Jia C. Exploring the potential of large language models in identifying metabolic dysfunction-associated steatotic liver disease: A comparative study of non-invasive tests and artificial intelligence-generated responses. Liver Int 2025;45(4):e16112. [CrossRef]
28. Geevarghese R, Sigel C, Cadley J, Chatterjee S, Jain P, Hollingsworth A, et al. Extraction and classification of structured data from unstructured hepatobiliary pathology reports using large language models: a feasibility study compared with rules-based natural language processing. J Clin Pathol 2025;78(2):135-138. [CrossRef]
29. Jeyaraman M, Ramasubramanian S, Balaji S, Jeyaraman N, Nallakumarasamy A, Sharma S. ChatGPT in action: Harnessing artificial intelligence potential and addressing ethical challenges in medicine, education, and scientific research. World J Methodol 2023;13(4):170-178. [CrossRef]
30. Park YJ, Pillai A, Deng J, Guo E, Gupta M, Paget M, et al. Assessing the research landscape and clinical utility of large language models: a scoping review. BMC Med Inform Decis Mak 2024;24(1):72. [CrossRef]
31. Ueda D, Kakinuma T, Fujita S, Kamagata K, Fushimi Y, Ito R, et al. Fairness of artificial intelligence in healthcare: review and recommendations. Jpn J Radiol 2024;42(1):3-15. [CrossRef]
32. Cascella M, Semeraro F, Montomoli J, Bellini V, Piazza O, Bignami E. The Breakthrough of Large Language Models Release for Medical Applications: 1-Year Timeline and Perspectives. J Med Syst 2024;48(1):22. [CrossRef]
33. Han T, Nebelung S, Khader F, Wang T, Müller-Franzes G, Kuhl C, et al. Medical large language models are susceptible to targeted misinformation attacks. NPJ Digit Med 2024;7(1):288. [CrossRef]
34. Suenghataiphorn T, Boonpiraks K, Prasitsumrit V, Kulthamrongsri N, Danpanichkul P. Enabling drug-induced liver injury surveillance through automated medication extraction from clinical notes: A medical information mart for intensive care IV real-world large language models validation study. Gastroenterology Res 2025;18(5):247-253. [CrossRef]
35. Williams M, Karim W, Gelman J, Raza M. Ethical data acquisition for LLMs and AI algorithms in healthcare. NPJ Digit Med 2024;7(1):377. [CrossRef]
36. Currie GM, Hawk KE, Rohren EM. Generative artificial intelligence biases, limitations and risks in nuclear medicine: An argument for appropriate use framework and recommendations. Semin Nucl Med 2025;55(3):423-436. [CrossRef]
37. Suenghataiphorn T, Tribuddharat N, Danpanichkul P, Kulthamrongsri N. Bias in Large Language Models Across Clinical Applications: A Systematic Review. arXiv 2025 abs/2504.02917. [Preprint]. doi: 10.48550/arXiv.2504.02917
38. Howell MD. Generative artificial intelligence, patient safety and healthcare quality: a review. BMJ Qual Saf 2024;33(11):748-754. [CrossRef]
39. Saenz AD; Mass General Brigham AI Governance Committee; Centi A, Ting D, You JG, Landman A, Mishuris RG. Establishing responsible use of AI guidelines: a comprehensive case study for healthcare institutions. NPJ Digit Med 2024;7(1):348. [CrossRef]
40. Suenghataiphorn T, Danpanichkul P, Tribuddharat N, Kulthamrongsri N. Toward real-time detection of drug-induced liver injury using large language models: A feasibility study from clinical notes. J Clin Exp Hepatol 2025;15(6):102627. [CrossRef]
41. Zhang Y, Wu L, Wang Y, Sheng B, Tham YC, Ji H; LLM-Liver Working Group. Unexpectedly low accuracy of GPT-4 in identifying common liver diseases from CT scan images. Dig Liver Dis 2024;56(4):718-720. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 236–240 DOI: 10.14744/hf.2026.46055

REVIEW ARTICLE

WHO 2024 Hepatitis B Guidelines: No more gray zone for low- and middle-income countries? An evaluation

Shanmugam Saravanan[1*], Ramachandran Vignesh[2], Esaki M Shankar[3], Raju Sivadoss[4], Sathasivam Sivamalar[5], Vijayakumar Velu[6], Pachamuthu Balakrishnan[5,7,8], Arcot R Venkateswaran[9]

1: Department of Microbiology, Saveetha Medical College (SMC), Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai, India
2: Preclinical Department, Faculty of Medicine, Royal College of Medicine Perak, Universiti Kuala Lumpur, Ipoh, Malaysia
3: Infection and Inflammation, Department of Biotechnology, Central University of Tamil Nadu, Thiruvarur, India
4: State Public Health Laboratory, Directorate of Public Health and Preventive Medicine, Chennai, India
5: Centre for Global Health Research, Meenakshi Academy of Higher Education and Research (MAHER), Chennai, India
6: Division of Microbiology and Immunology, Emory Vaccine Center, Emory University, Atlanta, GA, United States
7: Central Research Laboratory, Meenakshi Ammal Dental College and Hospital (MADCH), Chennai, India
8: Central Research Laboratory, Meenakshi Medical College Hospital and Research Institute (MMCHRI), Kanchipuram, India
9: Department of Medical Gastroenterology and Hepatology, Saveetha Medical College and Hospitals (SMCH), Saveetha Institute of Medical and Technical Sciences (SIMATS), Chennai, India

Points to Note

- **Synthesis of Current Evidence:** The WHO 2024 guidelines expand HBV treatment eligibility to 50% by lowering ALT/APRI thresholds and removing HBV DNA test dependency, significantly benefiting "gray zone" patients in LMICs.
- **Major Controversies:** The HIV-like "treat-all" strategy sparks debates regarding over-treatment risks due to lower test specificity, long-term drug toxicity, and financial sustainability in resource-limited settings.
- **Future Directions:** Refining simplified algorithms, validating non-invasive biomarkers, and integrating decentralized point-of-care models are required.

ABSTRACT

The World Health Organization (WHO) has established targets to reduce the incidence rates of viral hepatitis by 90% and the death rate by 65% by 2030. However, despite global efforts, a substantial treatment gap persists, with merely 3% of eligible patients worldwide receiving antiviral therapy as of 2022. With more than 254 million people living with chronic HBV infection and approximately 1.1 million related deaths annually, the updated 2024 WHO guidelines significantly expand treatment eligibility to help achieve this objective. This review discusses how the new changes would benefit gray zone patients, particularly those in low- and middle-income countries (LMICs) who were historically excluded from therapy. By introducing age-based thresholds, incorporating non-invasive grading methods, and persistent ALT elevation to the treatment network, the 2024 guidelines promise broader inclusion. This review highlights the significance of these changes and evaluates the potential impact on the gray zone patients in resource-limited settings.

Keywords: Chronic HBV, hepatitis B virus, HBV gray zone.

***The current affiliation of the author:** Dental Research Cell, Dr. D. Y. Patil Dental College & Hospital, Dr. D. Y. Patil Vidyapeeth (Deemed to be University), Pune, India.

How to cite this article: Saravanan S, Vignesh R, Shankar EM, Sivadoss R, Sivamalar S, Velu V, et al. WHO 2024 Hepatitis B Guidelines: No more gray zone for low- and middle-income countries? An evaluation. Hepatology Forum 2026; 7(3):236–240.

Received: June 16, 2025; **Revised:** November 12, 2025; **Accepted:** January 16, 2026; **Available Online:** July 27, 2026

Corresponding author: Ramachandran Vignesh; Preclinical Department, Faculty of Medicine, Royal College of Medicine Perak, Universiti Kuala Lumpur, Ipoh, Malaysia; **E-mail:** vignesh@unikl.edu.my

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

According to WHO estimates, 254 million people worldwide are afflicted by chronic hepatitis B (CHB) virus (HBV) infection, with a disproportionately high burden in low- and middle-income countries (LMICs). Chronic HBV infection is responsible for about 1.1 million deaths annually, primarily due to cirrhosis and hepatocellular carcinoma (HCC).[1] Between 2016 and 2040, there will likely be a more than twofold increase in HBV-related HCC deaths.[2,3] CHB is characterized by dynamic fluctuations in viral replication and host immune responses, which can lead to the risk of disease development over time. These interactions define four recognized phases of chronic HBV infection: immune tolerant (IT), immune active (IA), immune control (IC), and immune reactive (IR) phases (Fig. 1). The term 'gray zone' is frequently used to describe the indeterminate cases that do not fall into any of these four classical phases, often with fluctuating alanine aminotransferase (ALT) levels around the upper limit of normal (ULN).

According to the revised WHO CHB guidelines 2024, HBV treatment eligibility is determined based on the evidence of significant fibrosis, HBV DNA level > 2000 IU/mL, and elevated ALT level, and the presence of coinfections and comorbidities. The expanded treatment eligibility aims to capture a higher proportion of HBsAg-positive individuals. However, in resource-limited settings (RLS) without access to HBV DNA testing, persistently elevated ALT levels alone justify treatment initiation, irrespective of APRI scores. Hence, there remains a possibility that a proportion of gray zone CHB patients from LMICs with fluctuating ALT levels may remain untreated under the current guidelines. This is in contrast to the management of HIV or HCV, where early treatment is prioritized for all infected individuals regardless of disease stage. Despite evidence that antiviral therapy reduces the risk of HCC and liver-related mortality, only about 3% of CHB patients were receiving treatment as of 2022.[4] Consequently, gray zone patients from LMICs, many of whom are experiencing ongoing inflammation and fibrosis, might face an increased risk of progression to cirrhosis and hepatocellular carcinoma.[5,6] Given that a substantial liver inflammation is a key indication for initiating antiviral treatment, the absence of HBV DNA testing precludes several gray zone patients from treatment under current practice guidelines. This review advocates updating RLS treatment criteria by incorporating affordable alternatives to identify gray zone patients who require therapy.

Epidemiology of Gray Zone Patients

The current staging criteria of chronic HBV infection are insufficient for classifying about 30%-40% of patients in the gray zone.[6] Discussing therapy and prognosis for these patients, often referred to as being in the gray zone, presents challenges. Recent studies suggest that many patients in this category exhibit benign outcomes without

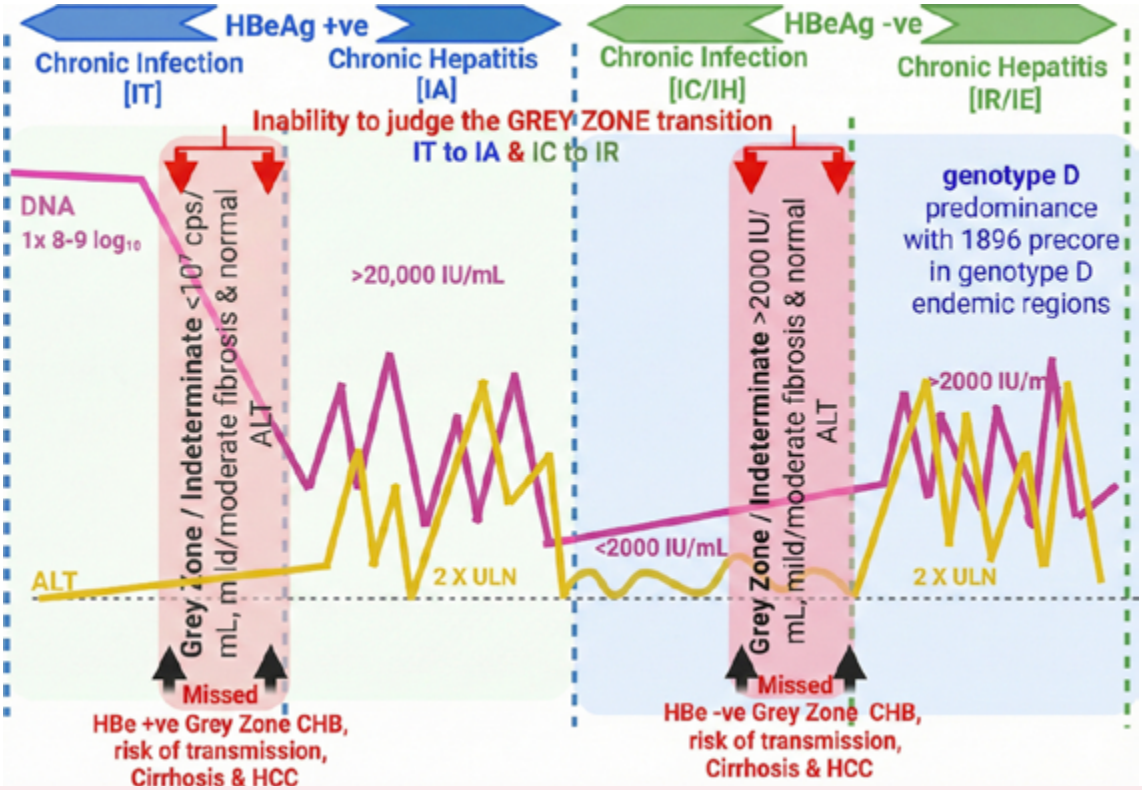


Figure 1. Defined clinical phases of chronic HBV infection and an emerging indeterminate/gray zone chronic HBV (author-created figure).

IT: Immune tolerance; IA: Immune active; IC: Immune control; IR: Immune reactivation; IE: Immune escape; OBI: Occult HBV infection; SN: Surface antigen negative; FC: Functional cure.

treatment, leading to proposals to delay antiviral therapy, especially for those in the HBeAg-negative gray zone.[5] However, prior studies suggest that patients in this gray area who do not receive treatment are more likely than those in other phases to experience bad clinical outcomes, including liver cirrhosis and hepatocellular carcinoma (HCC).[7,8] Existing studies primarily rely on serum ALT and HBV DNA levels for classification. Still, liver histology could provide more accurate insights, as levels of serum markers and HBV DNA may fluctuate. A study conducted on 3366 treatment-naïve CHB patients without cirrhosis found that 38.7% of them were characterized as being in an 'indeterminate' phase at the beginning. Out of these patients, 52.7% remained in the indeterminate phase after ten years.[7] In patients who remained in the indeterminate category, the 10-year cumulative incidence of HCC was found to be higher than in those who remained in the inactive category (HR: 14.1). Moreover, a study of 2,150 treatment-naïve, HBeAg-negative, non-cirrhotic patients with CHB found that patients classified in the indeterminate or gray-zone groups had an increased risk of HCC.[9] An additional study reported an HCC incidence of 0.41 cases per 100 patient-years (95% CI, 0.35–0.48) among untreated patients in the inactive phase.[10] In patients with HBV DNA levels between 2000 and 20,000 IU/mL, this rate is comparable to that observed in the REVEAL-HBV study (0.30 per 100 patient-years).

Preventing cirrhosis and HCC is still the primary goal of HBV therapy in the absence of curative treatments. Antiviral suppressive therapy is considered for a broader range of HBV-infected patients due to the significant positive link between HBV DNA levels and HCC risk found in the REVEAL-HBV cohort study, regardless of ALT and fibrosis stage. It is encouraged to use caution when comparing these studies because higher initial levels of HBV DNA (up to 10^6 IU/mL) are linked to an increased risk of HCC among individuals with CHB who have tested negative for HBeAg. Moreover, the beginning of the investigations revealed that the patients involved in these studies had different baseline levels of HBV DNA.[11]

Hsu et al.[12] found that 36.6% of 198 untreated patients fell into the gray zone when ALT >40 IU/L was used as the threshold. Like the previous research, 28.0% of the patients were categorized as being in the gray zone according to the AASLD standards. This classification was based on their serum ALT levels and HBV DNA. Histological analysis increased the gray zone classification to 49%, reinforcing its utility in staging. Considerable variability exists between international guidelines, underscoring the need for globally harmonized criteria.[6] According to the Global hepatitis report 2024, less than 30% of low and middle-income countries (LMICs) have access to performing HBV DNA assays, highlighting the significant challenge in diagnosis.

WHO 2024 Treatment Guidelines: Key Changes for Gray Zone Patients?

The updated 2024 WHO HBV guidelines offer four options for meeting treatment eligibility that will capture a much higher proportion (about 50%) of all HBsAg-positive people versus about 8–15%. While the aspartate aminotransferase-to-platelet ratio index (APRI) continues to be recommended as the preferred non-invasive test to assess for the presence of significant fibrosis or cirrhosis among adults in resource-limited settings, new recommendations have brought down the thresholds for establishing the presence of significant fibrosis or cirrhosis.

Considering that only a low proportion of LMICs have capacity and access to HBV DNA assays, the updated guidelines recommend treatment initiation in case of persistently abnormal ALT levels (defined as two ALT values >ULN at unspecified intervals during a 6-to-12-month period), regardless of APRI score, in the absence of HBV DNA assay.

Since pre-2024 guidelines excluded about 30 to 40% of patients in the gray zone due to the strict reliance on HBV DNA and ALT thresholds, these updated recommendations could increase the treatment coverage significantly in LMICs. A recent cross-sectional study compared the rates of HBV treatment eligibility among 10,042 treatment-naïve patients according to the 2024 guidelines with eligibility rates across other international guidelines, which displayed significantly higher treatment-eligible rates.[13] A recent study from China that retrospectively analyzed 1454 CHB patients found that about 47.5% belonged to the gray zone category. Of these, about 46.7% had significant liver histological changes based on liver biopsy, and antiviral therapy was indicated in them.[14]

Hence, there is no doubt that the updated guidelines would help broaden the antiviral treatment coverage, thereby aiming to improve access to therapy and patient outcomes. Earlier initiation of antiviral treatment in chronic HBV patients, especially the gray zone patients, would benefit from the reduction in the risk of fibrosis progression and development of HCC.[15]

Impact of the WHO 2024 HBV Guidelines on LMICs

According to modelling studies, to meet the WHO 2030 HBV elimination targets, the treatment coverage needs to be increased to 80% among people eligible for antiviral treatment. While less than 20% of people living with HBV infection (PLWHB) were eligible for antiviral treatment as per the WHO 2015 treatment criteria, the WHO 2024 guidelines aim to increase this to 50% of PLWHB. A study found that about 67% of treatment-naïve patients with CHB will meet treatment eligibility based on the 2024 guidelines.[16] The newer guidelines are expected to have a positive impact on the nations representing about two-thirds of the global disease burden.[1] The diagnosis and monitoring recommendations have been curated based on the clinical setting and the availability of resources, keeping the LMICs with high disease burden in mind. Significant fibrosis/cirrhosis based on APRI score is sufficient to initiate therapy. In regions with access, point-of-care HBsAg and HBV DNA testing are recommended as primary care options based on their excellent diagnostic accuracy. However, considering the limited access to HBV DNA PCR in LMICs, HBV viral load is no longer a barrier to treatment initiation.

To enable more straightforward implementation with accessible diagnostic tools, the treatment criteria have been simplified in the revised guidelines. With Hepatitis B, the leading cause of death in LMICs, treating advanced fibrosis and cirrhosis irrespective of HBV DNA or ALT levels broadens the treatment eligibility. These updated guidelines also serve to avoid the gray zones associated with different ranges of ALT and HBV DNA levels.

Lowering the APRI threshold for diagnosis of advanced fibrosis and cirrhosis as per the revised guidelines is particularly important and relevant to resource-limited settings like African regions. When the APRI cut-off was >2 for cirrhosis, about 50% of individuals eligible for treatment were missed in Ethiopia.[17] A recent study that compared the treatment coverage between the WHO 2024 hepatitis B guidelines and the WHO 2015 hepatitis B guidelines, included 6925 treatment-naïve CHB patients, found that only 36.2% of patients met the treatment criteria as per the previous guidelines, while the treatment eligibility rate rose to 63.8% in the case of the 2024 guidelines. Interestingly, if HBV DNA testing was not accessible, the treatment coverage remained as high as 61.6%, which is relevant to the LMIC settings.[4]

Gray Zone and the Persistent Gaps in LMICs

It is understood that using the 2024 WHO treatment criteria would increase the treatment coverage to about 80%, as opposed to 20% being eligible for treatment as per 2015 guidelines, and considered a solution for eliminating HBV globally by 2030. Following the HIV test-and-treat model of care, a treat-all strategy is put forward to curb the HBV load worldwide. However, this sparks a lot of debate on the possible benefits of expanded treatment indications, because in contrast to HIV infection, a small percentage of HBV-infected patients could achieve a functional cure spontaneously over time. Also, compared to HIV, there is an effective HBV vaccine available, and several CHB patients belong to the HBeAg-negative chronic infection phase, associated with a very low risk of hepatic complications. Furthermore, expanded treatment eligibility and antiviral treatment raise concerns about toxicity and the need for monitoring treatment toxicity. Since there is no clear indication on when the antiviral therapy should be stopped, the potential for long-term treatment-related toxicity must be balanced against the possible risk of hepatitis flare following the discontinuation of treatment. It is important that no study has ever been conducted to evaluate the pros and cons of this strategy in sub-Saharan Africa. Further studies and more data are required on the toxicity of nucleoside analogues in HBV-infected individuals, especially from LMICs, where there would be limited access to laboratory monitoring. In addition, in resource-limited settings like LMICs, broadened treatment eligibility leading to an increase in the proportion of those initiating treatment also brings up the need for additional long-term cost implications and sustainability. Although several LMICs are in the process of improving their access to generic drugs, the costs of HBV treatment remain too high for many countries.[18]

Lowering of cut-offs of non-invasive tests for liver fibrosis was one of the strategies of the WHO 2024 guidelines aimed at identifying a maximum number of individuals with significant liver fibrosis, including cirrhosis. However, this raises the concern of prioritizing the sensitivity of the testing method over specificity, which could lead to overtreatment of patients. Likewise, the revised cut-offs of APRI and FibroScan are found to be associated with reduced performance characteristics (sensitivities and specificities) for the detection of significant liver fibrosis or cirrhosis.[16]

Conclusion

In summary, the revised WHO hepatitis B guidelines represent a progressive step toward expanding CHB treatment and reducing missed opportunities, particularly in LMICs. By eliminating HBV DNA dependency and embracing age, APRI and ALT as treatment criteria, more gray zone patients are likely to be covered than ever before. While these changes are expected to significantly expand diagnosis and treatment access, ultimately improving individual outcomes and advancing global HBV elimination goals, there still remain several barriers to the management and treatment of hepatitis B in resource-limited settings. The current research gaps, particularly regarding the LMICs, need to be focused further on refining simplified algorithms, validating additional non-invasive biomarkers, and ensuring equitable access to diagnostics and treatment in high-burden regions. Thus, in LMICs, successful implementation will require the integration of fragmented healthcare services and targeted allocation of limited domestic resources to ensure sustained delivery of HBV care.

Ethics Committee Approval: This article is a review study and does not contain any original studies with human participants or animals performed by any of the authors. Therefore, ethical approval was not required for this study. The authors declare that they have complied with all academic and publishing ethical standards.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: No specific financial support was received for the preparation of this manuscript. VV is supported by the Emory National Primate Research Center through NIH Grant No. ORIP/OD P51OD011132.

Use of AI for Writing Assistance: The authors declare that tools such as Grammarly and Quillbot were used for language assistance.

Author Contributions: Concept: SSa, RV, PB; Design: SSa, RV, PB; Supervision: SSa, PB, EM, RS; Literature Search: RV, SSa, SSi; Writing: RV, SSa, SSi; Critical Reviews: SSa, PB, VV, ARV.

Peer-review: Externally peer-reviewed.

References

1. World Health Organization. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: World Health Organization; 2024.

2. Vo Quang E, Shimakawa Y, Nahon P. Epidemiological projections of viral-induced hepatocellular carcinoma in the perspective of WHO global hepatitis elimination. Liver Int 2021;41(5):915-927. [CrossRef]
3. Singal AG, Kanwal F, Llovet JM. Global trends in hepatocellular carcinoma epidemiology: implications for screening, prevention and therapy. Nat Rev Clin Oncol 2023;20(12):864-884. [CrossRef]
4. Wang J, Zhang S, Zhu C, Wu C, Huang R. Treatment coverage of the 2024 updated WHO guidelines for patients with chronic hepatitis B. J Hepatol 2025;82(6):e309-e310. [CrossRef]
5. Wang J, Yan X, Zhu L, Liu J, Qiu Y, Li Y, et al. Significant histological disease of patients with chronic hepatitis B virus infection in the grey zone. Aliment Pharmacol Ther 2023;57(5):464-474. [CrossRef]
6. Gan QY, Wang JX, Qian F, Wang YL, Huang Y, Zhang ZL, et al. Clinical and histological features of patients with chronic hepatitis B virus infection in the grey zone. J Viral Hepat 2023;30(10):803-809. [CrossRef]
7. Huang DQ, Li X, Le MH, Le AK, Yeo YH, Trinh HN, et al. Natural history and hepatocellular carcinoma risk in untreated chronic hepatitis B patients with indeterminate phase. Clin Gastroenterol Hepatol 2022;20(8):1803-1812.e5. [CrossRef]
8. Jiang H, Yu H, Huang Y, Li M, Yang B, Xi X, et al. Natural history and prognosis of chronic hepatitis B patients in the indeterminate phase. J Gastroenterol Hepatol 2025;40(3):720-730. [CrossRef]
9. Tseng TC, Hosaka T, Liu CJ, Suzuki F, Hong CM, Kumada H, et al. Hepatitis B core-related antigen stratifies the risk of liver cancer in HBeAg-negative patients with ındeterminate phase. Am J Gastroenterol 2022;117(5):748-757. [CrossRef]
10. Choi GH, Kim GA, Choi J, Han S, Lim YS. High risk of clinical events in untreated HBeAg-negative chronic hepatitis B patients with high viral load and no significant ALT elevation. Aliment Pharmacol Ther 2019;50(2):215-226. [CrossRef]
11. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al; REVEAL-HBV Study Group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295(1):65-73. [CrossRef]
12. Hsu YN, Pan CQ, Abbasi A, Xia V, Bansal R, Hu KQ. Clinical presentation and disease phases of chronic hepatitis B using conventional versus modified ALT criteria in Asian Americans. Dig Dis Sci 2014;59(4):865–871. [CrossRef]
13. Wang J, Zhang S, Zhu C, Wu C, Huang R. WHO 2024 Hepatitis B guidelines and treatment-eligible rate among treatment-naive patients. JAMA Netw Open 2024;7(9):e2435777. [CrossRef]
14. Lin W, Ding R, Sun S, Lu W, Wang Y, Zhou X, et al. Liver histological study of patients with chronic hepatitis B virus infection in the grey zone. BMC Infect Dis 2025;25(1):385. [CrossRef]
15. Lei Y, Mohamed A, Kennedy PT. Minimising risk in CHB management: A zero-risk approach. J Viral Hepat 2024;(31 Suppl 2):56-60. [CrossRef]
16. Wong GL-H, Lemoine M. The 2024 updated WHO guidelines for the prevention and management of chronic hepatitis B: Main changes and potential implications for the next major liver society clinical practice guidelines. J Hepatol 2025;82(5):918-925. [CrossRef]
17. Johannessen A, Stockdale AJ, Henrion MYR, Okeke E, Seydi M, Wandeler G, et al. Systematic review and individual-patient-data meta-analysis of non-invasive fibrosis markers for chronic hepatitis B in Africa. Nat Commun 2023;14(1):45. [CrossRef]
18. Jaquet A, Muula G, Ekouevi DK, Wandeler G. Elimination of viral hepatitis in low and middle-income countries: Epidemiological research gaps. Curr Epidemiol Rep 2021;8(3):89-96. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 241–248 DOI: 10.14744/hf.2026.50793

REVIEW ARTICLE

MELD 3.0: Exploring and expanding its utility beyond transplantation

Pavan Kumar Reddy Kalluru[1], Hassan Emad Buhulaigah[2], Kishan Kumar Allikesam[3], Deekshitha Kuchi[3], Abdul Muqtadir[1], Nirmal Onteddu[4], Apoorva Cherukuri[2], Teja Allagadda[5], Madhusree Kamakkagari[6], Hossein Rajali[2]

1: Department of Internal Medicine, West Anaheim Medical Center, Anaheim, California, USA
2: Department of Gastroenterology, West Anaheim Medical Center, Anaheim, California, USA
3: Department of General Medicine, Sri Venkateswara Medical College, Tirupati, India
4: Department of Internal Medicine, University of Florida College of Medicine – Jacksonville, Jacksonville, Florida, USA
5: Department of General Surgery, Vinayaka Missions Medical College and Hospitals, Puducherry, India
6: Department of General Medicine, Apollo Institute of Medical Sciences and Research, Chittoor, India

Points to Note

- **Synthesis of Current Evidence:** MELD 3.0 shows prognostic value beyond transplantation, including TIPS, alcohol-associated hepatitis, SBP, cardiac transplantation, HCC, and oncology-related hepatic dysfunction.
- **Major Controversies:** Its performance varies by setting and may be limited by calibration issues, albumin-related confounding, and underestimation of risk in hepatic hydrothorax.
- **Future Directions:** Large prospective, multicenter studies are needed to validate context-specific use and compare MELD 3.0 with existing scores.

ABSTRACT

The model for end-stage liver disease (MELD) score has evolved into a cornerstone of liver transplantation prioritization. With the recent development of MELD 3.0, which incorporates serum albumin and sex-adjusted variables, its predictive accuracy and applicability have expanded significantly. This review examines the potential clinical applications of MELD 3.0 beyond transplant selection, highlighting its utility as a broader prognostic tool across various hepatic and systemic conditions. Data from multiple domains suggest that MELD 3.0 provides meaningful clinical insight. In orthotopic heart transplantation, MELD 3.0 has demonstrated superior predictive power for short-term mortality and postoperative intensive care unit resource utilization. In acute variceal hemorrhage, it has maintained good discriminatory ability, although calibration challenges limit its use as a standalone tool. Among patients with hepatocellular carcinoma and renal insufficiency, MELD 3.0 has shown moderate predictive value for survival but has been outperformed by albumin-bilirubin-based models. In transjugular intrahepatic portosystemic shunt procedures, MELD 3.0 has effectively stratified pre- and postprocedural risk, enhancing dynamic patient monitoring and decisions regarding transplant timing. For alcohol-associated hepatitis, MELD 3.0 has surpassed older models in predicting mortality and the need for renal replacement therapy, particularly in women and malnourished patients. In oncology, MELD 3.0 has contributed to mortality risk assessment in hepatic visceral crisis when combined with inflammatory markers. However, its performance has been less robust in hepatic hydrothorax, where mortality has occurred at lower MELD scores, and in spontaneous bacterial

How to cite this article: Reddy Kalluru PK, Buhulaigah HE, Allikesam KK, Kuchi D, Muqtadir A, Onteddu N, et al. MELD 3.0: Exploring and expanding its utility beyond transplantation. Hepatology Forum 2026; 7(3):241–248.

Received: September 17, 2025; **Revised:** January 07, 2026; **Accepted:** January 08, 2026; **Available Online:** June 09, 2026

Corresponding author: Abdul Muqtadir; Department of Internal Medicine, West Anaheim Medical Center, California, USA; **E-mail:** abdulmuqtadir96@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

peritonitis, where it has performed comparably to other MELD variants. Collectively, these findings underscore the growing relevance of MELD 3.0 as a generalizable risk stratification tool across acute and chronic liver-related conditions. Although further prospective validation is warranted, its incorporation into routine hepatology and multidisciplinary care pathways may enhance prognostic precision and inform therapeutic decision-making beyond transplantation.

Keywords: MELD score, liver diseases/diagnosis, risk assessment.

Lay Summary

The MELD score is a well-known medical system used worldwide to rank patients who urgently need a liver transplant. Recently, a newer and more accurate version called MELD 3.0 was developed, which now takes into account gender differences and protein levels in the blood.

While originally designed only for liver transplants, this review study shows that MELD 3.0 is highly valuable for many other medical conditions. We found that this new score helps doctors accurately predict health risks in patients undergoing heart transplants, those suffering from severe alcohol-related liver disease, and patients undergoing specialized liver procedures (like TIPS). However, it is slightly less precise for certain specific conditions, such as liver cancer or severe fluid buildup in the lungs.

Overall, our study highlights that MELD 3.0 is not just a tool for transplant lists. It is a powerful, everyday calculator that can help doctors in various fields spot high-risk patients earlier, predict complications, and make better treatment decisions for patients with both liver and heart diseases.

Introduction

The model for end-stage liver disease (MELD) score was first formulated in the early 21st century to assess mortality risk in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS). This scoring system, which is based on objective laboratory criteria, quickly gained widespread adoption for prioritizing liver transplantation, ultimately superseding the more subjective Child-Turcotte-Pugh (CTP) classification for organ allocation.[1,2] Subsequently, multiple modifications were made to the original MELD score to capture the evolving nature of liver disease, culminating in the proposal of MELD 3.0. MELD 3.0 is the most recent update in this arena and was designed to address long-standing inequalities in liver transplant allocation, particularly for women.[3] This improvement was achieved by incorporating serum albumin and sex variables, along with improved calibration of other variables, compared with the original MELD score.[3] However, it is important to note that MELD 3.0 has not yet been prospectively validated across all geographic regions, ethnic groups, or transplantation settings, particularly between living-donor liver transplantation (LDLT) and deceased-donor liver transplantation (DDLT). Therefore, its universal applicability should be interpreted with caution, and further large-scale, multicenter validation is warranted before widespread clinical adoption.

Although the MELD 3.0 score was originally developed in the transplantation setting, its refinement raises an important question: Can this tool be adapted for broader use in clinical hepatology and general medicine? In recent years, there has been a growing trend toward using scoring systems such as MELD 3.0 across a variety of clinical settings rather than restricting them to a single, isolated purpose. This shift has been made possible because the components of the MELD 3.0 scoring system reflect broader systemic dysfunction, making it applicable beyond its original context. Notably, the precursors to MELD 3.0, MELD and MELD-Na, have already demonstrated utility beyond liver transplantation.[4,5] This broader application may be even more significant and precise with MELD 3.0 because of its superior calibration. Albumin, in particular, adds a valuable dimension by indirectly reflecting nutritional reserve and systemic inflammation, two critical elements in evaluating frailty and long-term prognosis.[3] However, the inclusion of albumin also introduces context-dependent limitations. Exogenous albumin administration, which is commonly used in acute liver decompensation, alcoholic hepatitis, and oncologic settings, may transiently elevate serum albumin levels, thereby artificially lowering the calculated MELD 3.0 score. This effect may mask the true severity of hepatic dysfunction in acute or intervention-intensive clinical scenarios. Accordingly, the prognostic performance of MELD 3.0 must be interpreted in light of treatment-related confounding, particularly in settings where albumin infusion is frequent.

This narrative review explores the evolving role of MELD 3.0 across various clinical settings while also drawing comparisons with other scoring systems where applicable.

Discussion

Orthotopic Heart Transplantation

Orthotopic heart transplantation (HTx) is considered the gold standard for treating end-stage heart failure (HF).[6] Assessing postoperative outcomes is critical in these major procedures, and various tools have been used for this purpose. The use of MELD 3.0 in this clinical setting is particularly useful and feasible because of the nature of its components, as well as the frequent coexistence of heart failure and liver disease, which share several risk factors, including alcohol abuse, drug abuse, chronic inflammation, autoimmune

disorders, and infections.[7] In addition, patients with heart failure are at increased risk of developing hepatic dysfunction, which can adversely affect transplant outcomes.

In 2012, Chokshi et al.[8] studied 617 adult patients to evaluate 30-day outcomes and 10-year survival rates. This study used MELD or modified MELD, a score in which albumin replaced INR, and found that high pretransplant scores were associated with worse 30-day outcomes and lower 10-year survival rates. In 2018, a study conducted in Brazil used MELD excluding INR (MELD-IX), another MELD-based model, and found that higher preoperative scores were associated with a poor prognosis in patients undergoing HTx.[9]

Following this research trajectory, Ptak et al.[10] conducted a 2024 study using MELD 3.0 in 106 patients with advanced HF undergoing HTx. The primary endpoint of the study was 6-month mortality, and the secondary endpoint was the length of ICU stay after HTx. MELD 3.0 scores for all patients were calculated 1 month before HTx and again 1 week after the procedure. According to the study results, 16% of patients died within 6 months after HTx, and all of them had a significantly higher mean 1-week post-HTx MELD 3.0 score of 18.3 (range: 14.5–22.7) compared with the mean score of 13.9 (range: 9.5–16.4) among survivors, with $p<0.01$. Receiver operating characteristic (ROC) analysis identified a MELD 3.0 cutoff point of 17.3, and patients exceeding this threshold had longer ICU stays, with a mean difference of 5 days ($p=0.01$). Conversely, pre-HTx MELD 3.0 scores did not differ significantly between the two groups ($p=0.36$), suggesting limited prognostic value in the preoperative phase. In summary, the MELD 3.0 score appears to be a promising postoperative prognostic indicator for patients with advanced HF undergoing HTx, and its ability to predict posttransplant ICU burden emphasizes the importance of postoperative risk stratification in improving outcomes.

However, in this study, MELD 3.0 was analyzed without direct comparison with other MELD score variants. This limitation restricts the interpretability of the findings, as assessing a single prognostic model in isolation does not allow determination of whether MELD 3.0 truly outperforms other scores. Therefore, the results should be viewed as demonstrating the potential applicability of MELD 3.0 in this population rather than establishing its superiority. Moreover, the study did not report baseline hepatic characteristics or specify whether patients undergoing HTx had preexisting liver disease. As not all HTx recipients have liver pathology, this omission makes it difficult to determine whether MELD 3.0 functioned as a true cardiometabolic prognostic score or whether its predictive ability was partly driven by underlying hepatic dysfunction. In addition, the available evidence to date is confined to this single study, which limits generalizability, and further research is warranted for validation.

Acute Variceal Hemorrhage

With a substantial 6-week mortality risk of 15%–25%, acute variceal hemorrhage (AVH) is one of the most serious decompensating events in patients with cirrhosis.[11,12] Accurately predicting short-term mortality in these patients is crucial for clinical decision-making, risk stratification, and therapeutic intervention planning. Although conventional prognostic models, such as MELD and Child-Turcotte-Pugh (CTP) scores, have been widely used for mortality prediction in AVH, the advent of MELD 3.0 has prompted research into its relative utility in this acute context.[13]

One of the first systematic assessments of the ability of MELD 3.0 to predict 6-week mortality after variceal bleeding was conducted by Buckholz and colleagues in a multicenter study involving five academic medical centers and a US cohort of 354 patients with endoscopically confirmed AVH.[14] Compared with the classic MELD score (AUROC 0.76) and CTP score (AUROC 0.77), MELD 3.0 demonstrated an AUROC of 0.77 for identifying patients at increased risk of mortality. All three models showed statistically equivalent discriminatory performance, suggesting that the enhanced components of MELD 3.0 do not significantly improve mortality prediction accuracy over existing models in the AVH setting. The study also revealed important calibration differences between models when externally validated across multiple centers. After recalibration, the CTP score demonstrated superior calibration and overall performance compared with both MELD 3.0 and traditional MELD scores. The recalibrated MELD 3.0 showed acceptable calibration ($p=0.26$) but exhibited increased heterogeneity in observed mortality at higher scores across different cohorts, potentially limiting its reliability in clinical practice. The acute nature of variceal bleeding may cause components of the MELD 3.0 score, such as sodium and creatinine levels, to deviate substantially from a patient's chronic baseline values during hospitalization. This deviation may misrepresent the patient's underlying organ function.[14] The study also established clinically relevant mortality thresholds. A MELD 3.0 score of less than 12 corresponded to less than 5% 6-week mortality, whereas a score greater than 20 corresponded to greater than 20% 6-week mortality. However, these findings are limited by calibration challenges in acute settings.[14]

Hepatocellular Carcinoma Patients with Renal Insufficiency

There is a bidirectional relationship between kidney dysfunction and hepatocellular carcinoma (HCC).[15] Studies have shown that more than 25% of individuals with HCC have renal insufficiency (RI), often developing as a result of cirrhosis.[16] It is well known that splanchnic vasodilation occurs in patients with cirrhosis, resulting in reduced effective arterial blood volume. This, in turn, triggers compensatory vasoconstrictive mechanisms, ultimately causing renal hypoperfusion.[16,17] Conversely, growing evidence suggests that patients with end-stage renal disease (ESRD) are at increased risk of developing liver cancer.[18,19]

To evaluate how well liver function models predict outcomes in this high-risk patient population, Ho et al.[20] conducted a cohort study evaluating five liver reserve models in patients with HCC and RI: albumin-bilirubin (ALBI), easy ALBI, platelet-albumin-bilirubin (PALBI), platelet-albumin (PAL), and MELD 3.0. The study included

1,120 patients and assessed the performance of these models in stratifying overall survival. Although all five models significantly predicted survival (all p<0.001), their prognostic accuracy varied. This was assessed using the corrected Akaike information criterion (AICc) and the homogeneity index. A lower AICc and a higher homogeneity index indicate better model performance. Among the models, MELD 3.0 showed moderate predictive value, with an AICc of 11,364 and a homogeneity score of 156.026. However, it was outperformed by the ALBI-based models. The ALBI model demonstrated the best prognostic accuracy, with the lowest AICc (11,281.79) and the highest homogeneity index (239.031), making it the most reliable tool for predicting overall survival in patients with HCC and RI.

Transjugular Intrahepatic Portosystemic Shunt Creation

Researchers at the Mayo Clinic created the first MELD score in the early 2000s with the specific purpose of predicting short-term mortality in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS).[1] The MELD score was then adopted in 2002 to prioritize liver transplant allocation and subsequently became an established tool in transplant medicine.[2] The original use of the MELD score in TIPS-related risk stratification has gradually evolved, and more recent versions have been tailored for transplantation. This section revisits the foundational purpose of the MELD score by evaluating the performance of the most recent version, MELD 3.0, in the context of TIPS procedures. TIPS achieves high technical success rates of 94%–95% and clinical success in 92% of cases.[21] However, long-term outcomes remain variable, with survival rates of 87.5% at 1 month, 66.8% at 1 year, and 44.7% at 5 years after the procedure.[22,23] These outcomes are heavily influenced by appropriate patient selection and preoperative risk stratification, areas in which the MELD 3.0 scoring system offers significant utility.

Pre-TIPS MELD 3.0 scores are especially useful for identifying patients at the highest risk of poor outcomes. A retrospective review of 855 patients with cirrhosis who underwent TIPS between December 2011 and October 2019 assessed the prognostic performance of MELD 3.0, MELD, MELD-Na, Child-Pugh, and Freiburg Index of Post-TIPS Survival (FIPS) scores. The c-index for MELD 3.0 in predicting 3-month mortality was 0.727 (95% CI: 0.645–0.808), significantly outperforming MELD (0.663), MELD-Na (0.672), and FIPS (0.582) (p<0.05 for all). The Child-Pugh score showed slightly higher c-indices for 3-, 6-, and 12-month mortality but was comparable to MELD 3.0 overall. A MELD 3.0 score of 14 was suggested as a meaningful cutoff to distinguish between high- and low-risk patients.[24]

Following TIPS placement, serial measurements of MELD 3.0 provide valuable dynamic prognostic information. An increase of 3 points in MELD-Na, which closely correlated with MELD 3.0, within 6 months after the procedure is associated with a 1.8-fold increase in long-term mortality, independent of the initial baseline score.[25] This finding highlights the importance of reevaluating transplant needs at 6 months. Indeed, according to the Advancing Liver Therapeutic Approaches (ALTA) retrospective study, among patients who achieved early transplant-free survival, 62% maintained a 1-year survival rate of 88% and a 3-year survival rate of 57%, even without transplantation.[25] This multicenter ALTA retrospective study included 1,127 adult patients who underwent TIPS, with a total follow-up of 2,040 person-years. Competing risk regression analyses demonstrated that both MELD-Na and MELD 3.0 were independently associated with post-TIPS mortality. Compared with MELD-Na<15, hazard ratios for mortality were 1.1 (p=0.42) for MELD-Na 15–19, 1.3 (p=0.04) for MELD-Na 20–24, and 1.7 (p<0.01) for MELD-Na≥25.[25]

In the context of TIPS, this allows better identification of candidates for whom the procedure can serve as definitive therapy ("destination TIPS") versus those who may require it as a bridge to transplantation. Notably, patients with stable MELD 3.0 scores after TIPS have low complication rates, with only an 8% rate of hepatic encephalopathy-related hospitalizations, supporting the long-term viability of TIPS in selected individuals.[25] Overall, MELD 3.0 serves a dual purpose in TIPS management: it guides initial risk stratification and enables ongoing prognostic monitoring. Integrating MELD 3.0 into both procedural planning and 6-month follow-up assessments allows clinicians to better evaluate transplant candidacy and avoid unnecessary listings for patients likely to achieve sustained transplant-free survival.[24–26] Findings from the ALTA group further support the implementation of MELD 3.0-guided reassessment protocols, potentially redefining TIPS from a bridge to transplantation to a long-term, standalone therapy in carefully selected patients.[25]

Alcohol-Associated Hepatitis

Alcohol-associated hepatitis (AH) remains a formidable clinical challenge, characterized by acute liver injury due to excessive alcohol consumption and associated with high morbidity and mortality. Severe AH, often defined by a Maddrey Discriminant Function (MDF) score of 32 or higher, carries a short-term mortality risk approaching 50% within 28 days, with overall 90-day mortality rates ranging from 30% to 40%.[27–30] The clinical course of severe AH is often complicated by multiorgan failure, particularly acute kidney injury (AKI), which is a major determinant of poor prognosis. Accurate risk stratification is therefore essential for guiding therapeutic decisions, including the use of corticosteroids and consideration for liver transplantation. Models such as the Age-Bilirubin-INR-Creatinine (ABIC) score, MDF, MELD, and MELD-Na have historically been used to estimate short-term mortality in AH.[27] However, these models have underestimated disease severity in malnourished individuals. By including factors such as serum sodium and albumin, which more accurately reflect the patient's nutritional status and overall health, MELD 3.0 has addressed this limitation and improved risk assessment and prognosis.[3]

In a large multinational retrospective cohort study that included 2,124 patients from 28 centers in 10 countries, MELD 3.0 outperformed MELD-Na and MDF in predicting 30-day and 90-day mortality, with area under the curve (AUC) values of 0.761 and 0.757,

respectively. Importantly, the classification accuracy of MELD 3.0 was consistent across various geographic regions and patient subgroups, although its performance was comparable to that of the original MELD and ABIC scores. This may be attributed to differences in alcohol exposure, as well as environmental, genetic, and epigenetic factors. Notably, MELD 3.0 demonstrated clinical value in identifying patients at risk for severe multiorgan dysfunction, as it was the most accurate predictor of the need for renal replacement therapy (RRT) during hospitalization (AUC 0.844). Given that renal impairment is a key driver of mortality in AH, this predictive capability is clinically meaningful. The study also highlighted that 6-month survival remained poor, at only 57%, reflecting the aggressive natural history of severe AH despite advances in supportive care. Although further prospective validation is warranted, these findings support the integration of MELD 3.0 into routine clinical practice for AH, both for mortality risk stratification and for anticipating the need for intensive interventions such as RRT, thereby expanding its utility well beyond the transplantation setting.[31]

Additionally, in a study conducted in 2024, MELD scores were applied at patient admission to evaluate AH severity and predict response to corticosteroids. The study found that patients with MELD scores greater than 30 showed poor or no response to corticosteroids (odds ratio, 2.42). This association exists because elevated MELD scores correlate with clinical factors such as age, cirrhosis, hypoalbuminemia, and RI, which collectively predict poor corticosteroid response. ROC curve analyses revealed that, compared with other scoring systems such as MDF, MELD-Na, ABIC, and the Glasgow Alcoholic Hepatitis Score (GAHS), MELD 3.0 had the highest AUC for predicting mortality at 1 month and 1 year. A MELD 3.0 threshold above 20 showed high sensitivity, at approximately 91%–92%, making it an important tool for early risk assessment and mortality prediction.[30]

One important limitation to acknowledge is the inclusion of albumin in the MELD 3.0 calculation, particularly for patients with alcoholic hepatitis or renal insufficiency. These patients frequently receive albumin supplementation early in their clinical course, which may artificially elevate measured albumin levels and confound risk estimation. Although the model incorporates the correlation between albumin and creatinine, this potential source of bias remains clinically relevant.

Hepatic Visceral Crisis in Patients with Solid Tumors

Hepatic visceral crisis (HVC) is a fatal syndrome often observed in solid tumors of the breast, colorectal system, and pancreas and results from the rapid deterioration of liver function due to metastatic burden. This condition is reflected by elevated liver enzymes, hyperbilirubinemia (>1.5 times the upper limit), and clinical signs such as hepatocellular failure without biliary obstruction.[32,33]

A unique study by Tay et al.[34] investigated the combined utility of MELD scoring systems and the Systemic Immune-Inflammatory Index (SII) in predicting outcomes in patients with solid tumors experiencing HVC. All three MELD variants—original MELD, MELD-Na, and MELD 3.0—showed considerable predictive significance in their descriptive investigation of 295 patients, with patients scoring ≥20 having an approximately two-fold higher risk of death. In these high-scoring groups, median overall survival was significantly lower: 1.28 versus 2.16 months for MELD 3.0 ($p=0.039$), 0.88 versus 1.44 months for original MELD ($p<0.001$), and 0.85 versus 1.64 months for MELD-Na ($p<0.001$). An SII ≥626.28 was also found to be a strong predictor of mortality, with 78.7% sensitivity and 100% specificity on ROC analysis. Cox regression identified several factors influencing survival, with MELD-Na ≥20 increasing the probability of death by 2.41-fold.[34] This study provides clinicians with useful, affordable, and objective tools for assessing prognosis in patients with cancer and liver disease, marking a significant advance in the application of MELD scoring beyond transplantation settings. The combination of MELD scores with inflammatory markers such as SII offers enhanced sensitivity and specificity while eliminating sex-based disparities in mortality estimation, positioning this approach as valuable for clinical decision-making in oncology practice. In addition, the study showed that the predictive performance of MELD, MELD-Na, and MELD 3.0 was comparable despite the inclusion of albumin in the MELD 3.0 model. Nonetheless, MELD 3.0 might be expected to perform better in HVC given the typically low albumin levels in these patients. This discrepancy highlights the need for further evaluation of MELD 3.0 in oncology-related hepatic dysfunction. As in the heart transplantation domain, evidence in this setting remains limited; to date, available data are confined to a single study, which limits generalizability and warrants further validation.

Hepatic Hydrothorax

Hepatic hydrothorax (HH) is a serious complication of advanced cirrhosis, characterized by the development of transudative pleural effusions in the absence of underlying cardiac or pulmonary disease. It affects approximately 5%–16% of patients with cirrhosis, particularly those with more advanced liver dysfunction, such as Child-Pugh class B or C.[35,36] Compared with cirrhosis with ascites alone, HH is associated with significantly poorer outcomes, with reported 1-year mortality rates ranging from 50% to 60%.[35,37,38] Median survival after HH onset is typically less than 1 year, and short-term mortality is notably high; studies have reported 30-day, 90-day, and 1-year mortality rates of 10%–29%, 26%–45%, and 51%–59%, respectively.[35,37,39]

Crucially, emerging data suggest that patients with HH tend to die at lower MELD or MELD-Na scores than those with refractory ascites, implying that conventional MELD-based scoring may underestimate disease severity in these patients.[39,40] For instance, one study found that the median MELD score at death among patients with HH was 22.5, compared with 32.5 among patients with cirrhosis without HH.[40] This indicates that HH contributes additional mortality risk that is not fully captured by the MELD or MELD-Na scoring systems. Unfortunately, even MELD 3.0 has shown limited utility in accurately predicting mortality in patients with HH.[39,40]

Table 1. Key findings overview

Clinical condition	Primary endpoint	Comparison to other scores	Clinical utility
Orthotopic Heart Transplantation	6-month mortality	Not compared to other MELD variants	Predicts ICU stay (5 days difference, p=0.01)
Acute Variceal Hemorrhage	6-week mortality	Comparable to traditional scores	Limited by calibration variability in acute settings
HCC with Renal Insufficiency	Overall survival	Inferior to ALBI-based models (AICc: 11,281.79)	Moderate predictive value, inferior to ALBI-based models
TIPS Procedures	3-month mortality	Superior to prior MELD variants (p<0.05)	Dynamic monitoring; 3-point increase = 1.8x mortality risk
Alcohol-Associated Hepatitis	30-day & 90-day mortality	Comparable to the MELD and ABIC scores	Best predictor of RRT need (AUC 0.844)
Hepatic Visceral Crisis	Overall survival	Comparable to MELD-Original and MELD-Na	Enhanced when combined with SII; 2-fold mortality risk
Hepatic Hydrothorax	Mortality	Inferior across MELD variants	Underestimates the mortality risk in this group of patients
Spontaneous Bacterial Peritonitis	In-hospital & 3-month mortality	Comparable to other MELD variants (p>0.05)	Reliable for short-term mortality prediction

MELD: Model for end-stage liver disease; HCC: Hepatocellular carcinoma; ALBI: Albumin-bilirubin; AICc: Akaike information criterion; TIPS: Transjugular intrahepatic portosystemic shunt; ABIC: Age-bilirubin-INR-creatinine; RRT: Renal replacement therapy; AUC: Area under the curve; SII: Systemic immune-inflammatory index.

Spontaneous Bacterial Peritonitis

Spontaneous bacterial peritonitis (SBP) is the most common bacterial infection encountered in patients with cirrhosis.[41] Its prevalence ranges from 1.5% to 3% in outpatients and may reach 10% to 30% in hospitalized patients with cirrhosis.[42] Microcirculatory changes due to cirrhosis and portal hypertension disrupt intestinal mucosal blood flow and compromise intestinal barrier integrity, facilitating the translocation of bacterial pathogens into the peritoneal cavity and leading to SBP.[43] It is important to recognize that infections such as SBP can increase the mortality rate fourfold in patients with cirrhosis.[44] Therefore, accurate prognostic tools are needed to enable early intervention and reduce mortality.

Lin et al.[45] assessed the predictive power of several scoring systems for short-term mortality in patients with cirrhosis experiencing their first episode of SBP in a retrospective study. The performance of multiple scoring models, including CTP, MELD, MELD-Na, integrated MELD (iMELD), and MELD 3.0, was examined in a total of 327 patients. In-hospital mortality, as well as 3- and 6-month mortality after SBP diagnosis, were the main outcomes evaluated. MELD 3.0 outperformed the other models for 3-month mortality (AUROC=0.760) and in-hospital mortality (AUROC=0.786). Although MELD 3.0 did not demonstrate statistically significant superiority over previous MELD-based models (p>0.05 for all comparisons), it did significantly outperform the CTP score (p<0.001). The iMELD score had the highest AUROC (0.752) for predicting 6-month mortality and was significantly superior to CTP (p<0.0001), although its advantage over the other MELD-based scores was not statistically significant (p>0.05). Compared with more traditional scoring methods such as CTP, MELD 3.0 shows potential as a reliable model for predicting short-term mortality in patients with cirrhosis and SBP.

Conclusion

The MELD 3.0 score demonstrates notable prognostic utility across a variety of hepatic and extrahepatic clinical contexts. In cardiac transplantation, findings demonstrate the potential applicability of MELD 3.0 for predicting 6-month mortality and ICU length of stay. In acute variceal hemorrhage, although MELD 3.0 performs comparably to traditional scores such as MELD and Child-Turcotte-Pugh (CTP), its practical use is limited by calibration variability, making simpler tools more suitable in acute settings. Among patients with hepatocellular carcinoma and renal insufficiency, MELD 3.0 shows prognostic value but is surpassed by liver-specific scores such as ALBI. In TIPS procedures, MELD 3.0 improves patient selection and timing for transplant evaluation, supporting its use beyond traditional models. It also outperforms other scores in alcohol-associated hepatitis, particularly in assessing the need for renal replacement therapy and addressing sex- and nutrition-related disparities. In oncology, MELD 3.0 combined with inflammatory markers helps stratify risk in patients with hepatic visceral crisis. However, in hepatic hydrothorax, it underestimates mortality risk, highlighting the need for condition-specific tools. In spontaneous bacterial peritonitis, MELD 3.0 offers superior short-term mortality prediction, reinforcing its value in high-risk cirrhotic populations. For a concise overview, the main results are tabulated in Table 1. Overall, MELD 3.0 enhances prognostic accuracy but requires context-specific application to maximize its clinical impact. Before MELD 3.0 can be universally implemented, large-scale prospective studies across multiple regions and transplant settings are required to confirm its generalizability and validate its superiority over existing scoring systems.

Ethics Committee Approval: Ethics committee approval was not required, as this study is a review article and did not involve human participants, animal subjects, or identifiable personal data.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: Artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) were not used in the production of submitted work.

Authors' contributions: Concept: PKRK, HEB, AC; Design: KKA, DK, AM, TA; Supervision: NO, MK, HR; Data Collection and/or Processing: AM, AC; Analysis and/or Interpretation: PKRK, HEB; Literature Review: PKRK, KKA; Writing: DK, AC, HEB, MK; Critical Review: NO, TA, MK.

Peer-review: Externally peer-reviewed.

References

1. Singal AK, Kamath PS. Model for end-stage liver disease. J Clin Exp Hepatol 2013;3(1):50-60. [CrossRef]
2. Bernardi M, Gitto S, Biselli M. The MELD score in patients awaiting liver transplant: strengths and weaknesses. J Hepatol 2011;54(6):1297-1306. [CrossRef]
3. Kim WR, Mannalithara A, Heimbach JK, Kamath PS, Asrani SK, Biggins SW, et al. MELD 3.0: the model for end-stage liver disease updated for the modern era. Gastroenterology 2021;161(6):1887-1895.e4. [CrossRef]
4. Mazumder NR, Fontana RJ. MELD 3.0 in advanced chronic liver disease. Annu Rev Med 2024;75:233-245. [CrossRef]
5. Annamalai A, Harada MY, Chen M, Tran T, Ko A, Ley EJ, et al. Predictors of mortality in the critically ill cirrhotic patient: is the model for end-stage liver disease enough? J Am Coll Surg 2017;224(3):276-282. [CrossRef]
6. Wilhelm MJ. Long-term outcome following heart transplantation: current perspective. J Thorac Dis 2015;7(3):549-551.
7. Xanthopoulos A, Starling RC, Kitai T, Triposkiadis F. Heart failure and liver disease: cardiohepatic interactions. JACC Heart Fail 2019;7(2):87-97. [CrossRef]
8. Chokshi A, Cheema FH, Schaefle KJ, Jiang J, Collado E, Shahzad K, et al. Hepatic dysfunction and survival after orthotopic heart transplantation: application of the MELD scoring system for outcome prediction. J Heart Lung Transplant 2012;31(6):591-600. [CrossRef]
9. Moraes ACO, Fonseca-Neto OCLD. The use of MELD score (model for end-stage liver disease) and derivatives in cardiac transplantation. Arq Bras Cir Dig 2018;31(2):e1370. [CrossRef]
10. Ptak J, Sokolski M, Gontarczyk J, Mania R, Byszuk P, Krupka D, et al. Postoperative, but not preoperative, MELD-3.0 prognosticates 3-month procedural success in patients undergoing orthotopic heart transplantation. J Clin Med 2024;13(19):5816. [CrossRef]
11. Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W; Practice Guidelines Committee of the American Association for the Study of Liver Diseases; Practice Parameters Committee of the American College of Gastroenterology. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. Hepatology 2007;46(3):922-938. [CrossRef]
12. Garcia-Tsao G, Abraldes JG, Berzigotti A, Bosch J. Portal hypertensive bleeding in cirrhosis: risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the Study of Liver Diseases. Hepatology 2017;65(1):310-335. [CrossRef]
13. Al Sibae MR, Cappell MS. Accuracy of MELD scores in predicting mortality in decompensated cirrhosis from variceal bleeding, hepatorenal syndrome, alcoholic hepatitis, or acute liver failure as well as mortality after non-transplant surgery or TIPS. Dig Dis Sci 2011;56(4):977-987. [CrossRef]
14. Buckholz A, Wong R, Curry MP, Baffy G, Chak E, Rustagi T, et al. MELD, MELD 3.0, versus Child score to predict mortality after acute variceal hemorrhage: a multicenter US cohort. Hepatol Commun 2023;7(10):e0258. [CrossRef]
15. Chidambaranathan-Reghupaty S, Fisher PB, Sarkar D. Hepatocellular carcinoma (HCC): epidemiology, etiology and molecular classification. Adv Cancer Res 2021;149:1-61. [CrossRef]
16. Ho S, Liu P, Hsu C, Ko CC, Huang YH, Su CW, et al. ALBI grade in dialysis patients with hepatocellular carcinoma: prognostic impact and staging strategy. J Gastrointest Oncol 2021;12(2):722-734. [CrossRef]
17. Ginès P, Schrier RW. Renal failure in cirrhosis. N Engl J Med 2009;361(13):1279-1290. [CrossRef]
18. Yeh H, Chiang CC, Yen TH. Hepatocellular carcinoma in patients with renal dysfunction: pathophysiology, prognosis, and treatment challenges. World J Gastroenterol 2021;27(26):4104-4142. [CrossRef]
19. Lee CH, Hsieh SY, Chang CC, Wang IK, Huang WH, Weng CH, et al. Hepatocellular carcinoma in hemodialysis patients. Oncotarget 2017;8(42):73154-73161. [CrossRef]
20. Ho SY, Liu PH, Hsu CY, Tseng HT, Huang YH, Su CW, et al. Albumin-based liver reserve models vs. MELD 3.0 in prognostic prediction for hepatocellular carcinoma patients with renal insufficiency. Int J Mol Sci 2023;24(23):16987. [CrossRef]
21. Tandon B, Ramachandran J, Narayana S, Muller K, Pathi R, Wigg AJ. Outcomes of transjugular intrahepatic portosystemic shunt procedures: a 10-year experience. J Med Imaging Radiat Oncol 2021;65(6):655-662. [CrossRef]
22. Kim HK, Kim YJ, Chung WJ, Kim SS, Shim JJ, Choi MS, et al. Clinical outcomes of transjugular intrahepatic portosystemic shunt for portal hypertension: Korean multicenter real-practice data. Clin Mol Hepatol 2014;20(1):18-27. [CrossRef]
23. Perello MP, Mur JP, Vives MS, Riutort JMM, Artigues AP, Garcia CN, et al. Long-term follow-up of transjugular intrahepatic portosystemic shunt (TIPS) with stent-graft. Diagn Interv Radiol 2019;25(5):346-352. [CrossRef]
24. Song J, Wang X, Yan Y, Xiang T, Luo X. MELD 3.0 score for predicting survival in patients with cirrhosis after transjugular intrahepatic portosystemic shunt creation. Dig Dis Sci 2023;68(7):3185-3192. [CrossRef]
25. Nobel YR, Boike JR, Mazumder NR, Thornburg B, Hoffman R, Kolli KP, et al. Predictors of long-term clinical outcomes after TIPS: an ALTA group study. Hepatology 2025;81(4):1244-1255. [CrossRef]
26. Lin HY, Loi PL, Ng J, Shen L, Teo WQ, Chung A, et al. MELD3.0 is superior to MELDNa and MELD for prediction of mortality in patients with cirrhosis: an external validation in a multi-ethnic population. JGH Open 2024;8(6):e13098. [CrossRef]
27. Morales-Arráez D, Ventura-Cots M, Altamirano J, Abraldes JG, Cruz-Lemini M, Thursz MR, et al. The MELD score is superior to the Maddrey discriminant function score to predict short-term mortality in alcohol-associated hepatitis: a global study. Am J Gastroenterol 2022;117(2):301-310. [CrossRef]
28. Clemente-Sánchez A, Oliveira-Mello A, Bataller R. Moderate alcoholic hepatitis. Clin Liver Dis 2021;25(3):537-555. [CrossRef]
29. Mitri J, Almeqdadi M, Karagozian R. Prognostic and diagnostic scoring models in acute alcohol-associated hepatitis: a review comparing the performance of different scoring systems. World J Hepatol 2023;15(8):954-963. [CrossRef]

30. Singeap AM, Minea H, Petrea O, Robea MA, Balmuș IM, Duta R, et al. Real-world utilization of corticosteroids in severe alcoholic hepatitis: eligibility, response, and outcomes. Medicina (Kaunas) 2024;60(2):311. [CrossRef]
31. Díaz LA, Fuentes-López E, Ayares G, Idalsoaga F, Arnold J, Valverde MA, et al. MELD 3.0 adequately predicts mortality and renal replacement therapy requirements in patients with alcohol-associated hepatitis. JHEP Rep 2023;5(8):100727. [CrossRef]
32. Puskulluoglu M, Pieniążek M, Rudzińska A, Pietruszka A, Pacholczak-Madej R, Grela-Wojewoda A, et al. Cisplatin monotherapy as a treatment option for patients with HER-2 negative breast cancer experiencing hepatic visceral crisis or impending visceral crisis. Oncol Ther 2024;12(3):419-435. [CrossRef]
33. Sbitti Y, Slimani K, Debbagh A, et al. Visceral crisis means short survival among patients with luminal A metastatic breast cancer: a retrospective cohort study. World J Oncol 2017;8(4):105-109. [CrossRef]
34. Tay F, Buyukkor M, Duran AO. Prognostic importance of combined use of MELD scores and SII in hepatic visceral crisis in patients with solid tumours. J Coll Physicians Surg Pak 2023;33(8):879-883. [CrossRef]
35. Wilkins H, Britt E, Bhatnagar M, Pippard B. Hepatic hydrothorax. J Thorac Dis 2024;16(2):1662-1673. [CrossRef]
36. Yoon JH, Kim HJ, Jun CH, Cho SB, Jung Y, Choi SK. Various treatment modalities in hepatic hydrothorax: what is safe and effective? Yonsei Med J 2019;60(10):944-951. [CrossRef]
37. Romero S, Lim AK, Singh G, Kodikara C, Shingaki-Wells R, Chen L, et al. Natural history and outcomes of patients with liver cirrhosis complicated by hepatic hydrothorax. World J Gastroenterol 2022;28(35):5175-5187. [CrossRef]
38. Matei D, Craciun R, Crisan D, Procopet B, Mocan T, Pasca S, et al. Hepatic hydrothorax-an independent decompensating event associated with long-term mortality in patients with cirrhosis. J Clin Med 2021;10(16):3688. [CrossRef]
39. Chin A, Bastaich DR, Dahman B, Kaplan DE, Taddei TH, John BV. Refractory hepatic hydrothorax is associated with increased mortality with death occurring at lower MELD-Na compared to cirrhosis and refractory ascites. Hepatology 2024;79(4):844-856. [CrossRef]
40. Bucurica S, Parolă I, Vasile AG, Maniu I, Mititelu MR. The impact of hepatic hydrothorax on the outcome of liver cirrhosis: a comparative study. J Clin Med 2025;14(1):212. [CrossRef]
41. Marciano S, Díaz JM, Dirchwolf M, Gadano A. Spontaneous bacterial peritonitis in patients with cirrhosis: incidence, outcomes, and treatment strategies. Hepat Med 2019;11:13-22. [CrossRef]
42. Oladimeji AA, Temi AP, Adekunle AE, Taiwo RH, Ayokunle DS. Prevalence of spontaneous bacterial peritonitis in liver cirrhosis with ascites. Pan Afr Med J 2013;15:128. [CrossRef]
43. Shizuma T. Spontaneous bacterial and fungal peritonitis in patients with liver cirrhosis: a literature review. World J Hepatol 2018;10(2):254-266. [CrossRef]
44. Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality fourfold and should be used in determining prognosis. Gastroenterology 2010;139(4):1246-1256.e5. [CrossRef]
45. Lin YT, Chen WT, Wu TH, Liu Y, Liu LT, Teng W, et al. A validated composite score demonstrates potential superiority to MELD-based systems in predicting short-term survival in patients with liver cirrhosis and spontaneous bacterial peritonitis-a preliminary study. Diagnostics (Basel) 2023;13(15):2578. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 249–255 DOI: 10.14744/hf.2026.79050

ORIGINAL RESEARCH

Artificial intelligence-based multiclass classification of etiologies in patients with elevated liver enzymes: A prospective cohort study

Yavuz Ozden, Omer Yuzugulen, Nuh Mehmet Buyukberber

Department of Gastroenterology, University of Health Sciences, Kayseri City Hospital, Kayseri, Türkiye

Highlights & Insights

- **Scientific Gap:** Persistent liver enzyme elevation has overlapping etiologies, making diagnostic evaluation sequential and test-intensive.
- **Key Finding:** An explainable multiclass AI model differentiated five major etiologies with an overall accuracy of 0.86 using routine clinical and laboratory data.
- **Clinical Impact:** The model may support structured triage and targeted confirmatory testing, but external validation is required before clinical use.

ABSTRACT

Background and Aim: Elevated liver enzymes are a common reason for hepatology referral, but etiological overlap complicates diagnosis. Most artificial intelligence applications address binary tasks, whereas routine practice requires multiclass discrimination. We developed and internally validated an explainable multiclass model to differentiate five major causes of persistent liver enzyme elevation.

Materials and Methods: This prospective proof-of-concept cohort included 280 consecutive adults with unexplained persistent aminotransferase elevation. Final diagnoses—metabolic dysfunction-associated steatotic liver disease, viral hepatitis, alcohol-related liver disease, drug-induced liver injury, or autoimmune hepatitis—were independently adjudicated by three hepatologists. Data were split into training (70%) and independent test (30%) sets, and four supervised algorithms were evaluated. To assess incorporation bias, a basic model using routine clinical and biochemical variables was compared with an extended model including serological markers. Interpretability was assessed using SHapley Additive exPlanations.

Results: eXtreme gradient boosting achieved the best test-set performance, with an overall accuracy of 0.86 (95% CI 0.78–0.93) and balanced accuracy of 0.87 (95% CI 0.82–0.92). Class-specific AUROC values ranged from 0.92 to 0.95. Serological markers improved discrimination for autoimmune hepatitis (AUROC increase, 0.15; $p<0.03$) and viral hepatitis (increase, 0.11; $p<0.02$). Interpretability analysis identified clinically plausible predictors. Misclassifications occurred in 12 cases (14.3%), mainly in overlapping drug-induced liver injury–autoimmune hepatitis presentations.

Conclusion: An explainable multiclass model differentiated five major etiologies of persistent liver enzyme elevation. Serological markers added value for autoimmune and viral etiologies. External validation is required before clinical implementation.

Keywords: Aminotransferases, artificial intelligence, liver diseases.

How to cite this article: Ozden Y, Yuzugulen O, Buyukberber NM. Artificial intelligence-based multiclass classification of etiologies in patients with elevated liver enzymes: A prospective cohort study. Hepatology Forum 2026; 7(3):249–255.

Received: February 16, 2026; **Revised:** February 25, 2026; **Accepted:** March 04, 2026; **Available Online:** July 02, 2026

Corresponding author: Yavuz Ozden; Department of Gastroenterology, University of Health Sciences, Kayseri City Hospital, Kayseri, Türkiye; **E-mail:** yavuzozden@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

Persistent elevation of liver enzymes is a frequent reason for hepatology referral and often presents a diagnostic dilemma rather than a final diagnosis. The main etiologies encountered in routine practice include metabolic dysfunction-associated steatotic liver disease (MASLD), viral hepatitis, alcohol-related liver disease (ALD), drug-induced liver injury (DILI), and autoimmune hepatitis (AIH). These conditions may present with overlapping clinical and biochemical features, particularly in patients with metabolic risk factors, borderline alcohol intake, recent drug exposure, or low-titer autoantibody positivity.[1,2] Consequently, diagnostic evaluation often proceeds through sequential laboratory testing, imaging, and occasionally histopathology, with variable diagnostic yield.[3–6]

Machine learning (ML) methods may support this process by modeling complex interactions among routine clinical and laboratory variables.[4,7–10] However, most AI applications in hepatology have focused on binary classification or single-disease prediction within selected cohorts.[6,11,12] This does not fully reflect routine hepatology practice, where several competing etiologies often need to be considered simultaneously in patients with abnormal liver biochemistry. Multiclass etiological discrimination is therefore a clinically relevant but still insufficiently studied application of artificial intelligence (AI).[3,13]

Before such models can be adopted clinically, several issues must be addressed, including class imbalance, small sample sizes in less frequent diagnoses, generalizability, and incorporation bias when disease-defining tests are used as predictors.[14] Interpretability is also essential. SHapley Additive exPlanations (SHAP) can help determine whether model predictions are driven by clinically plausible variables rather than opaque statistical patterns.[15,16]

We hypothesized that a multiclass ML model based on routinely available clinical and laboratory data could distinguish the major causes of persistent liver enzyme elevation. In this prospective proof-of-concept cohort study, we developed and internally validated an explainable AI-based model to differentiate MASLD, viral hepatitis, ALD, DILI, and AIH. To address incorporation bias, we compared a basic model excluding disease-defining serological markers with an extended model that included viral serologies, autoantibodies, and immunoglobulin G. We also examined SHAP-based explanations and misclassification patterns to assess clinical plausibility.

Materials and Methods

Study Design and Participants

We conducted a prospective, single-center observational cohort study at a tertiary academic medical center in Türkiye. Consecutive adults aged ≥18 years referred for newly detected, unexplained liver enzyme elevation were screened between October 15, 2025, and February 15, 2026. Persistent elevation was defined as alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) levels >1.5 times the upper limit of normal on two measurements at least 4 weeks apart.

The study was approved by the Kayseri City Hospital Institutional Ethics Committee (Approval No: 614; October 13, 2025) and conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. All participants gave written informed consent. The study was reported in accordance with the TRIPOD statement, incorporating TRIPOD-AI recommendations where applicable.[17] The completed checklist was submitted as Supplementary File 1.

Eligible patients had persistent ALT and/or AST elevation and completed a diagnostic evaluation allowing definitive etiological classification. Exclusion criteria were known chronic liver disease of established etiology, decompensated liver disease, active extrahepatic malignancy, pregnancy, incomplete diagnostic workup, or loss to follow-up before adjudication. Overall, 280 patients met the criteria and formed the final cohort.

Etiological Classification and Reference Standard

Each patient was assigned to one of five mutually exclusive categories using predefined criteria. MASLD (n=100, 35.7%) was defined as hepatic steatosis on imaging plus at least one cardiometabolic risk factor after exclusion of secondary causes.[1] Viral hepatitis (n=78, 27.9%) was defined as chronic hepatitis B or C confirmed by positive hepatitis B surface antigen (HBsAg) with detectable HBV DNA or positive anti-hepatitis C virus antibody (anti-HCV) with detectable HCV RNA. DILI (n=50, 17.9%) was diagnosed using a Roussel Uclaf Causality Assessment Method (RUCAM) score ≥6.[2] ALD (n=32, 11.4%) was defined by alcohol intake exceeding established EASL thresholds without competing causes.[18] AIH (n=20, 7.1%) was diagnosed using a simplified International Autoimmune Hepatitis score ≥7 or compatible histopathology.[19] No patient met criteria for more than one category.

The primary outcome was the adjudicated final etiology. Three hepatologists independently reviewed all available clinical, laboratory, imaging, and histopathological data and were blinded to model outputs. Disagreements were resolved by consensus.

Data Collection and Preprocessing

Baseline data were collected prospectively using a structured electronic case report form. Candidate predictors were selected from previous literature and routine hepatology practice.[1,3,5] Variables included age, sex, body mass index, alcohol intake, medication exposure, comorbidities, complete blood count, ALT, AST, alkaline phosphatase, γ-glutamyl transferase, total bilirubin, albumin, international normalized ratio, fasting glucose, lipid profile, HBsAg, anti-HCV, antinuclear antibody, anti-smooth muscle antibody, and immunoglobulin G. All patients underwent abdominal ultrasonography; transient elastography was recorded when available.

Missing data were <10% for all predictors and were imputed using multiple imputation by chained equations. Categorical variables were one-hot encoded. To avoid information leakage, synthetic minority over-sampling was applied only within cross-validation folds of the training set. Continuous variables were standardized using training-set parameters and applied unchanged to the test set.

Table 1. Baseline characteristics according to etiological category (n=280)

Characteristic	MASLD (n=100)	Viral hepatitis (n=78)	DILI (n=50)	ALD (n=32)	AIH (n=20)	p
Age (years)	55.8±12.1	49.6±14.8	52.4±13.9	48.3±15.5	41.9±16.8	<0.001
Male sex, n (%)	62 (62.0)	49 (62.8)	20 (40.0)	19 (59.4)	2 (10.0)	<0.001
BMI (kg/m^2)	32.8±4.9	27.4±4.3	28.6±5.1	29.1±4.8	25.9±3.7	<0.001
ALT (U/L)*	82 (55–120)	115 (78–168)	148 (92–215)	96 (68–140)	130 (85–190)	<0.001
AST (U/L)*	60 (42–95)	78 (52–115)	100 (65–155)	112 (82–170)	95 (60–140)	<0.001
AST/ALT ratio*	0.72 (0.60–0.92)	0.75 (0.58–0.95)	0.68 (0.55–0.82)	1.50 (1.10–1.90)	0.73 (0.55–0.98)	<0.001
GGT (U/L)*	70 (40–125)	65 (38–110)	98 (55–210)	198 (140–380)	88 (50–160)	<0.001
ALP (U/L)*	92 (70–125)	105 (80–140)	110 (85–165)	125 (90–180)	118 (85–160)	0.012
Platelets (×10^9/L)	248±72	214±68	232±80	192±85	176±70	0.001

*Median (IQR), Continuous variables: ANOVA or Kruskal-Wallis; Categorical: χ^2 test; MASLD: Metabolic dysfunction-associated steatotic liver disease; DILI: Drug-induced liver injury; ALD: Alcohol-related liver disease; AIH: Autoimmune hepatitis; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyl transferase; ALP: Alkaline phosphatase.

Model Development and Validation

Because this was a proof-of-concept study without established effect sizes, no formal a priori power calculation was performed. Enrollment was planned to include at least 20 patients in the smallest diagnostic class to support one-vs-rest AUROC estimation.

The dataset was split by stratified sampling into training (70%, n=196) and independent test (30%, n=84) sets. Four supervised algorithms were trained and compared: random forest, eXtreme gradient boosting, support vector machine with radial basis function kernel, and multilayer perceptron. Nested 5-fold cross-validation was performed within the training set, using macro-averaged F1-score as the primary optimization metric.

To address incorporation bias, we compared two modeling strategies. The basic model included demographic variables, clinical history, routine biochemistry, complete blood count, and metabolic parameters, but excluded viral serologies, autoantibodies, and immunoglobulin G. The extended model included all basic-model predictors plus HBsAg, anti-HCV, antinuclear antibody, anti-smooth muscle antibody, and immunoglobulin G. Class-specific AUROCs were compared using DeLong's test.[20]

Performance and Statistical Analysis

Final performance was assessed on the independent test set using overall accuracy, balanced accuracy, macro-precision, macro-recall, macro F1-score, and class-specific one-vs-rest AUROC. AUROC confidence intervals were calculated using the DeLong method,[20] and other confidence intervals were estimated by bootstrapping with 1,000 iterations. SHapley Additive exPlanations (SHAP) were applied to the best-performing model to generate global and individual-level explanations.[15,16]

Continuous variables are presented as mean±standard deviation or median with interquartile range, and categorical variables as counts and percentages. Between-group comparisons used analysis of variance or Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables. Exact p values were reported where available. Analyses were performed in Python version 3.9.18. Two-sided p values <0.05 were considered statistically significant.

Results

Cohort Characteristics and Etiological Distribution

The cohort included 280 patients. The mean age was 51.8±15.1 years, and 152 patients (54.3%) were male. MASLD was the most frequent etiology (n=100, 35.7%), followed by viral hepatitis (n=78, 27.9%), DILI (n=50, 17.9%), ALD (n=32, 11.4%), and AIH (n=20, 7.1%). Each patient was assigned to a single etiological category.

Baseline characteristics are summarized in Table 1. Age, sex distribution, BMI, liver biochemistry, and platelet count differed significantly across etiological groups. BMI was highest in MASLD, whereas the AST/ALT ratio and GGT levels were highest in ALD.

Model Performance

The dataset was split by stratified sampling into training (n=196, 70%) and independent test (n=84, 30%) sets. The test set included 30 MASLD, 23 viral hepatitis, 15 DILI, 10 ALD, and six AIH cases.

Among the four evaluated algorithms, XGBoost showed the most consistent performance and was selected as the final model. On the independent test set, XGBoost correctly classified 72 of 84 patients, corresponding to an overall accuracy of 0.86 (95% CI 0.78–0.93). Balanced accuracy was 0.87 (95% CI 0.82–0.92), macro precision 0.87 (95% CI 0.82–0.92), macro recall 0.89 (95% CI 0.84–0.94), and macro F1-score 0.87 (95% CI 0.83–0.93) (Table 2).

Sensitivity Analysis and Multiclass Discrimination

The extended model outperformed the basic model on the independent test set. Overall accuracy increased from 0.73 to 0.86,

Table 2. Comparative performance of machine learning models on the independent test set (n=84)

Model	Accuracy (95% CI)	Balanced accuracy (95% CI)	Macro precision (95% CI)	Macro recall (95% CI)	Macro F1-score (95% CI)
XGBoost	0.86 (0.78–0.93)	0.87 (0.82–0.92)	0.87 (0.82–0.92)	0.89 (0.84–0.94)	0.87 (0.83–0.93)
Random forest	0.83 (0.74–0.91)	0.84 (0.78–0.90)	0.83 (0.77–0.89)	0.85 (0.79–0.91)	0.84 (0.78–0.90)
SVM (RBF)	0.80 (0.71–0.88)	0.81 (0.74–0.87)	0.79 (0.72–0.85)	0.82 (0.76–0.88)	0.80 (0.74–0.86)
MLP	0.81 (0.72–0.89)	0.82 (0.75–0.88)	0.81 (0.74–0.87)	0.83 (0.77–0.89)	0.82 (0.76–0.88)

CIs obtained via bootstrapping (1,000 iterations). CI: Confidence interval; SVM: Support vector machine; RBF: Radial basis function; MLP: Multilayer perceptron.

Table 3. Class-specific AUROC comparison between basic and extended models

Etiology	Basic model AUROC (95% CI)	Extended model AUROC (95% CI)	ΔAUROC	p-value (DeLong)
MASLD	0.88 (0.81–0.94)	0.95 (0.91–0.98)	+0.07	0.07
Viral hepatitis	0.83 (0.74–0.91)	0.94 (0.89–0.97)	+0.11	<0.02
DILI	0.86 (0.78–0.93)	0.93 (0.87–0.96)	+0.07	0.06
ALD	0.84 (0.74–0.92)	0.92 (0.86–0.96)	+0.08	0.08
AIH	0.80 (0.66–0.92)	0.95 (0.90–0.98)	+0.15	<0.03

AUROC comparisons performed using DeLong test for correlated ROC curves. CI: Confidence interval; AUROC: Area under the receiver operating characteristic curve; MASLD: Metabolic dysfunction-associated steatotic liver disease; DILI: Drug-induced liver injury; ALD: Alcohol-related liver disease; AIH: Autoimmune hepatitis.

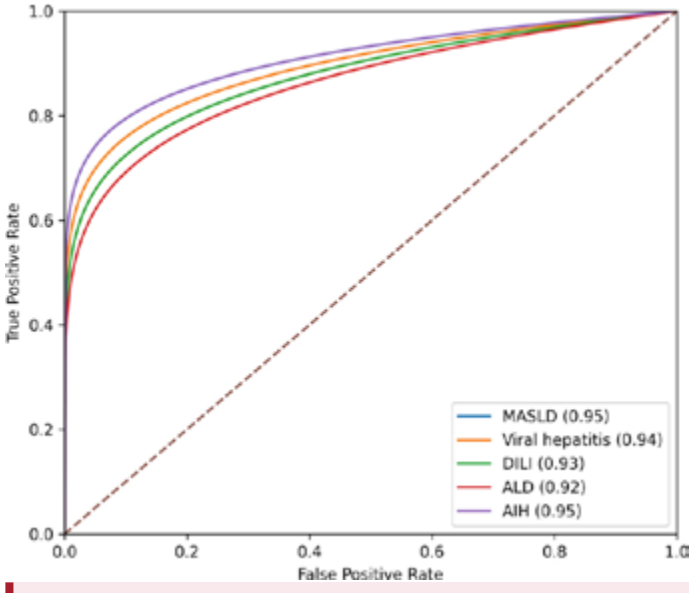


Figure 1. One-vs-rest receiver operating characteristic (ROC) curves for the extended XGBoost model. ROC curves demonstrating class-specific discrimination of the extended XGBoost model on the independent test set (n=84). Area under the ROC curve (AUROC) values (95% confidence intervals, DeLong method) were: (i) Metabolic dysfunction-associated steatotic liver disease: 0.95 (0.91–0.98). (ii) Viral hepatitis: 0.94 (0.89–0.97). (iii) Drug-induced liver injury: 0.93 (0.87–0.96). (iv) Alcohol-related liver disease: 0.92 (0.86–0.96). (v) Autoimmune hepatitis: 0.95 (0.90–0.98). The diagonal dashed line represents chance-level performance (AUROC=0.50). Class-specific ROC curves were generated using a one-vs-rest approach.

and macro F1-score improved from 0.72 to 0.87. The largest AUROC gains were observed for AIH (0.80 to 0.95; p=0.03) and viral hepatitis (0.83 to 0.94; p=0.02). Improvements for MASLD, DILI, and ALD were modest and not statistically significant (ΔAUROC ≤0.08), including DILI (ΔAUROC=0.07; p=0.06) (Table 3). Because the independent test set included only six AIH cases, class-specific estimates for AIH should be interpreted cautiously.

One-vs-rest analysis showed strong class-specific discrimination for the extended XGBoost model (Fig. 1). AUROC values were 0.95 for MASLD, 0.94 for viral hepatitis, 0.93 for DILI, 0.92 for ALD, and 0.95 for AIH.

Explainability and Misclassification Analysis

SHAP analysis identified GGT, AST/ALT ratio, platelet count, age, and BMI as the most influential predictors (Fig. 2a). Higher GGT and a higher AST/ALT ratio contributed to ALD predictions, whereas higher BMI favored MASLD. Among serological markers, anti-HCV and ANA contributed mainly to viral hepatitis and AIH classification, respectively. A representative local SHAP plot for a DILI case is shown in Figure 2b.

Overall, 12 patients (14.3%) were misclassified by the extended model. The most frequent bidirectional error involved DILI and AIH (n=6), including four DILI cases classified as AIH and two AIH cases classified as DILI. Four misclassifications occurred between ALD and MASLD, and two occurred between DILI and viral hepatitis. These errors largely reflected overlapping clinical and biochemical features rather than systematic overprediction of a single category (Table 4).

Discussion

In this prospective proof-of-concept cohort study, an explainable multiclass machine learning model differentiated five major etiologies of persistent liver enzyme elevation with good performance on an

Table 4. Systematic characterization of misclassified cases (n=12)

True diagnosis	Predicted diagnosis	Key features	Contributing factors
DILI	AIH	ANA 1:80, recent antibiotic use	Borderline RUCAM (5–6)
DILI	AIH	Mixed hepatocellular-cholestatic injury	Low-titer autoantibodies
DILI	AIH	ALT 180 U/L	ANA positive
DILI	AIH	Drug exposure	Overlapping serology
AIH	DILI	Recent antibiotic use	Incomplete antibody profile
AIH	DILI	No biopsy	Borderline IgG elevation
ALD	MASLD	BMI 34 kg/m^2	Alcohol near threshold
ALD	MASLD	Steatosis on USG	Metabolic syndrome
ALD	MASLD	GGT elevated	Overlapping metabolic features
DILI	Viral hepatitis	Mild anti-HCV positivity	Drug exposure
Viral hepatitis	DILI	ALT 160 U/L	Recent medication
MASLD	ALD	AST/ALT ratio borderline	Alcohol intake near diagnostic threshold

Misclassifications reflected overlapping clinical and biochemical patterns rather than systematic model bias. MASLD: Metabolic dysfunction-associated steatotic liver disease; DILI: Drug-induced liver injury; ALD: Alcohol-related liver disease; AIH: Autoimmune hepatitis; BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: γ-glutamyl transferase; ANA: Antinuclear antibody; USG: Ultrasound; RUCAM: Roussel uclaf causality assessment method; IgG: Immunoglobulin G.

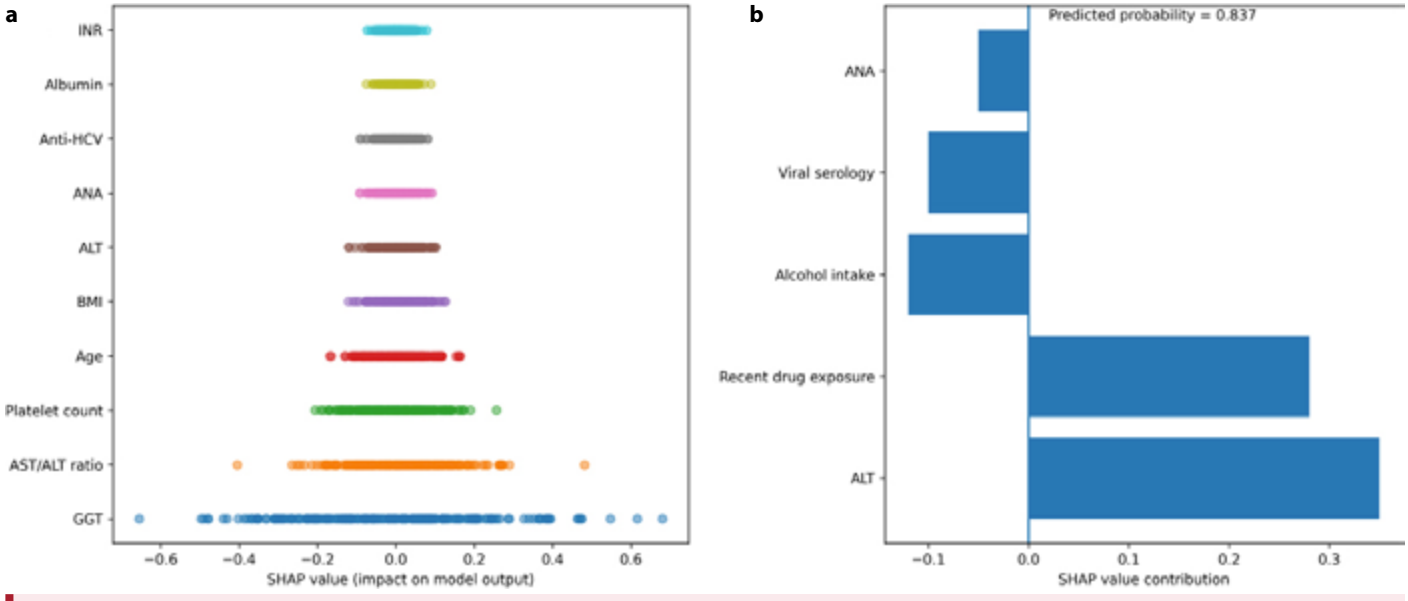


Figure 2. SHAP-based interpretability analysis of the extended model **(a)** Global feature importance (SHAP summary plot). Features are ranked according to mean absolute SHAP values, reflecting their overall contribution to model predictions across the independent test set. Each point represents an individual patient. Horizontal dispersion reflects the magnitude and direction of feature impact on model output. **(b)** Representative local SHAP contribution plot for a DILI case. Horizontal bar plot illustrating feature-level contributions to the predicted probability of drug-induced liver injury. Positive values increase predicted probability, whereas negative values decrease it. In this example, elevated ALT and recent drug exposure contributed positively, while low alcohol intake and negative viral serology reduced competing etiologies. The final predicted probability for DILI was 0.837.

SHAP: SHapley Additive exPlanations; DILI: Drug-induced liver injury; ALT: Alanine aminotransferase.

independent test set. The final XGBoost model achieved an overall accuracy of 0.86, and class-specific discrimination was consistently high across MASLD, viral hepatitis, DILI, ALD, and AIH. SHAP-based analysis showed clinically plausible predictor patterns, supporting the interpretability of the model outputs.[15,16] These findings suggest that multiclass AI may support the structured evaluation of patients with unexplained liver enzyme abnormalities, particularly when several etiologies are clinically plausible.

A key concern in this setting is incorporation bias, because some predictors are also used in diagnostic adjudication. To address this, we compared a basic model excluding disease-defining serological markers with an extended model including viral serologies, autoantibodies, and immunoglobulin G. The extended model improved macro F1-score from 0.72 to 0.87. The largest AUROC gains were seen for AIH (0.80 to 0.95; p=0.03) and viral hepatitis (0.83 to 0.94; p=0.02), whereas improvements for MASLD, DILI, and ALD were modest and not statistically significant (ΔAUROC ≤0.08). The AIH estimates should be interpreted cautiously because only six AIH cases were included in the independent test set.

Most previous AI studies in hepatology have focused on binary or single-disease tasks, such as steatotic liver disease detection, fibrosis assessment, hepatocellular carcinoma risk stratification, or outcome prediction.[5–7,11,12] In contrast, the present study addressed a multiclass diagnostic problem that more closely reflects routine hepatology practice. Patients with persistent liver enzyme elevation often have overlapping metabolic, alcohol-related, drug-related, viral, or autoimmune features.[1,2] A model that estimates several etiologies simultaneously may therefore be more clinically useful than a single-disease classifier in this setting.

The SHAP analysis supported the clinical plausibility of the model. GGT and the AST/ALT ratio contributed to ALD prediction,[18] whereas BMI favored MASLD classification.[1] Anti-HCV and ANA contributed mainly to viral hepatitis and AIH classification, respectively. Thus, the model appeared to integrate clinical, biochemical, and serological information rather than relying on a single diagnostic marker. The misclassification analysis also supported real-world diagnostic overlap. The most frequent bidirectional error involved DILI and AIH (n=6), a recognized diagnostic gray zone.[2,19] Additional errors occurred between ALD and MASLD, and between DILI and viral hepatitis. These patterns suggest clinical overlap rather than systematic model bias.

The main clinical value of this approach lies in structured triage rather than autonomous diagnosis. If externally validated, such a model could help clinicians prioritize confirmatory testing, medication review, alcohol-use assessment, or autoimmune evaluation. However, this study did not assess effects on clinician behavior, diagnostic testing, time to diagnosis, or patient outcomes.[21,22] Strengths include prospective consecutive enrollment, blinded adjudication by three hepatologists, separation of training and independent test sets, and nested cross-validation.[17] Limitations include the single-center design, limited AIH sample size, possible residual incorporation bias, limited assessment of isolated cholestatic presentations, and non-uniform use of liver biopsy. External validation in larger multicenter cohorts, calibration analysis, and decision-curve analysis are needed before clinical implementation.[14,23]

Conclusion

An explainable multiclass machine learning model differentiated five major etiologies of persistent liver enzyme elevation using routinely available clinical and laboratory data. Serological markers added value for AIH and viral hepatitis, while routine clinical and biochemical variables retained triage value for MASLD, DILI, and ALD. External validation is required before clinical implementation.

Online Appendix Link: https://file.paplino.com/hepatologyforum/files/1785308991-appendix-en.pdf

Ethics Committee Approval: The study was approved by the Kayseri City Hospital Institutional Ethics Committee (Approval No: 614; October 13, 2025).

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: The authors declare that no artificial intelligence was used in this study.

Author Contributions: Concept: YO; Design: YO; Supervision: YO, NMB; Materials: YO; Data Collection and/or Processing: YO, OY; Analysis and/or Interpretation: YO, OY, NMB; Literature Search: YO, OY; Writing: YO; Critical Reviews: YO, OY, NMB.

Acknowledgments: The authors are grateful to the clinical staff for their support in patient evaluation and systematic data collection.

Peer-review: Externally peer-reviewed.

References

1. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, Kleiner DE, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023;77(5):1797-1835. [CrossRef]
2. Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. Am J Gastroenterol 2021;116(5):878-898. [CrossRef]
3. Atabaki-Pasdar N, Ohlsson M, Whiting S, Frau F, Pomares-Millan H, Haid M, et al. Predicting and elucidating the etiology of fatty liver disease: a machine learning modeling and validation study in the IMI DIRECT cohorts. PLoS Med 2020;17(6):e1003149. [CrossRef]
4. Ahn JC, Connell A, Simonetto DA, Hughes C, Shah VH. Application of artificial intelligence for the diagnosis and treatment of liver diseases. Hepatology 2021;73(6):2546-2563. [CrossRef]
5. Ghosh S, Zhao X, Alim M, Brudno M, Bhat M. Artificial intelligence applied to 'omics data in liver disease: towards a personalised approach for diagnosis, prognosis and treatment. Gut 2025;74(2):295-311. [CrossRef]
6. Huang G, Jin Q, Mao Y. Predicting the 5-year risk of nonalcoholic fatty liver disease using machine learning models: prospective cohort study. J Med Internet Res 2023;25:e46891. [CrossRef]
7. Calderaro J, Seraphin TP, Luedde T, Simon TG. Artificial intelligence for the prevention and clinical management of hepatocellular carcinoma. J Hepatol 2022;76(6):1348-1361. [CrossRef]
8. Wang T, Shao W, Huang Z, Tang H, Zhang J, Ding Z, Huang K. MOGONET integrates multi-omics data using graph convolutional networks allowing patient classification and biomarker identification. Nat Commun 2021;12(1):3445. [CrossRef]
9. Clift AK, Coupland CAC, Hippisley-Cox J. Development and internal-external validation of statistical and machine learning models for breast cancer prognostication: cohort study. BMJ 2023;380:e073800. [CrossRef]

10. Ye J, Zhuang X, Li X, Gong X, Sun Y, Wang W, et al. Novel metabolic classification for extrahepatic complication of metabolic associated fatty liver disease: a data-driven cluster analysis with international validation. Metabolism 2022;136:155294. [CrossRef]
11. Newsome PN, Sasso M, Deeks JJ, Paredes A, Boursier J, Chan WK, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol 2020;5(4):362-373. [CrossRef]
12. Fujii H, Iwaki M, Hayashi H, Toyoda H, Oeda S, Hyogo H, et al. Clinical outcomes in biopsy-proven nonalcoholic fatty liver disease patients: a multicenter registry-based cohort study. Clin Gastroenterol Hepatol 2023;21(2):370-379. [CrossRef]
13. Choi BK, Choi YJ, Sung MD, Ha WS, Chu MK, Kim WJ, et al. Development and validation of an artificial intelligence model for the early classification of the etiology of meningitis and encephalitis: a retrospective observational study. EClinicalMedicine 2023;61:102051. [CrossRef]
14. Mohsen F, Al-Absi HRA, Yousri NA, El Hajj N, Shah Z. A scoping review of artificial intelligence-based methods for diabetes risk prediction. NPJ Digit Med 2023;6(1):197. [CrossRef]
15. Ali S, Akhlaq F, Imran AS, Kastrati Z, Daudpota SM, Moosa M. The enlightening role of explainable artificial intelligence in medical & healthcare domains: a systematic literature review. Comput Biol Med 2023;166:107555. [CrossRef]
16. Nazir S, Ali S, Khan A, Iqbal J, Daudpota SM, Akram MU. Survey of explainable artificial intelligence techniques for biomedical imaging with deep neural networks. Comput Biol Med 2023;153:106668. [CrossRef]
17. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med 2015;162(1):55-63. [CrossRef]
18. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of alcohol-related liver disease. J Hepatol 2018;69(1):154-181. [CrossRef]
19. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol 2015;63(4):971-1004. Erratum in: J Hepatol 2015;63(6):1543-4. [CrossRef]
20. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. Biometrics 1988;44(3):837-845. [CrossRef]
21. Kelly CJ, Karthikesalingam A, Suleyman M, Corrado G, King D. Key challenges for delivering clinical impact with artificial intelligence. BMC Med 2019;17:195. [CrossRef]
22. Allam A, Feuerriegel S, Rebhan M, Krauthammer M. Analyzing patient trajectories with artificial intelligence. J Med Internet Res 2021;23(12):e29812. [CrossRef]
23. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal. BMJ 2020;369:m1328. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 256–261 DOI: 10.14744/hf.2026.99845

ORIGINAL RESEARCH

Acetaminophen toxicity: Patterns of liver injury, effects on hospital length of stay, and the need for inpatient psychiatric care

Nazli Begum Ozturk, Ben L. Da, Ghideon Ezaz, Thomas D. Schiano

Division of Liver Diseases and Recanati/Miller Transplantation Institute, Icahn School of Medicine, Mount Sinai, New York, United States

Highlights & Insights

- **Scientific Gap:** The effects of overdose intent and psychiatric comorbidities on LT evaluation and psychiatric care needs remain unclear.
- **Key Finding:** In 165 patients, 67.9% had psychiatric comorbidities and 58.2% intentional overdose. ALF occurred in 43.0%. Psychiatric factors did not affect LT listing, transplantation, or mortality.
- **Clinical Impact:** Early hepatology–psychiatry collaboration may improve care planning and ensure objective LT decisions in acetaminophen overdose.

ABSTRACT

Background and Aim: Acetaminophen toxicity is the most common cause of acute liver failure (ALF) in the United States. Among patients with acetaminophen toxicity, a vast majority have intentional overdose and concurrent psychiatric comorbidities. We aimed to analyze patient characteristics, patterns of overdose, and outcomes in patients with acetaminophen overdose at our liver transplantation (LT) center.

Materials and Methods: Patients ≥18 years of age with acetaminophen overdose between 2011 and 2020 at our institution were identified. Patient demographics, clinical and laboratory data, patterns of overdose (intentional vs. unintentional), psychiatric comorbidities, need for admission to inpatient psychiatry service, transplant wait listing, need for transplantation, and death were assessed. Categorical variables are presented as counts with percentages, continuous variables as median with interquartile range IQR (Q1-Q3), and $p<0.05$ was considered significant.

Results: A total of 165 (118 female, 47 male) patients were admitted with acetaminophen toxicity. Seventy-one (43.0%) patients met criteria for ALF. The median age was 32 years (IQR 25–49), and 112 (67.9%) patients had concurrent psychiatric comorbidities. Ninety-six (58.2%) patients had intentional overdose, while 69 (41.8%) patients had unintentional overdose. Twenty-three (13.9%) patients were listed for LT, and seven (4.2%) patients underwent LT. Eighty-one (49.1%) patients were subsequently admitted to the inpatient psychiatry service. Eleven (6.7%) patients died, five of whom were on the LT list. There was no significant difference in LT listing between patients with and without psychiatric comorbidities.

Conclusion: The majority of the patients with acetaminophen overdose survived to discharge. Most cases of acetaminophen overdose were intentional and were significantly associated with the presence of a psychiatric comorbidity. Intentional and unintentional overdoses had similar rates of ALF. Inpatient psychiatric hospitalization was frequently required, particularly for patients with intentional overdose.

Keywords: Acetaminophen, acute liver failure, acute liver injury.

How to cite this article: Ozturk NB, Da BL, Ezaz G, Schiano TD. Acetaminophen toxicity: Patterns of liver injury, effects on hospital length of stay, and the need for inpatient psychiatric care. Hepatology Forum 2026; 7(3):256–261.

Received: November 25, 2025; **Revised:** January 26, 2026; **Accepted:** June 02, 2026; **Available Online:** July 27, 2026

Corresponding author: Nazli Begum Ozturk; Division of Liver Diseases and Recanati/Miller Transplantation Institute, Icahn School of Medicine, Mount Sinai, New York, United States; **E-mail:** nazlibegumozturk@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

Acetaminophen toxicity is the most common cause of acute liver failure (ALF) in the United States.[1–3] Approximately half of the acetaminophen overdoses are intentional for purposes of self-harm, and the remainder occur as unintentional for purposes of pain control with excessive intake over several days to weeks ("therapeutic misadventure").[3,4] ALF due to acetaminophen usually carries a favorable outcome, with approximately two-thirds of the patients recovering without liver transplantation (LT).[5–7] Early identification of patients with acetaminophen overdose, coupled with timely initiation of treatment with N-acetylcysteine (NAC), significantly improves outcomes.[8]

Psychiatric comorbidities are more prevalent in patients with ALF due to acetaminophen overdose compared to other etiologies of ALF, and may lead to concerns regarding LT listing, particularly due to challenges with psychosocial assessment in the setting of hepatic encephalopathy (HE) and intentional overdose.[6,9] Several registry studies have reported that patients with ALF due to acetaminophen were less commonly listed for LT compared to non-acetaminophen drug-induced liver injury, autoimmune hepatitis, and hepatitis B virus.[10] However, for patients with ALF due to acetaminophen toxicity, there are limited data on patterns of acetaminophen overdose and psychiatric comorbidities in patients being listed for or undergoing LT. In addition, there are limited data regarding the utilization of inpatient psychiatric services after an acetaminophen overdose. The goal of our study was to describe acetaminophen overdose patterns and assess the effects of psychiatric comorbidities and overdose intent on LT listing and final disposition at a large LT center.

Materials and Methods

Patients ≥18 years of age admitted with acetaminophen overdose at our institution between 2011 and 2020 were identified using an electronic medical record search. Patients with pre-existing liver disease were excluded. Patient demographics, clinical and laboratory data, pattern of overdose, concurrent overdoses, psychiatric comorbidities, LT listing, and disposition were obtained from electronic medical records. Acute liver injury was defined when the international normalized ratio (INR) ≥2, alanine aminotransferase (ALT) >=10xULN, and onset of illness <2 weeks without preexisting liver disease; ALF was defined when INR ≥1.5 with any grade of HE and onset of illness <26 weeks without preexisting liver disease. Intentional and unintentional overdoses were determined based on evaluation of a psychiatrist or transplant hepatologist. All patients underwent a rigorous psychosocial evaluation by experienced transplant social workers and psychiatrists. Assessments were completed through discussion with family members when necessary for confirmation of psychiatric comorbidities per DSM-5 criteria. In addition, the presence of a psychiatric comorbidity and prior hospitalizations related to psychiatric comorbidities were determined by clinical social workers or psychiatrists through review of available outside medical records. A history of previous psychiatric hospitalization did not necessarily indicate an active psychiatric diagnosis during the index hospitalization and was analyzed separately from current psychiatric comorbidity. Patients were transferred to inpatient psychiatry care once intensive care unit (ICU) or general medical care was no longer required, following psychiatric evaluation and clearance by the medical team. All tests were two-tailed, and p<0.05 was considered significant. Ethics approval was obtained from the Miller Transplantation Institutional Review Board (Approval No. IRB-19-02876; January 13, 2020), and the study was conducted in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the Institutional Review Board due to the retrospective design of the study.

Statistical Analysis

Statistical analyses were performed using Prism, version 9 (San Diego, CA, USA). Categorical variables are presented as counts with percentages, and continuous variables as median with interquartile range (IQR). Chi-square, analysis of variance, and Kruskal–Wallis tests were used for statistical analysis.

Results

A total of 165 (118 female, 47 male) patients were included in the study. Seventy-one (43.0%) patients had ALF, and 15 (9.1%) patients had acute liver injury. The median age was 32 years (IQR 25–49). Of all patients, 112 (67.9%) patients had concurrent psychiatric comorbidities, and 96 (58.2%) patients had intentional overdose. Acetaminophen co-ingestion with alcohol was present in 27 (16.4%) patients, opioids in 28 (17.0%), and benzodiazepines in 20 (12.1%) patients. All patients received NAC, which was administered for a median duration of 48 h (IQR 24–72). Seventeen (10.3%) patients required renal replacement therapy (RRT). Twenty-three (13.9%) patients were listed for LT, and seven (4.2%) patients underwent LT within a median of 3 days (IQR 1–6). All patients who were listed for LT and all patients who underwent LT had ALF. Eighty-one (49.1%) patients were admitted to the inpatient psychiatry service after initial medical management. The median length of stay in the ICU or general medicine services was 4 days (IQR 3–7), and subsequently in the inpatient psychiatry service was 9 days (IQR 4–19.5). The median length of stay was 12 days (IQR 5–24) in patients with ALF, compared with 7 days (IQR 2.8-16) in those without ALF (p=0.4736). A total of 11 (6.7%) patients died, five of whom were on the LT list, and six patients who were not considered candidates for LT.

Table 1 shows the characteristics of patients with intentional versus unintentional acetaminophen overdose. Patients with intentional overdose were younger (p<0.005), more commonly had previous inpatient psychiatry admissions (p<0.0005), and had longer total length of stay (p<0.05) compared to patients with unintentional overdose. The great majority of the patients (90%) with unintentional overdose who had inpatient psychiatry admission had a history of a psychiatric comorbidity. Table 2 shows the comparison between patients with and without psychiatric comorbidities. Table 3 shows individual psychiatric comorbidities, with major depressive disorder (MDD) being the most common, followed by MDD and generalized anxiety disorder.

Table 1. Clinical and laboratory characteristics of patients with intentional and unintentional acetaminophen overdose

	Intentional overdose (n=96)	Unintentional overdose (n=69)	p
Acute liver failure	42 (43.8%)	29 (42.0%)	0.8270
Acute liver injury	9 (9.4%)	6 (8.7%)	0.8819
Female gender	67 (69.8%)	51 (73.9%)	0.5657
Age (years)	29.0 (23.3–45.0)	41.0 (27.0–56.5)	**0.0019**
Body mass index (kg/m^2)	26.2 (22.1–32.3)	25.9 (22.1–29.9)	0.5487
Alcohol co-ingestion	19 (19.79%)	8 (11.59%)	0.1623
iAST (IU/L)	151 (24.5–4954)	1443 (37.5–5253)	0.1626
iALT (IU/L)	147 (21.0–5373)	2150 (39.0–5469)	0.7411
iINR	1.30 (1.10–2.90)	1.90 (1.20–3.93)	0.5617
iTotal bilirubin (mg/dL)	0.90 (0.50–3.20)	1.40 (0.60–3.45)	0.3890
pAST (IU/L)	809 (32.3–6333)	2218 (66.0–7772)	0.2927
pALT (IU/L)	947 (30.8–7528)	3092 (48.5–6019)	0.9556
pINR	1.60 (1.20–3.20)	2.00 (1.20–4.10)	0.8874
pTotal bilirubin (mg/dL)	1.40 (0.82–4.05)	1.80 (0.80–4.05)	0.4461
Renal replacement therapy	10 (10.4%)	7 (10.1%)	0.9552
Listed for liver transplantation	13 (13.5%)	10 (14.5%)	0.8629
Liver transplantation	4 (4.2%)	3 (4.3%)	0.9549
Inpatient psychiatric admission	71 (74.0%)	10 (14.5%)	**0.0001**
Length of stay (medical, days)	4 (3–7)	5 (2–9.5)	0.2095
Length of stay (total, days)	9.0 (4.0–19.5)	5.0 (2.0–11.5)	**0.0278**
Death	5 (5.20%)	6 (8.69%)	0.3788

'i' indicates initial values at admission, 'p' indicates peak values during hospitalization. Categorical variables are presented as numbers and percentages, and continuous variables as medians with interquartile ranges (Q1–Q3). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International normalized ratio. Reference values: ALT: 0–40 IU/L; AST: 0–40 IU/L; INR: 0.8–1.2, total bilirubin: 0.2–1.0 mg/dL

Discussion

Acetaminophen overdose is the leading cause of ALF in the USA, remaining one of the leading causes of LT.[1,11] As ALF requires emergent consideration of LT, a comprehensive assessment of psychiatric comorbidities or substance-use disorder sometimes can be challenging. Given the presence of HE in ALF, a comprehensive psychosocial evaluation often cannot be completed. Our study describes the characteristics of patients with acetaminophen overdose with a special emphasis on the patterns of overdose, psychiatric comorbidities, and utilization of inpatient psychiatric services, LT listing, and transplantation at a tertiary transplant center.

In our patient cohort, the vast majority of the patients had one or more psychiatric comorbidities (67.9%) and had intentional overdose (58.2%). Patients with intentional overdose were significantly younger than those with unintentional overdose and, as expected, were more frequently admitted to an inpatient psychiatry service, and ultimately had a significantly longer total length of stay. In addition, intentional overdose was significantly more common in patients with underlying psychiatric comorbidities compared to those without. A multicenter cohort study by the ALF Study Group (ALFSG) analyzed 1190 patients with ALF due to acetaminophen overdose between 1998 and 2018 and reported that 41.9% of patients presented with intentional overdose, and 53.9% had psychiatric comorbidity.[12] In this study, 23.0% of the patients were listed for LT, 8.4% of the patients received LT, and LT listing was not affected by the presence of psychiatric comorbidity, similar to our large tertiary center results.[12] Another study from 2019, including 207 patients with acetaminophen overdose, the LT rate was 1.5%, and death was <1%.[13] The same study also reported that 76.3% of the overdoses were intentional, and that MDD was the most common psychiatric diagnosis, followed by alcohol-use disorder.[13] Similarly, another study using ALFSG data, including 93 patients with acetaminophen overdose (50 with unintentional overdose, 43 with intentional overdose), reported that psychiatric comorbidities were more common in patients with intentional overdose, with MDD being the most common comorbidity, aligning with the findings of our study.[3]

Need for inpatient psychiatric hospitalization should be anticipated in these patients, whether they are expected to medically improve or go on to require LT. This planning ahead may ultimately help to decrease the length of stay, and for patients who may need LT, ap-

Table 2. Comparison of patients with and without psychiatric comorbidities

Variables	Psychiatric comorbidity present (n=112)	No psychiatric comorbidity (n=53)	p
Acute liver failure	51 (45.5%)	20 (37.7%)	0.3477
Acute liver injury	9 (8.0%)	6 (11.3%)	0.4961
Female gender	78 (69.7%)	40 (75.5%)	0.4416
Age (years)	32.0 (24.3–47.8)	38.0 (26.0–51.5)	0.2036
Body mass index (kg/m^2)	25.7 (22.0–29.9)	26.7 (22.6–32.8)	0.0753
Intentional overdose	76 (67.9%)	20 (37.7%)	**0.0002**
Alcohol co-ingestion	16 (14.3%)	11 (20.8%)	0.2971
iAST (IU/L)	306 (29.3–4527)	977 (22.5–5751)	0.5715
iALT (IU/L)	293 (24.3–475)	1442 (20.0–5952)	0.4917
iINR	1.5 (1.10–3.40)	1.70 (1.20–3.10)	0.6328
iTotal bilirubin (mg/dL)	1.0 (0.50–3.20)	1.30 (0.60–3.90)	0.7138
pAST (IU/L)	871 (37.0–6333)	2724 (66.0–7135)	0.5705
pALT (IU/L)	1065 (35.3–6001)	2771 (47.5–6582)	0.8592
pINR	1.70 (1.20–4.00)	1.90 (1.30–3.15)	0.5185
Renal replacement therapy	13 (11.6%)	4 (7.5%)	0.4262
Listed for liver transplantation	18 (16.1%)	5 (9.4%)	0.2504
Liver transplantation	6 (5.4%)	1 (1.9%)	0.3046
Previous inpatient psychiatric admission	67 (59.8%)	14 (26.4%)	**0.0001**
Length of stay (medical, days)	5.0 (3.0–7.75)	4.0 (2.0–7.0)	0.2274
Length of stay (total, days)	11.0 (5.0–21.0)	5.0 (2.0–15.0)	0.2339

'i' indicates initial values at admission, 'p' indicates peak values during hospitalization. Numbers are given with percentage and continuous variables with median and IQR (Q1-Q3). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; INR: International normalized ratio. Reference values: ALT: 0–40 IU/L; AST: 0–40 IU/L; INR: 0.8–1.2, total bilirubin: 0.2–1.0 mg/dL.

propriate and timely psychiatric treatments with patient engagement in care could help in LT listing. Patients who recover from the ALF, when out of the ICU, often require a bedside sitter (with the associated costs) while recovering on the medical floor, awaiting the improvement of their liver tests or insurance clearance for inpatient psychiatric services. While on the medical floor, the patients may not receive the timely psychiatric care they require, so earlier transfer to the inpatient psychiatry service is essential.

In the current study, the LT listing rate was 13.9%, the LT rate was 4.2%, and death was 6.7%. Consistent with other reports, our data show that the disease severity of ALF due to acetaminophen was the main consideration for LT listing, and the presence of intentional overdose or presence of psychiatric comorbidity did not preclude patients from listing. Interestingly, the medical and total length of stay was not statistically significant in patients with ALF compared to those without ALF in our study, which may reflect the relatively small sample size and limited statistical power to detect differences between the groups. Another ALFSG study of 910 patients with ALF due to acetaminophen toxicity reported that 88% of the patients had psychiatric comorbidity.[6] The same study also reported that there was no difference in LT listing, and in those undergoing LT, and overall death among patients with and without psychiatric comorbidity were similar to our study.[6]

Simkin et al.,[14] reported that one-third of the patients with acetaminophen overdose had concurrent alcohol intake. Another large study reported that patients with unintentional overdoses more commonly had concurrent alcohol intake before the presentation of ALF compared to patients with intentional acetaminophen overdose.[15] The same study also reported that concurrent use of alcohol was present in 44.7% of the patients, and a psychiatric comorbidity was present in 42.3% of patients.[15] In our study, 16.4% of the patients had concurrent alcohol co-ingestion, opioids in 17.0% of the patients, and benzodiazepines in 12.1% of the patients; the presence of alcohol co-ingestion was not statistically significant in patients with intentional overdose compared to unintentional overdose.

In our study, patients listed for LT were more likely to require RRT and had a longer duration of NAC treatment and total length of stay. As expected, admission laboratory values, including ALT, INR, white blood cells, and lactic acid, were significantly higher in listed patients compared to those who were not listed. Similarly, peak values of aspartate aminotransferase, ALT, INR, and total bilirubin were significantly elevated in the listed patients compared to those who were not listed. Correspondingly, another study reported that the patients listed for LT received more interventions, including prolonged NAC treatment, extended use of RRT, longer vasopressor support, increased use of

Table 3. Psychiatric comorbidities (n=112)

	n (%)
MDD	46 (41.1)
MDD and GAD	14 (12.5)
Schizophrenia	11 (9.8)
Bipolar disorder	7 (6.3)
GAD	6 (5.4)
BPD and MDD	4 (3.6)
BPD	3 (2.7)
PTSD and MDD	3 (2.7)
Bipolar disorder, GAD and MDD	2 (1.8)
Bipolar disorder and MDD	2 (1.8)
Bipolar disorder and schizophrenia	2 (1.8)
Bipolar disorder, MDD and BPD	2 (1.8)
Bipolar disorder and GAD	1 (0.9)
BPD and bipolar disorder	1 (0.9)
BPD, MDD and GAD	1 (0.9)
Eating disorder and GAD	1 (0.9)
Impulse control disorder	1 (0.9)
Eating disorder and MDD	1 (0.9)
Panic disorder	1 (0.9)
PTSD and BPD	1 (0.9)
PTSD, BPD, and MDD	1 (0.9)
MDD and schizophrenia	1 (0.9)

BPD: Borderline personality disorder; MDD: Major depressive disorder; PTSD: Post-traumatic stress disorder; GAD: Generalized anxiety disorder.

ICP monitors, and the presence of intentional overdose or psychiatric comorbidities did not differ significantly between listed and non-listed patients, aligning with our findings.[6] Although some studies have reported that intentional acetaminophen overdose is associated with worse outcomes, morbidity, and mortality, our study found that patients with intentional overdose were significantly younger, with no differences in rates of ALF, LT, or death.[16]

Limitations of our study include its retrospective and single-center nature and potential selection bias. For most patients, the exact time of acetaminophen ingestion was not clear. Intentional/unintentional overdose information was obtained based on the transplant hepatologist or psychiatrist's assessments. Patient demographics, patterns of overdose, utilization of psychiatry services, LT listing and transplantation, and mortality may differ from centers with no transplant services or community hospitals. Strengths of our study include having a large number of patients with acetaminophen overdose and ALF, and analyzing specifically the overdose patterns, psychiatric comorbidities, and identifying the patient characteristics for LT listing and transplantation.

Conclusion

The majority of the patients with acetaminophen overdose in the current study recovered during index hospitalization, although inpatient psychiatric care was frequently required, particularly after intentional overdose. Rates of acute liver injury, ALF, LT listing and transplantation, and mortality did not differ significantly between intentional and unintentional overdoses. Future prospective and multicenter studies with long-term follow-up are needed to validate these findings and further characterize the prevalence and outcomes of psychiatric comorbidities in patients with acetaminophen overdose, with or without ALF.

Ethics Committee Approval: Ethics approval was obtained from the Miller Transplantation Institutional Review Board (Approval No. IRB-19-02876; January 13, 2020), and the study was conducted in accordance with the Declaration of Helsinki.

Informed Consent: The requirement for informed consent was waived by the Institutional Review Board due to the retrospective design of the study.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: The authors have no financial or personal disclosures relevant to this manuscript.

Use of AI for Writing Assistance: Artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) were not used in the production of this work.

Author Contributions: Concept: NBO, BLD, GE, TDS; Design: NBO, BLD, GE, TDS; Supervision: NBO, BLD, GE, TDS; Funding: TDS; Materials: NBO, BLD; Data Collection and/or Processing: NBO, BLD, GE; Analysis and/or Interpretation: NBO, BLD, GE; Literature Review: NBO; Writing: NBO, TDS; Critical Review: GE, TDS.

Peer-review: Externally peer-reviewed.

References

1. Shingina A, Mukhtar N, Wakim-Fleming J, Alqahtani S, Wong RJ, Limketkai BN, et al. Acute liver failure guidelines. Am J Gastroenterol 2023;118(7):1128-1153. [CrossRef]
2. Ozturk NB, Herdan E, Saner FH, Gurakar A. A comprehensive review of the diagnosis and management of acute liver failure. J Clin Med 2023;12(23):7451. [CrossRef]
3. Pezzia C, Sanders C, Welch S, Bowling A, Lee WM; Acute Liver Failure Study Group. Psychosocial and behavioral factors in acetaminophen-related acute liver failure and liver injury. J Psychosom Res 2017;101:51-57. [CrossRef]
4. Yoon E, Babar A, Choudhary M, Kutner M, Pyrsopoulos N. Acetaminophen-induced hepatotoxicity: a comprehensive update. J Clin Transl Hepatol 2016;4(2):131-142. [CrossRef]
5. Ostapowicz G, Fontana RJ, Schiødt FV, Larson A, Davern TJ, Han SH, et al; U.S. Acute Liver Failure Study Group. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002;137(12):947-54. [CrossRef]

6. Simmons OL, Meinzer C, Rule J, Lee WM; Acute Liver Failure Study Group. Liver transplantation for acetaminophen-induced acute liver failure: Role of psychiatric comorbidity in listing decisions and outcomes. Dig Dis Sci 2020;65(6):1861-1868. [CrossRef]
7. Fontana RJ. Acute liver failure including acetaminophen overdose. Med Clin North Am 2008;92(4):761-794, viii. [CrossRef]
8. Licata A, Minissale MG, Stankevičiūtė S, Sanabria-Cabrera J, Lucena MI, Andrade RJ, et al. N-Acetylcysteine for Preventing Acetaminophen-Induced Liver Injury: A Comprehensive Review. Front Pharmacol 2022;13:828565. [CrossRef]
9. Rubin JB, Hameed B, Gottfried M, Lee WM, Sarkar M; Acute Liver Failure Study Group. Acetaminophen-induced acute liver failure is more common and more severe in women. Clin Gastroenterol Hepatol 2018;16(6):936-946. [CrossRef]
10. Reddy KR, Ellerbe C, Schilsky M, Stravitz RT, Fontana RJ, Durkalski V, et al; Acute Liver Failure Study Group. Determinants of outcome among patients with acute liver failure listed for liver transplantation in the United States. Liver Transpl 2016;22(4):505-515. [CrossRef]
11. Gurakar A, Conde Amiel I, Ozturk NB, Artru F, Selzner N, Psoter KJ, et al. An international, multicenter, survey-based analysis of practice and management of acute liver failure. Liver Transpl 2024;30(12):1217-1225. [CrossRef]
12. MacDonald AJ, Speiser JL, Ganger DR, Nilles KM, Orandi BJ, Larson AM, et al; US Acute Liver Failure Study Group. Clinical and neurologic outcomes in acetaminophen-induced acute liver failure: A 21-year multicenter cohort study. Clin Gastroenterol Hepatol 2021;19(12):2615-2625.e3. [CrossRef]
13. Thusius NJ, Romanowicz M, Bostwick JM. Intentional or inadvertent acetaminophen overdose—how lethal it really is? Psychosomatics 2019;60(6):574-581. [CrossRef]
14. Simkin S, Hawton K, Kapur N, Gunnell D. What can be done to reduce mortality from paracetamol overdoses? A patient interview study. QJM 2012;105(1):41-51. [CrossRef]
15. Craig DG, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ. Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity. Br J Clin Pharmacol 2012;73(2):285-294. [CrossRef]
16. Gyamlani GG, Parikh CR. Acetaminophen toxicity: suicidal vs. accidental. Crit Care 2002;6(2):155-159. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 262–268 DOI: 10.14744/hf.2026.96331

ORIGINAL RESEARCH

Shifts in liver biopsy indications and histopathological diagnoses: A report from a tertiary care center in Türkiye

Yunus Emre Dalkilic[1], Yavuz Emre Parlar[2], Cem Simsek[2], Zehranur Kiki[3], Osman Dag[4], Cenk Sokmensuer[3], Hatice Yasemin Balaban[2]

1: Department of Internal Medicine, School of Medicine, Hacettepe University, Ankara, Türkiye
2: Department of Internal Medicine, Division of Gastroenterology, School of Medicine, Hacettepe University, Ankara, Türkiye
3: Department of Pathology, School of Medicine, Hacettepe University, Ankara, Türkiye
4: Department of Biostatistics, School of Medicine, Hacettepe University, Ankara, Türkiye

Highlights & Insights

- **Scientific Gap:** Although non-invasive methods for assessing liver fibrosis have become increasingly available, long-term data on how liver biopsy indications and histopathological diagnoses have changed over time remain limited.
- **Key Finding:** The total number of percutaneous liver biopsies remained relatively stable between 2000–2011 and 2012–2022. However, biopsy indications shifted over time, with fewer biopsies performed for treatment monitoring and hepatomegaly evaluation. Histopathological diagnoses also changed, showing a decline in chronic hepatitis C and significant increases in MASH, autoimmune hepatitis, and primary biliary cholangitis.
- **Clinical Impact:** These findings suggest that liver biopsy continues to play an important role in selected patients, particularly when non-invasive tests are insufficient for diagnostic clarification, fibrosis assessment, or treatment planning.

ABSTRACT

Background and Aim: Despite advances in non-invasive methods, liver biopsy remains essential for diagnosis, prognosis, and treatment planning, and this study aimed to evaluate trends in its indications and pathological findings.

Materials and Methods: A total of 1533 adult liver biopsies at a tertiary referral hospital (2000–2022) were retrospectively reviewed for indications and diagnoses.

Results: The annual number of liver biopsies performed remained stable over the last two decades (730 vs. 803; p=0.06). The mean patient age was 43±15 years, with 52% being female. The leading indications were abnormal liver function tests (53.4%), fibrosis/cirrhosis (40.9%), treatment follow-up (2.7%), hepatomegaly (1.6%), and fever of unknown origin (0.9%). Between 2000–2011 and 2012–2022, the indications for liver biopsy changed significantly: biopsies for fibrosis/cirrhosis increased, whereas those for evaluation of treatment response and disease monitoring and for hepatomegaly decreased (p=0.01, p<0.001, and p=0.02, respectively). In the post-COVID-19 period, abnormal liver function tests became the predominant indication (42.2% vs. 69.2%), whereas fibrosis/cirrhosis decreased (54.2% vs. 28%). The most frequent pathological diagnosis was chronic hepatitis B virus (HBV) infection (38.6%), followed by chronic hepatitis C virus (HCV) (11.5%), metabolic dysfunction-associated steatohepatitis (MASH) (8.5%), autoimmune hepatitis (AIH) (7.7%), and primary biliary cholangitis (PBC) (4.2%). Across decades, MASH (6.4% vs. 10.3%; p=0.008), AIH (4% vs. 11.1%), and PBC (1.1% vs. 7%) increased significantly (p<0.001), while chronic HCV declined (17.3% vs. 6.1%; p<0.001). Chronic HBV remained stable (38.2% vs. 38.9%).

Conclusion: Over the past 22 years, the annual number of liver biopsies remained stable, with abnormal liver function tests as the leading indication, a decline in fibrosis/cirrhosis evaluation, chronic hepatitis B as the most common diagnosis, and a gradual rise in autoimmune liver diseases and MASH.

Keywords: Chronic liver diseases, etiology trends, liver biopsy indication.

How to cite this article: Dalkilic YE, Parlar YE, Simsek C, Kiki Z, Dag O, Sokmensuer C, Balaban HY. Shifts in liver biopsy indications and histopathological diagnoses: A report from a tertiary care center in Türkiye. Hepatology Forum 2026; 7(3):262–268.

Received: January 20, 2026; **Revised:** March 11, 2026; **Accepted:** April 15, 2026; **Available Online:** June 08, 2026

Corresponding author: Yunus Emre Dalkilic; Department of Internal Medicine, School of Medicine, Hacettepe University, Ankara Türkiye; **E-mail:** dlklc.ynsemr@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

Chronic liver diseases (CLD) are a major cause of morbidity and are associated with 2 million deaths from liver disease each year.[1] CLD is the 11th leading cause of death worldwide.[2] Chronic liver disease contributes to both mortality and reduced quality of life, imposing a substantial economic burden. Accurate identification of underlying etiologies is therefore essential, as the global burden of liver disease and its causes have changed over the years across the world.[3] Global hepatitis elimination programs have reduced the burden of viral liver disease, whereas rising obesity and type 2 diabetes have driven the increasing prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and its progressive form, metabolic dysfunction-associated steatohepatitis (MASH).[4] Furthermore, alcohol-related liver disease (ALD) remains a major problem in many parts of the world.[5]

The first liver biopsy was performed by Paul Ehrlich in 1883, followed by a successful percutaneous liver biopsy (PLB) in 1925 in Germany. After a century, the liver biopsy still plays an important role in predicting prognosis and treatment planning.[6] Liver biopsy can be done in a variety of ways, including percutaneous, transjugular, laparoscopic, and intraoperative approaches.[7–9] Despite advances in serologic and radiologic techniques,[10] histopathologic evaluation of liver biopsy remains the most reliable way to diagnose liver diseases and lesions,[11] and so remains the gold standard diagnostic method.[7,12]

Over time, advances in technology and shifts in clinical practice have altered the indications and use of liver biopsy. Updated guidelines, together with improved imaging and biochemical tests, have introduced non-invasive alternatives that allow assessment of liver fibrosis through serum biomarkers or measurement of liver stiffness by ultrasound or magnetic resonance (MR), reducing the need for biopsy in selected patients. Although liver biopsy is still considered the reference standard for the definitive diagnosis and prognosis assessment of many liver diseases, non-invasive tests have reduced the need for follow-up biopsies.[13] In addition, the cost of biopsy processing and pathological evaluation remains an important consideration within healthcare systems. Given the evolving feasibility, cost, and indications of liver biopsy over time, this study aimed to examine temporal trends in biopsy indications and pathological diagnoses in an urban tertiary care center in Ankara, Türkiye.

Materials and Methods

Study Design

This retrospective, single-center, cross-sectional study included adult patients who underwent PLB for benign liver diseases at a tertiary referral hospital between January 2000 and March 2022. Biopsy indications were classified into six predefined categories and compared, together with pathological diagnoses, between two consecutive decades. The study protocol was approved by the Hacettepe University Ethics Committee (dated April 19, 2022, and numbered GO 22/406), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

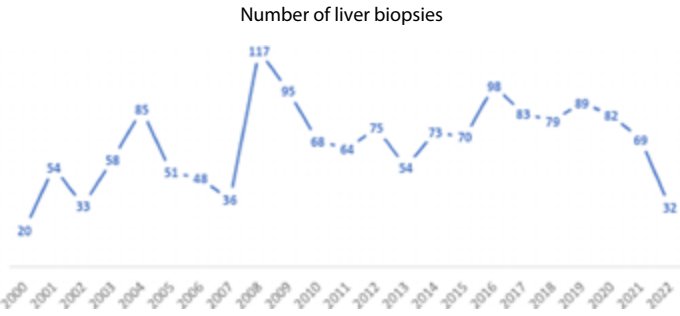


Figure 1. Distribution of liver biopsy numbers by years.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences Statistics for Windows, version 31.0 (IBM Corp., Armonk, NY, USA) and R. Data distribution was assessed with the Shapiro-Wilk test. Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate. Categorical variables were compared using the Chi-square test. The Poisson rate test and independent samples t-test were applied where appropriate. A value of $p < 0.05$ was considered statistically significant.

Results

A total of 5003 liver biopsies were retrospectively reviewed, of which 1533 PLB were included. Excluded cases comprised biopsies performed for malignancy (n=2503), non-needle biopsy techniques (n=507), and specimens referred from other centers for re-evaluation (n=460).

The mean and median annual numbers of PLB were 66 and 69, respectively. Comparison of the two decades showed 730 biopsies in 2000–2011 and 803 in 2012–2022, with no significant difference by Poisson rate test (p=0.06). The highest number of PLBs was recorded in 2008 (n=117), followed by a marked decline during the COVID-19 pandemic, reaching 32 biopsies in 2022 (Fig. 1).

The mean age at biopsy was 43±15 years, and 52% of patients were female (Table 1). Smoking and alcohol use were reported in 9% and 2% of patients, respectively. The most frequent comorbidities were diabetes mellitus (12.7%), hyperlipidemia (10.6%), and hypertension (10.3%), followed by malignancy (6.5%), rheumatologic disease (6.2%), chronic kidney disease (3.6%), thyroid disease (3.4%), and coronary artery disease (2.5%).

The Indications of PLB

The most common indication for PLB was abnormal liver function tests (53.4%), followed by assessment of liver fibrosis or cirrhosis (40.9%). Less frequent indications included treatment response and disease monitoring (2.7%), evaluation of hepatomegaly (1.6%), and fever of unknown origin (0.9%) (Table 2). Postmortem and donor evaluations accounted for a small proportion of procedures.

Table 1. Characteristics of patients who underwent liver biopsy (n=1533)

Sociodemographic characteristics of patients	n (%)
Age; years, mean±standard deviation	43±15
Gender, n (%)	
Female	789 (52)
Male	744 (48)
Smoking, n (%)	
Non-smoker	1397 (91)
Smoker	136 (9)
Duration: Pack-years, median (interquartile range)	15 (10–20)
Alcohol	
Does not use	1495 (98)
Uses	37 (2)
Other comorbidities	
Diabetes mellitus	195 (12.7)
Hyperlipidemia	163 (10.6)
Hypertension	158 (10.3)
History of malignancy	99 (6.5)
Solitary	67 (4.4)
Hematologic**	32 (2.1)
Rheumatologic diseases	95 (6.2)
Rheumatoid arthritis	22 (1.4)
Sjögren's syndrome	15 (1.0)
Systemic lupus erythematosus	10 (0.7)
Other***	48 (3.1)
Chronic kidney disease	55 (3.6)
Thyroid disease	52 (3.4)
Hashimoto's disease	24 (1.6)
Multinodular goiter	23 (1.5)
Graves' disease	3 (0.2)
Toxic multinodular goiter	2 (0.1)
Coronary artery disease	39 (2.5)

*Breast (n=24), lung (n=21), prostate (n=8), stomach (n=4), colon (n=8), and brain tumors (n=2). **Leukemia and its subgroups (n=10), lymphoma and its subgroups (n=10), multiple myeloma (n=8), and myelodysplastic syndrome (n=4). ***Gout (n=16), osteoarthritis (n=8), familial Mediterranean fever (n=6), seronegative spondyloarthropathies (n=5), systemic sclerosis (n=3), inflammatory myopathies (n=3), mixed connective tissue diseases (n=3), Still's Disease (n=3), and small vessel and large vessel vasculitis (n=1).

Comparison of the two decades (2000–2011 vs. 2012–2022) revealed a clear change in biopsy indications, with a significant increase in biopsies performed for fibrosis and cirrhosis assessment in the latter period (p=0.01). In contrast, biopsies for treatment monitoring and investigation of hepatomegaly declined significantly (p<0.001 and p=0.02, respectively).

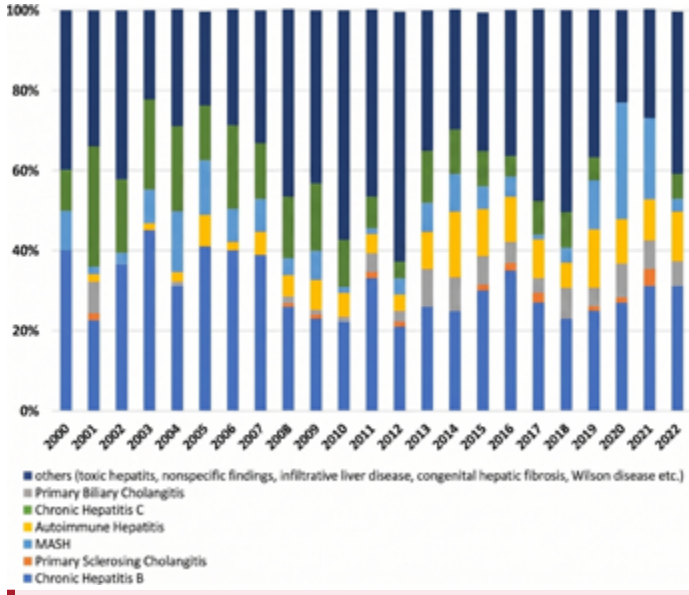


Figure 2. Trends in pathology diagnoses after percutaneous liver biopsy between 2000 and 2022.

The impact of the COVID-19 pandemic was assessed by comparing the pre-pandemic (2017–2019) and pandemic (2020–2022) periods. The number of PLBs decreased by 27%, from 251 before to 182 during the pandemic. Patient characteristics were comparable between periods with respect to mean age (44±16 vs. 45±15 years), sex (56.1% vs. 51.6% female), smoking (13.5% vs. 11%), and alcohol use (2% vs. 3.3%). In contrast, biopsy indications shifted during the pandemic. Assessment of fibrosis and cirrhosis declined from 54.2% to 28%, whereas evaluation of abnormal liver enzymes became the most frequent indication (69%). Diabetes mellitus and hyperlipidemia were more common during the pandemic period (12.4% vs. 23.1%, p=0.004, and 6.8% vs. 20.3%, p<0.001, respectively) (Table 3).

The Final Pathology Diagnosis with PLB

The most frequent pathological diagnosis was chronic hepatitis B virus infection (38.6%), followed by chronic hepatitis C virus (HCV) (11.5%), MASH (8.5%), autoimmune hepatitis (AIH) (7.7%), and primary biliary cholangitis (PBC) (4.2%). The distribution of pathological diagnoses changed significantly over time (Fig. 2).

Across the two decades, chronic hepatitis B remained the most frequent diagnosis (38.2% vs. 38.9%), whereas Wilson's disease and primary sclerosing cholangitis were consistently rare (≤1%). In contrast, the proportions of MASH (6.4% vs. 10.3%), AIH (4.0% vs. 11.1%), and PBC (1.1% vs. 7.0%) increased markedly, whereas chronic hepatitis C showed a substantial decline (17.3% vs. 6.1%). Other benign liver diseases accounted for 23.8–31.8% of diagnoses (Table 4).

Table 2. The change in indications for liver biopsy between decades

Indication	All years, n (%)	2000–2011, n (%)	2012–2022, n (%)	p
Abnormal liver function tests	818 (53.4)	396 (54.2)	422 (52.6)	0.51[a]
Evaluation of fibrosis and cirrhosis	627 (40.9)	274 (37.5)	353 (44.0)	**0.01[a]**
Evaluation of treatment response and disease monitoring	42 (2.7)	32 (4.4)	10 (1.2)	**<0.001[a]**
Assessment of hepatomegaly etiology	24 (1.6)	17 (2.3)	7 (0.9)	**0.02[a]**
Evaluation for fever of unknown origin	14 (0.9)	6 (0.8)	8 (1)	0.72[a]
Other*	8 (0.5)	5 (0.7)	3 (0.4)	0.49[b]
Total	1533 (100.0)	730 (100.0)	803 (100.0)	0.06[c]

*Postmortem evaluation (n=3) and Donor liver evaluation (n=5). a: Chi-Square test; b: Fisher's Exact test; c: Poisson Rate test.

Table 3. The characteristics of patients who underwent liver biopsy before and during the pandemic

Patient characteristics	Before the pandemic (n=251) n (%)	During the pandemic (n=182) n (%)	p
Age; year, mean±standard deviation	44±16	45±15	0.506[a]
Gender			
Female	141 (56.1)	94 (51.6)	0.403[b]
Male	110 (43.9)	88 (48.4)	0.403[b]
Smoking	34 (13.5)	20 (11)	0.517[b]
Alcohol use	5 (2.0)	6 (3.3)	0.588[b]
Concomitant diseases			
Diabetes mellitus	31 (12.4)	42 (23.1)	**0.004[b]**
Hypertension	29 (11.6)	29 (15.9)	0.2[b]
Hyperlipidemia	17 (6.8)	37 (20.3)	**<0.001[b]**
Rheumatologic diseases	22 (8.8)	22 (12.1)	0.26[b]
Chronic kidney disease	9 (3.6)	3 (1.6)	0.37[c]
Coronary artery disease	8 (3.2)	5 (2.7)	1c
Indications for biopsy			
Abnormal liver function tests	106 (42.2)	126 (69.2)	**<0.001[b]**
Evaluation of fibrosis and cirrhosis	136 (54.2)	51 (28.0)	**<0.001[b]**
Evaluation of treatment response and disease monitoring	1 (0.4)	2 (1.1)	0.58[c]
Evaluation for fever of unknown origin	4 (1.6)	1 (0.5)	0.4[c]
Other*	4 (1.6)	2 (1.1)	1[c]
Total patients	251 (100.0)	182 (100.0)	**<0.001[d]**

Postmortem (n=1), Rejection (n=1), donor evaluation (n=1), etiology of hepatomegaly (n=1). a: Independent Samples t-Test; b: Chi-Square Test; C: Fisher's Exact Test; d: Poisson Rate Test.

Discussion

This retrospective study analyzed 1533 PLBs performed between 2000 and 2022, demonstrating stable biopsy volumes over time, except for a 27% decline during the COVID-19 pandemic. During the study period, biopsy indications shifted from fibrosis and cirrhosis assessment toward evaluation of abnormal liver function tests, reflecting the impact of the pandemic and advances in imaging and non-invasive tests.

Makar et al.[14] compared 427 parenchymal liver biopsies (2017–2018) with 166 biopsies from a decade earlier (2007–2008) and grouped indications as elevated liver enzymes, chronic viral hepatitis, or other causes. Over time, biopsies for elevated liver enzymes increased markedly (45.8–68.6%), whereas those for chronic viral hepatitis declined (33.1–6.6%). In this study, the most common indication for PLB was abnormal liver function tests (53.4%), whereas viral hepatitis – particularly hepatitis B – remained a major indication

Table 4. The trends across decades for pathology diagnoses after percutaneous liver biopsy

Histopathological diagnosis	All-years, n (%)	2000–2011, n (%)	2012–2022, n (%)	p
Chronic hepatitis B	591 (38.6)	279 (38.2)	312 (38.9)	0.834[a]
Chronic hepatitis C	176 (11.5)	127 (17.3)	49 (6.1)	**<0.001[a]**
Metabolic dysfunction associated steatohepatitis	130 (8.5)	47 (6.4)	83 (10.3)	**0.008[a]**
Autoimmune hepatitis	118 (7.7)	29 (4)	89 (11.1)	**<0.001[a]**
Primary biliary cholangitis	64 (4.2)	8 (1.1)	56 (7)	**<0.001[a]**
Primary sclerosing cholangitis	13 (0.8)	5 (0.7)	8 (1.0)	0.585[b]
Wilson's disease	14 (0.9)	6 (0.8)	8 (1.0)	0.793[b]
Autoimmune hepatitis- primary biliary cholangitis variant	11 (0.7)	2 (0.3)	9 (1.1)	**0.068[b]**
Others*	416 (27.1)	227 (31.2)	189 (23.5)	**0.001[a]**
Total	1533 (100.0)	730 (100.0)	803 (100.0)	0.06[c]

*Toxic hepatitis, non-specific findings, infiltrative liver diseases, hemochromatosis, etc. a: Chi-Square Test; b: Fisher's Exact Test; c: Poisson Rate Test.

and pathological diagnosis. The shift in biopsy indications observed over time likely reflects advances in non-invasive diagnostic methods, which have reduced the need for biopsy in treatment monitoring and evaluation of hepatomegaly. Increased recognition of hepatic steatosis and the clinical relevance of fibrosis staging may also explain the growing proportion of biopsies performed for fibrosis and cirrhosis assessment. Notably, the main indication for PLB changed from fibrosis and cirrhosis evaluation in the pre-pandemic period (54.2%) to abnormal liver function tests during the COVID-19 pandemic (69.2%), probably reflecting changes in healthcare priorities. In parallel, wider use of imaging techniques and non-invasive tests has enabled the identification and staging of fibrosis in asymptomatic patients with compensated disease, as supported by the introduction of MR elastography and FibroScan in our center since 2017 and 2022, respectively. A recent study from a tertiary care center showed that MASLD was the most common indication for FibroScan, accounting for about 51% of referrals.[15] In contrast, viral hepatitis – particularly hepatitis B – remained a major indication in our biopsy-based cohort. This difference likely reflects the increasing use of non-invasive tests in patients with metabolic liver disease, whereas liver biopsy continues to be reserved for cases requiring histological staging or diagnostic clarification.

Idilman et al.[16] published a study in 2021 that analyzed etiologic trends in 898 cirrhosis patients followed up for at least 6 months. Chronic hepatitis B was the most common cause (34%), followed by chronic hepatitis C (18%) and MASLD (8%). These findings were confirmed by Abayli et al.[17] who retrospectively analyzed 554 liver biopsies of Turkish patients. The most common indication for liver biopsy was fibrosis staging in chronic hepatitis B, followed by elevation of abnormal liver function tests. The most common pathology diagnoses were 65% chronic hepatitis B, 16% MASLD, 3% chronic hepatitis C, and 3% AIH. Although the biopsy indications and pathology diagnoses were similar to these studies, our study is the first one showing the changing trends in benign liver diseases over decades, including the COVID-19 pandemic. Indeed, Abayli et al.[17] did exclude patients with non-specific histopathological findings, whereas Idilman et al.[16] analyzed only cirrhotic patients. In our study, the most common pathology diagnosis was chronic hepatitis B (38.6%), followed by chronic hepatitis C (11.5%), MASH (8.5%), AIH (7.7%), and PBC (4.2%). Non-specific findings at pathologic evaluation were detected in 19.0% patients. When the analysis was done according to two equal time periods (2000–2011 and 2012–2022), chronic hepatitis B remained to be the most common pathology diagnosis (38.2% vs. 38.9%, p=0.834). There were statistically significant increases in the rates of pathology diagnoses of MASH (6.4–10.3%, p=0.008), AIH (4–11.1%, p<0.001), PBC (1.1–7%, p<0.001), and for AIH-PBC variant (0.3–1.1%, p=0.068) whereas the diagnosis of chronic hepatitis C decreased (17.3–6.1%, p<0.001).

In a multicenter Mexican cohort including 4584 cirrhosis patients diagnosed between 2000 and 2019, the leading etiology shifted from chronic hepatitis C to MASLD, whereas ALD consistently ranked second.[18] A key difference between that study and ours lies in patient selection: while the former included only cirrhotic patients, our analysis encompassed all individuals undergoing PLB, irrespective of cirrhosis status. Similarly, in Brazil, Cunha-Silva et al.[19] evaluated 532 biopsies in 524 patients (55.3% male) with a median age of 49 years, reflecting differences in study populations across regions. The main diagnoses were HCV infection (47.0%), autoimmune and cholestatic liver diseases (12.6%), and MASLD (12.1%). Unlike reports from Latin American countries, where hepatitis C continues to play a major role in chronic liver disease, our findings reflect a different epidemiological pattern in Türkiye. In line with previous studies, MASLD increased over time; however, since liver biopsy was performed only in selected cases, biopsy-based data likely underestimate its true burden. This suggests that MASLD accounts for a larger share of chronic liver disease in Türkiye, highlighting the need for studies combining biopsy results with non-invasive tests and imaging to better define its prevalence. In contrast to hepatitis C, hepatitis B maintained a high proportion among PLB diagnoses, underscoring its ongoing public health relevance in Türkiye. Hepatitis B vaccine implementation was

done in 1989; the expanded vaccination program included newborn hepatitis B vaccine in 1998.[20] The antiviral treatments for both hepatitis B and C were reimbursed by the social security institution since 2000 and 2011, respectively.[21] Despite these measures, the persistently high rates of hepatitis B require further explanation. In clinical practice, although chronic hepatitis B is usually diagnosed through serological and biochemical tests, liver biopsy has traditionally been used to evaluate the fibrosis stage and disease severity. In addition, reimbursement policies for antiviral therapy in Türkiye have previously required histological confirmation in some cases, which may have contributed to the relatively high number of biopsies among patients with chronic hepatitis B. Therefore, the prominence of abnormal liver enzyme elevation as an indication for liver biopsy in our cohort should be interpreted cautiously, as it may partly reflect underlying hepatitis B-related disease assessment rather than a purely diagnostic indication.

This study has several strengths and limitations. Its main limitation is the single-center design, which may limit generalizability, and the retrospective nature of data collection, particularly for periods preceding electronic medical records. In contrast, the major strength lies in the large cohort, with 1533 PLBs analyzed from over two decades, allowing assessment of temporal changes in both biopsy indications and histopathological diagnoses in patients with benign liver disease.

Conclusion

This study demonstrates that PLB remains a key diagnostic tool despite evolving indications over time. Biopsy volumes were largely stable across decades, apart from a decline during the COVID-19 pandemic, whereas indications shifted from fibrosis and cirrhosis assessment toward evaluation of abnormal liver function tests. Chronic hepatitis B remained the most frequent diagnosis, alongside a gradual increase in autoimmune liver diseases and MASH over the past two decades in Türkiye. Despite the growing use of non-invasive tests, PLB continues to provide essential diagnostic and prognostic information in selected patients with liver disease.

Ethics Committee Approval: The study protocol was approved by the Hacettepe University Ethics Committee (dated April 19, 2022, and numbered GO 22/406), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: The authors declare that no artificial intelligence was used in this study.

Author Contributions: Concept: YED, HYB; Design: CS, HYB; Supervision: HYB, CS; Data Collection and/or Processing: YED, ZK, YEP; Analysis and/or Interpretation – YED, CS, OD; Literature Search: YED, ZK; Writing: YED, HYB; Critical Reviews – CS, OD, HYB, CS.

Peer-review: Externally peer-reviewed.

References

1. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol 2019;70(1):151-171. [CrossRef]
2. Griffin C, Agbim U, Ramani A, Shankar N, Kanwal F, Asrani SK. Underestimation of cirrhosis-related mortality in the medicare eligible population, 1999-2018. Clin Gastroenterol Hepatol 2023;21(1):223-225.e3. [CrossRef]
3. Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. J Hepatol 2023;79(2):516-537. [CrossRef]
4. Paik JM, Golabi P, Younossi Y, Mishra A, Younossi ZM. Changes in the Global Burden of Chronic Liver Diseases From 2012 to 2017: The Growing Impact of NAFLD. Hepatology 2020;72(5):1605-1616. [CrossRef]
5. Younossi ZM, Golabi P, Henry L. A comprehensive review of patient-reported outcomes in patients with chronic liver diseases. J Clin Gastroenterol 2019;53(5):331-341. [CrossRef]
6. Jain D, Torres R, Celli R, Koelmel J, Charkoftaki G, Vasiliou V. Evolution of the liver biopsy and its future. Transl Gastroenterol Hepatol 2021;6:20. [CrossRef]
7. Gilmore IT, Burroughs A, Murray-Lyon IM, Williams R, Jenkins D, Hopkins A. Indications, methods, and outcomes of percutaneous liver biopsy in England and Wales: an audit by the British Society of Gastroenterology and the Royal College of Physicians of London. Gut 1995;36(3):437-441. [CrossRef]
8. Sheela H, Seela S, Caldwell C, Boyer JL, Jain D. Liver biopsy: evolving role in the new millennium. J Clin Gastroenterol 2005;39(7):603-610. [CrossRef]
9. Abdi W, Millan JC, Mezey E. Sampling variability on percutaneous liver biopsy. Arch Intern Med 1979;139(6):667-669. [CrossRef]
10. Lai JC, Liang LY, Wong GL. Noninvasive tests for liver fibrosis in 2024: are there different scales for different diseases? Gastroenterol Rep (Oxf) 2024;12:goae024. [CrossRef]
11. Tannapfel A, Dienes HP, Lohse AW. The indications for liver biopsy. Dtsch Arztebl Int 2012;109(27-28):477-483. [CrossRef]
12. Neuberger J, Patel J, Caldwell H, et al. Guidelines on the use of liver biopsy in clinical practice from the British Society of Gastroenterology, the Royal College of Radiologists and the Royal College of Pathology. Gut 2020;69(8):1382-1403. [CrossRef]
13. Milani I, Leonetti F, Capoccia D. Non-invasive liver disease assessments: can they replace liver biopsy? Hepatobiliary Surg Nutr 2025;14(1):147-150. [CrossRef]
14. Makar M, Iqbal U, Sinha A, Berger A, Khara HS, Confer BD, et al. Changing trends in liver biopsy practices: A single-center analysis. Cureus 2023;15(10):e46424. [CrossRef]
15. Eris T, Hassan M, Hikal Y, Sawah E, Daneshgar F, Teker AG, et al. Changes in the etiology of chronic liver disease by referral to a FibroScan center: Increasing prevalence of the nonalcoholic fatty liver disease. Hepatol Forum 2023;4(1):7-13. [CrossRef]
16. Idilman R, Aydogan M, Oruncu MB, Kartal A, Elhan AH, Ellik Z, et al. Natural history of cirrhosis: Changing trends in etiology over the years. Dig Dis 2021;39(4):358-365. [CrossRef]
17. Abayli B, Abayli C, Gencdal G. Retrospective evaluation of liver transaminase abnormalities in asymptomatic and symptomatic patients according to liver biopsy results. J Contemp Med 2022;12(6):891-894. [CrossRef]

18. Gonzalez-Chagolla A, Olivas-Martinez A, Ruiz-Manriquez J, Servín-Rojas M, Kauffman-Ortega E, Chávez-García LC, et al. Cirrhosis etiology trends in developing countries: Transition from infectious to metabolic conditions. Report from a multicentric cohort in central Mexico. Lancet Reg Health Am 2022;7:100151. [CrossRef]
19. Cunha-Silva M, Torres LD, Fernandes MF, Secundo TML, Moreira MCG, Yamanaka A, et al. Changes in indications for outpatient percutaneous liver biopsy over 5 years: from hepatitis C to fatty liver disease. Gastroenterol Hepatol 2022;45(8):579-584. [CrossRef]
20. Toy M, Onder FO, Wormann T, Bozdayi AM, Schalm SW, Borsboom GJ, et al. Age- and region-specific hepatitis B prevalence in Turkey estimated using generalized linear mixed models: a systematic review. BMC Infect Dis 2011;11:337. [CrossRef]
21. Oancea CN, Butaru AE, Streba CT, Pirici D, Rogoveanu I, Diculescu MM, et al. Global hepatitis C elimination: history, evolution, revolutionary changes and barriers to overcome. Rom J Morphol Embryol 2020;61(3):643-653. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 269–276 DOI: 10.14744/hf.2026.10200

ORIGINAL RESEARCH

Endoscopic ultrasound strain elastography in MASLD: Evaluation against transient elastography and non-invasive markers

Ahmed Ezzat Helal[1], Mohamed ElBasiony[2,3], Ahmed Abdel-Razik[1], Nasser Mousa[1], Gamal Shiha[2,3]

1: Department of Tropical Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt
2: Hepatology and Gastroenterology Unit, Department of Internal Medicine, Faculty of Medicine, Mansoura University, Mansoura, Egypt
3: Egyptian Liver and Research Institute and Hospital (ELRIAH), Sherbin, Mansoura, Egypt

Highlights & Insights

- **Scientific Gap:** No prior studies have evaluated EUS strain elastography for steatosis and fibrosis assessment in MASLD.
- **Key Finding:** SH SD showed potential for detecting steatosis, while SR and SH Mode% were associated with significant and advanced fibrosis.
- **Clinical Impact:** EUS strain elastography may serve as an adjunctive tool during indicated upper GI endoscopy, but biopsy-based validation studies are needed.

ABSTRACT

Background and Aim: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a global health concern. Endoscopic ultrasound (EUS) combines multiple diagnostic modalities, including elastography. This study aimed to evaluate the diagnostic performance of EUS strain elastography parameters in patients with MASLD, compared with vibration-controlled transient elastography (VCTE) and non-invasive markers.

Materials and Methods: A total of 75 adults with MASLD underwent EUS strain elastography. Controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) were measured by VCTE. Assessments of non-invasive biomarkers, including the fibrosis index based on six parameters (FIB-6) and fatty liver index (FLI), were conducted.

Results: The liver strain histogram (SH) standard deviation (SD) could diagnose steatosis when referenced by CAP, with an area under the receiver operating characteristic curve (AUROC) of 0.707 (p=0.029). Both liver SH SD (AUROC=0.883, p<0.001) and liver SH mode percentage (Mode%) (AUROC=0.836, p<0.001) could diagnose steatosis when referenced by FLI (FLI ≥30). The liver strain ratio (SR) could diagnose advanced fibrosis (rule-in stage ≥F3) when referenced by LSM, yielding an AUROC of 0.677 and p=0.048. Liver SR (AUROC=0.707, p=0.002) and liver SH Mode% (AUROC=0.725, p<0.001) could diagnose significant fibrosis (stage ≥F2) when referenced by FIB-6 (FIB-6 ≥2.003).

Conclusion: SH SD shows potential for detecting steatosis, and SR with SH Mode% could be indicative of fibrosis (significant and advanced). However, further biopsy-based studies are needed.

Keywords: Elastography, endoscopic ultrasound, fatty liver, liver fibrosis, metabolic dysfunction-associated steatotic liver disease, steatosis.

How to cite this article: Helal AE, ElBasiony M, Abdel-Razik A, Mousa N, Shiha G. Endoscopic ultrasound strain elastography in MASLD: Evaluation against transient elastography and non-invasive markers. Hepatology Forum 2026; 7(3):269–276.

Received: January 25, 2026; **Revised:** April 19, 2026; **Accepted:** April 26, 2026; **Available Online:** June 10, 2026

Corresponding author: Ahmed Ezzat Helal; Department of Tropical Medicine, Faculty of Medicine, Mansoura University, Egypt; **E-mail:** ahmed_ezzat_92@hotmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) affects up to 25% of the global population.[1] While liver biopsy remains the gold standard for diagnosing steatosis and fibrosis, its invasive nature and associated risks led to the emergence of non-invasive markers.[2] Elastography operates on the premise that pathological tissues exhibit different physical characteristics from normal ones.[3] Clinical applications include strain elastography, vibration-controlled transient elastography (VCTE), and shear wave elastography (SWE).[4,5]

Endoscopic ultrasound (EUS) combines ultrasound B-mode imaging, real-time elastography, Doppler studies, and biopsy (if needed) during a single endoscopic session, which is referred to as "one-stop-shop."[6] Moreover, many patients with MASLD have indications for upper gastrointestinal (GI) endoscopy according to the American Association for the Study of Liver Diseases guidelines,[7] so EUS can be performed in the same session. EUS strain elastography enables real-time assessment of tissue stiffness from the gut lumen. Quantitative strain elastography markers include strain ratio (SR) and strain histogram (SH).[8,9]

A previous study showed that EUS SWE performs better than VCTE and fibrosis index based on four factors (FIB-4) in diagnosing fibrosis grades in MASLD patients and obese patients.[10] However, no studies have addressed EUS strain elastography for evaluating steatosis and fibrosis in patients with MASLD. We aimed to evaluate the diagnostic performance of EUS strain elastography quantitative parameters in assessing hepatic steatosis and fibrosis in patients with MASLD.

Materials and Methods

Study Design

This prospective cross-sectional study was conducted between January 2022 and February 2025. All procedures adhered to the ethical standards of the Declaration of Helsinki and the Mansoura University Institutional Research Committee (Code Number: MD.21.11.561, issued on December 12, 2021). Informed consent was obtained from all individual participants before enrollment.

Inclusion and Exclusion Criteria

Adults (≥18 years) diagnosed with MASLD, according to European Association for the Study of the Liver (EASL) guidelines, were included.[11] Patients were excluded if they had acute hepatitis, alternative chronic liver diseases, severe systemic illness, pregnancy, or declined participation.

Clinical Methods

VCTE was performed using the FibroScan® 502 Touch system, with measurements derived from 10 valid acquisitions with an XL probe (most patients were overweight and obese adults),[12] ensuring a median interquartile range of <30%. In patients with a body mass index >30, measurements were performed by two operators, and the median value was recorded.[13,14] Steatosis was assessed using the controlled attenuation parameter (CAP), and fibrosis was evaluated by liver stiffness measurement (LSM). CAP and LSM were interpreted according to EASL guidelines for steatosis (CAP ≥248) and advanced fibrosis (rule-in F3 with LSM ≥12), respectively.[11]

For additional evaluation of steatosis, the fatty liver index (FLI) was calculated (as shown in the following equation) and interpreted.[15] FLI <30 ruled out fatty liver, FLI ≥30 indicated a moderate likelihood of fatty liver, and FLI ≥60 indicated high probability. The fibrosis index based on six factors (FIB-6) was calculated and interpreted using a machine-learning model and a specialized online calculator,[16] with values ≥2.003 indicating significant fibrosis (stage ≥F2).[16] A biopsy was not done to minimize invasiveness during the initial evaluation of EUS strain elastography parameters in the MASLD population.

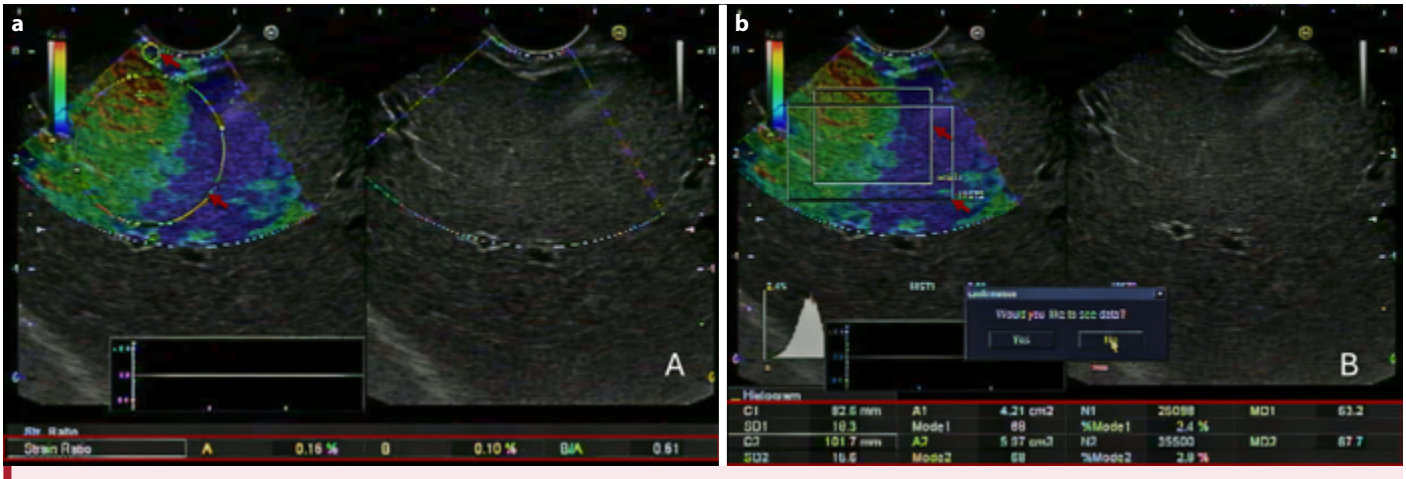


Figure 1. (a) An example of a strain ratio for the liver from the current study. The red arrows point to the regions of interest (the large circle from the target liver tissue, and the small circle from the reference stomach wall). The red rectangle at the bottom shows the strain (A: liver=0.16% and B: gut wall=0.10%), and the strain ratio is calculated automatically by the machine (B/A=0.61). **(b)** An example of a strain histogram for the liver from the current study. The red arrows point to the regions of interest (two regions of interest from the liver were examined here). The red rectangle at the bottom shows the results of the histogram analyses calculated automatically by the machine.

C: Circumference; A: Area; N: Number of pixels; MD: Median; SD: Standard deviation; Mode: Mode, and %Mode: Mode percentage.

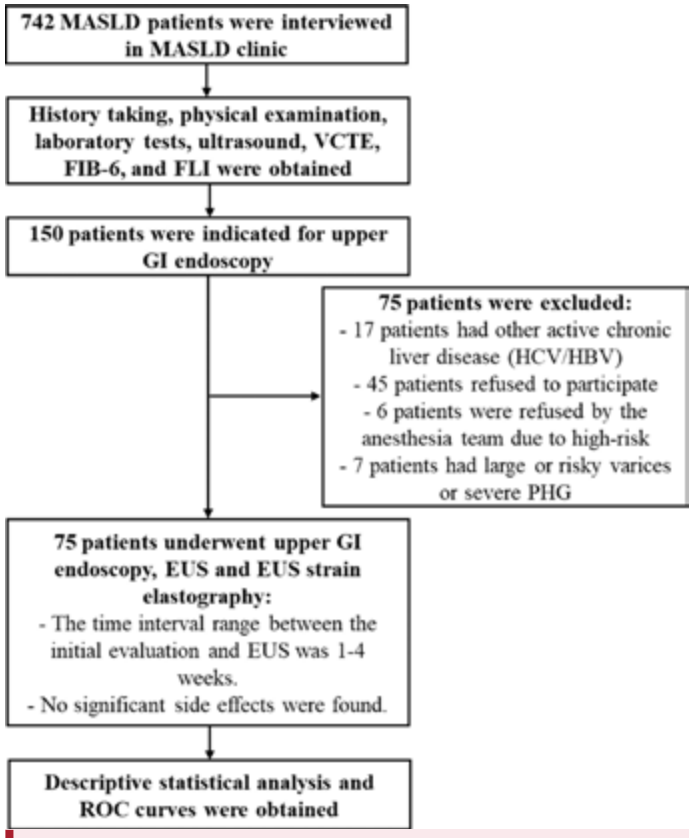


Figure 2. Flowchart of the study

FLI=[exp (0.953*loge [triglycerides] + 0.139*BMI + 0.718*loge [gamma glutamyl transferase] + 0.053*waist circumference−15.745)]/ (1 + exp (0.953*loge [triglycerides] + 0.139*BMI + 0.718*loge [gamma glutamyl transferase] + 0.053*waist circumference−15.745)] * 100).

A single expert endoscopist performed upper GI endoscopy and EUS under deep sedation in a specialized endoscopy unit, following the American Society for GI Endoscopy guidelines[7] and the European Society for GI Endoscopy guidelines,[17] respectively. A linear-array PENTAX® EG34-J10U echoendoscope coupled with a Hitachi HI VISION Avius® processor was used for the EUS evaluations.[18]

EUS-guided strain elastography was applied for the liver, measuring SR and SH within an avascular region of interest (ROI) in the left liver lobe, as shown in Figure 1. This is consistent with the approach of Schulman et al.[19] Robles-Medranda et al.[20] The machine automatically measured SH median (MD), standard deviation (SD), mode, and mode percentage (Mode%). Measurements were done using a transgastric approach.[19,20] SR was calculated automatically by the machine, comparing the ROI against a reference tissue, specifically the gut wall.[21] Reproducibility was maintained by reviewing stored cine-loop frames to verify a consistent color pattern across consecutive frames before recording any measurement.[18] Three to five measurements were obtained. These measurements were revised, and measurements with an inadequate area of interest (small size, vascularity, etc.) were excluded. The median of valid measurements was recorded and used in the analysis.[19]

Table 1. Baseline characteristics of the studied cohort

Variables	(n=75)
Age (years)	48.63 (±11)
Sex (%)	
Female	55 (73.3)
Male	20 (26.7)
Anthropometrics	
Waist (cm)	109.82 (±16.6)
BMI (kg/m^2)	37.67 (±7.7)
BMI categories (%)	
Normal (18.5≤BMI<25)	2 (2.7)
Overweight (25≤BMI<30)	7 (9.3)
Obesity (BMI≥30)	66 (88)
Comorbidities (%)	
Total number	42 (56)
Prediabetes	5 (6.7)
DM	22 (29.3)
HTN	28 (37.3)
Liver biochemical tests	
ALT (U/L)	24.62 (±14.86)
AST (U/L)	23.91 (±12.49)
ALP (IU/L)	89.88 (±35.03)
GGT (U/L)	30.01 (±19.81)
Total bilirubin (mg/dL)	0.63 (±0.33)
Albumin (g/dL)	4.23 (±0.282)
HbA1c and lipid profile	
HbA1c (%)	5.72 (±1.8)
Cholesterol (mg/dL)	205.57 (±42.67)
HDL (mg/dL)	45.38 (±8.55)
LDL (mg/dL)	133.38 (±42)
Triglycerides (mg/dL)	130.32 (±59.22)
Steatosis and fibrosis markers	
CAP (dB/m)	313 (±48)
FLI	80.4 (±23.6)
LSM (kPa)	7.3 (±6.6)
FIB-6	2.01 (±.0.57)
Steatosis grades by CAP (%)	
S0 (<248 dB/m)	3 (4)
S1 (248–268 dB/m)	7 (9.3)
S2 (268-280 dB/m)	10 (13.3)
S3 (≥280 dB/m)	55 (73.3)
Fibrosis grades by LSM (%)	
Rule-out F3 (<8 kPa)	57 (76)
Intermediate result for fibrosis (8–12 kPa)	4 (5.3)
Rule-in F3 (≥12 kPa)	14 (18.6)

DM: Diabetes mellitus; HTN: High blood pressure; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; HbA1c: Glycated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; FLI: Fatty liver index; LSM: Liver stiffness measurement; CAP: Controlled attenuation parameter; BMI: Body mass index.

Table 2. AUROC for EUS strain elastography parameters in diagnosing steatosis and advanced fibrosis referenced by VCTE

Variables	AUROC	Standard error	p	95% CI lower bound	95% CI upper bound
For steatosis*					
Liver SR	0.389	0.108	0.306	0.177	0.601
Liver SH MD	0.634	0.130	0.303	0.379	0.888
Liver SH SD**	0.707	0.095	0.029	0.521	0.892
Liver SH Mode	0.595	0.118	0.423	0.363	0.827
Liver SH Mode%	0.700	0.104	0.054	0.496	0.904
For advanced fibrosis***					
Liver SR	0.677	0.089	0.048	0.501	0.852
Liver SH MD	0.501	0.092	0.994	0.321	0.681
Liver SH SD	0.538	0.079	0.631	0.384	0.692
Liver SH Mode	0.506	0.099	0.956	0.311	0.700
Liver SH Mode%	0.415	0.086	0.319	0.247	0.583

AUROC: Area under the receiver operating characteristic curve; EUS: Endoscopic ultrasound; VCTE: Vibration-controlled transient elastography; CI: Confidence interval; SR: Strain ratio; SH MD: Strain histogram median. *CAP≥248; **Smaller values indicate a positive test; ***Rule-in fibrosis stages ≥F3: LSM≥12.

Table 3. AUROC for EUS strain elastography parameters in diagnosing steatosis and significant fibrosis referenced by the FLI and FIB-6, respectively

Variables	AUROC	Standard error	p	95% CI lower bound	95% CI upper bound
For steatosis*					
Liver SR	0.478	0.150	0.883	0.184	0.772
Liver SH MD	0.649	0.082	0.069	0.488	0.809
Liver SH SD**	0.883	0.059	<0.001	0.768	0.998
Liver SH Mode	0.542	0.123	0.734	0.301	0.782
Liver SH Mode%	0.836	0.092	<0.001	0.656	1.000
For significant fibrosis***					
Liver SR	0.707	0.066	0.002	0.577	0.837
Liver SH MD	0.583	0.072	0.247	0.442	0.725
Liver SH SD	0.603	0.070	0.137	0.467	0.740
Liver SH Mode	0.583	0.076	0.274	0.435	0.731
Liver SH Mode%**	0.725	0.064	<0.001	0.600	0.850

AUROC: Area under the receiver operating characteristic curve; FLI: Fatty liver index; FIB-6: Fibrosis index based on six parameters; EUS: Endoscopic ultrasound; CI: Confidence interval; SR: Strain ratio; SH MD: Strain histogram median. *FLI≥30; **Smaller values indicate a positive test; ***fibrosis stage ≥F2: FIB-6≥2.003.

Statistical Analysis

The sample size was calculated using the MedCalc® – version 23.0.9 (MedCalc Software Ltd, Ostend, Belgium) with a type I error of 0.01, a type II error of 0.01, and a reference of the receiver operating characteristic curve (ROC) of SH in diagnosing fibrosis in steatotic patients from the study by Robles-Medranda et al.[20] Statistical analyses were performed using the Statistical Package for the Social Sciences version 30.0.0 (IBM, New York, United States). Continuous variables were presented as mean±SD. Diagnostic performance was evaluated using the area under the ROC (AUROC), with statistical significance defined as $p<0.05$.

Results

Figure 2 summarizes the study flowchart. Table 1 shows that 73.3% of the study group was female (55 patients), with most subjects having obesity (88%) or being overweight (9.3%), and 56% having

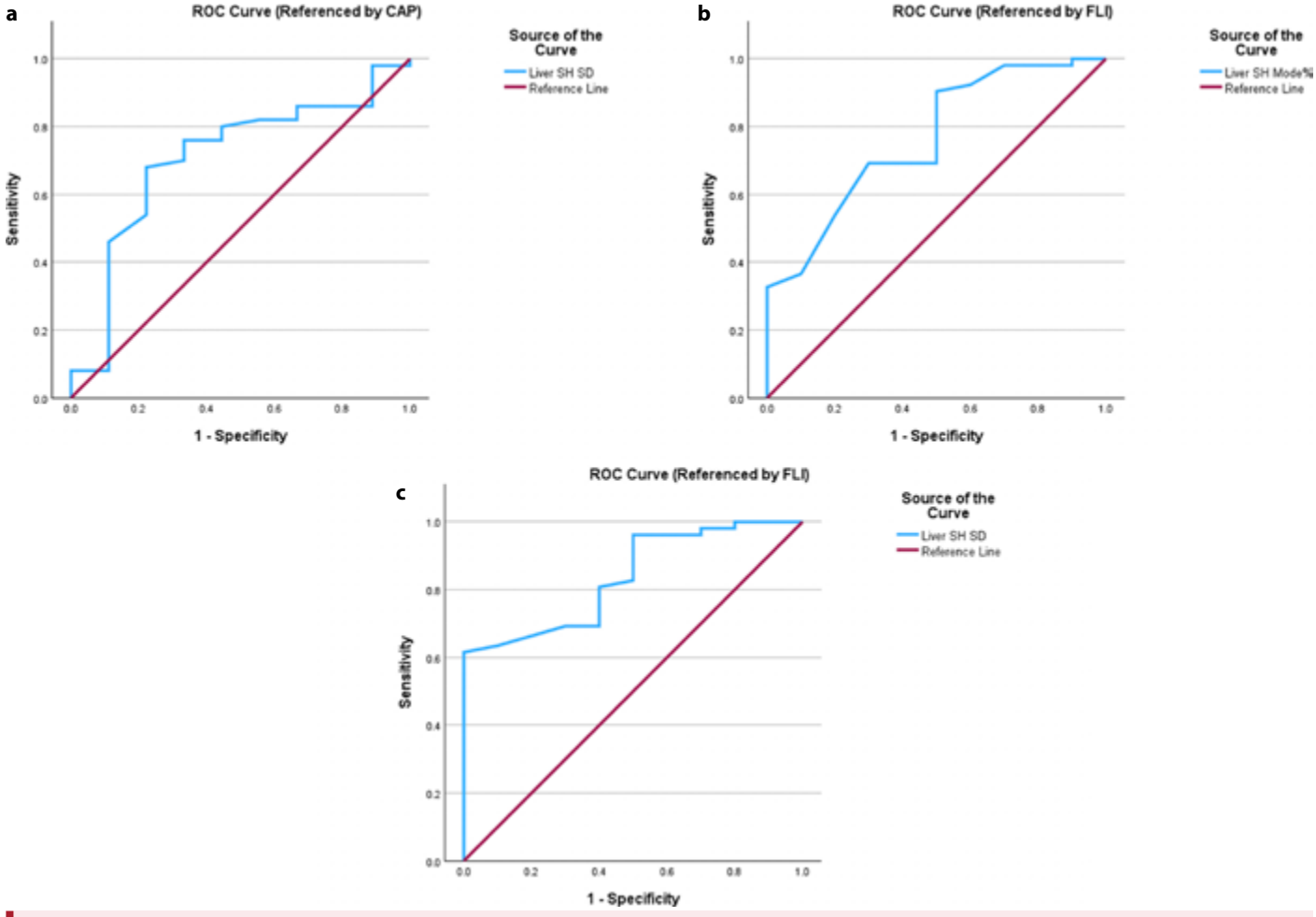


Figure 3. Receiver operating characteristic curve (ROC) for the diagnosis of steatosis by endoscopic ultrasound strain elastography parameters. **(a)** ROC curve of liver strain histogram (SH) standard deviation (SD) referenced by controlled attenuation parameter; **(b)** ROC curve of liver SH Mode% referenced by fatty liver index (FLI); **(c)** ROC curve of liver SH SD referenced by FLI.

comorbidities (diabetes mellitus, hypertension, or prediabetes). Glycated hemoglobin was slightly elevated (5.72±1.8%), and the subjects had dyslipidemia, characterized by elevated total cholesterol (205.57±42.67 mg/dL) and low-density lipoprotein (133.38±42 mg/dL). The CAP-assessed steatosis grades showed that most participants (55 individuals, 73.3%) had grade 3 (S3) steatosis. In the assessment of fibrosis grades using LSM, 57 participants (76%) were excluded from advanced fibrosis or grade 3 fibrosis (F3) (with reading <8 kPa).

Table 2 summarizes the diagnostic accuracy, measured by AUROC, of five EUS elastography parameters of the liver, referenced against VCTE, for detecting steatosis by CAP and advanced fibrosis by LSM. For diagnosing steatosis, the liver SH SD was the only statistically significant parameter, with an AUROC of 0.707 (p=0.029) and a 95% confidence interval of 0.521–0.892 (smaller Liver SH SD values indicate a positive test). At the same time, liver SH Mode% was nearly significant (AUROC=0.7, p=0.054). For diagnosing advanced fibrosis (rule-in stage ≥F3), the SR was the only statistically significant parameter, yielding an AUROC of 0.677, p=0.048, and a 95% confidence interval of 0.501–0.852.

Table 3 shows the AUROC of the five EUS elastography parameters referenced against FLI for steatosis and FIB-6 for fibrosis. For intermediate and high probability of steatosis (FLI≥30), both liver SH SD (AUROC=0.883, p<0.001) and liver SH Mode% (AUROC=0.836, p<0.000) were highly significant predictors. For significant fibrosis (≥F2: FIB-6≥2.003), liver SR (AUROC=0.707, p=0.002) and liver SH Mode% (AUROC=0.725, p<0.001) were both statistically significant (smaller liver SH Mode% values indicate a positive test). Figure 3 and 4 show the significant AUROCs for EUS strain elastography in diagnosing steatosis and fibrosis, respectively.

Discussion

To our knowledge, this is the first study to investigate the diagnostic performance of EUS strain elastography in patients with MASLD, evaluated against VCTE and non-invasive parameters. Previous studies explored EUS strain elastography in chronic liver disease and portal hypertension of mixed etiologies;[19,20] EUS B-mode imaging in non-alcoholic fatty liver disease (NAFLD) cohorts;[22]

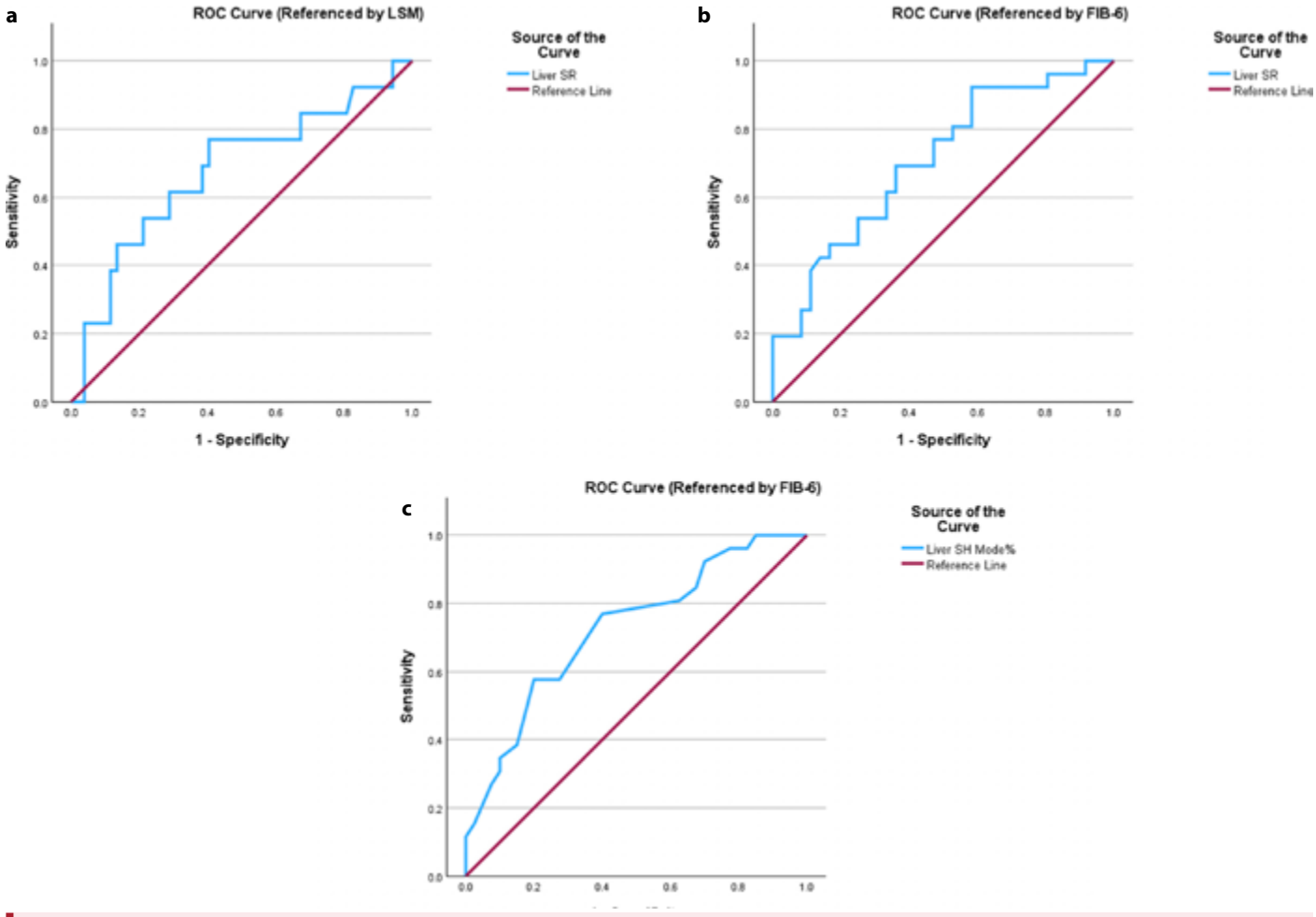


Figure 4. Receiver operating characteristic curve (ROC) for the diagnosis of fibrosis by endoscopic ultrasound strain elastography parameters. **(a)** ROC curve of liver strain ratio (SR) referenced by liver stiffness measurement for diagnosis of advanced fibrosis (rule-in F3); **(b)** ROC curve of liver SR referenced by FIB-6 for diagnosis of significant fibrosis (≥F2); **(c)** ROC curve of liver strain histogram Mode% referenced by fibrosis index based on six parameters for diagnosis of significant fibrosis (≥F2).

EUS SWE in MASLD,[10] and SR in cirrhotic and non-cirrhotic chronic liver disease due to different etiologies, including NAFLD.[23,24] Our findings, therefore, contribute novel evidence on the utility of EUS strain elastography in detecting both steatosis and fibrosis in patients with metabolic dysfunction, a group in whom conventional non-invasive techniques may be limited, as subcutaneous fat is the main limitation for VCTE performance,[25] and transcutaneous strain elastography varies according to the degree of external compression by the operator.[26] These results suggest that EUS elastography may serve as a valuable adjunctive tool in the diagnostic algorithm for MASLD, especially in patients with appropriate indications for upper GI endoscopy due to their liver condition, obesity-related GI complaints, or pre-bariatric evaluation.[7,27,28]

The liver SH SD showed the highest diagnostic performance for steatosis, with AUROCs of 0.883 when referenced by the FLI and 0.707 when referenced by the CAP. The liver SH Mode% also identified steatosis (AUROC=0.836, p<0.001 when referenced by FLI). A lower SD and a higher Mode% indicate less variability, reflecting greater tissue homogeneity. This homogeneity aligns with the well-known homogeneous pattern of a fatty liver, as observed in ultrasound examinations, computed tomography scans, and magnetic resonance imaging,[29] which is caused by the diffuse homogeneous fat infiltration observed at histopathology.[30]

AUROC analyses revealed that the liver SR and liver SH Mode% could diagnose significant and advanced fibrosis. Both showed significant AUROC when referenced to FIB-6 for ≥F2, and SR alone showed significant AUROC when referenced by LSM for ruling in F3. Robles-Medranda et al.[20] found that transcutaneous liver SR diagnoses portal hypertension in cirrhotic patients. Duman et al.[24] have also shown that SR can differentiate cirrhosis, chronic liver disease without cirrhosis, and healthy livers. The liver fibrosis index – using transcutaneous ultrasound-based strain elastography – diagnoses and stages liver fibrosis.[31] AbiMansour et al.[6] have shown that EUS SWE of the liver can detect advanced fibrosis and correlates with magnetic resonance elastography.

Wang et al.[10] showed that EUS SWE performs better than VCTE and FIB-4 in diagnosing fibrosis grades in patients with MASLD and obesity. Fibrosis may produce heterogeneous strain elastography patterns, as reflected by lower SH Mode% values. This can be attributed to fibrosis-related stiffness, which is often heterogeneous due to irregular patchy collagen deposition.[32] As a result, the combined use of liver SR and SH Mode% may improve fibrosis detection, as SR assesses stiffness and Mode% assesses associated heterogeneity.

This study's strengths include the introduction of novel EUS strain elastography parameters for diagnosing both steatosis and fibrosis (significant and advanced) in MASLD, providing new insights into their potential clinical applications. It adds to the growing body of evidence supporting the role of EUS elastography in assessing liver disease.

However, several limitations must be acknowledged. First, liver biopsy was not used as the reference standard for assessing steatosis and fibrosis. This was done to minimize invasiveness during the initial evaluation of EUS strain elastography parameters in patients with MASLD; however, further biopsy-based studies are needed to confirm these findings. Second, the study was conducted at a single center, which may limit the generalizability of the findings to broader and more diverse populations. More studies should evaluate the prognostic value of EUS strain elastography parameters, assess their cost-effectiveness, and explore their performance across different ethnicities.

Conclusion

EUS strain elastography parameters may help identify steatosis and fibrosis in patients with MASLD. Specifically, SH SD shows potential for detecting steatosis, and SR with SH Mode% could be indicative of fibrosis (significant and advanced). However, further biopsy-based studies are needed.

Ethics Committee Approval: All procedures adhered to the ethical standards of the Declaration of Helsinki and the Mansoura University Institutional Research Committee (Code Number: MD.21.11.561, issued on December 12, 2021).

Conflict of Interest: The authors have no conflicts of interest to disclose.

Financial Disclosure: This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Use of AI for Writing Assistance: Artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) were not used in the production of submitted work.

Author Contributions: Concept: GS, NM, AA; Design: GS, NM, AA; Supervision: GS, NM, AA; Materials: AH, ME; Data Collection and/or Processing: AH, ME; Analysis and/or Interpretation: AH; Literature Review: AH; Writing: AH; Critical Review: GS, NM, AA, AH, ME.

Peer-review: Externally peer-reviewed.

References

1. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64(1):73-84. [CrossRef]
2. Papatheodoridi M, Cholongitas E. Diagnosis of non-alcoholic fatty liver disease (NAFLD): Current concepts. Curr Pharm Des 2018;24(38):4574-4586. [CrossRef]
3. Dhar J, Samanta J. The expanding role of endoscopic ultrasound elastography. Clin J Gastroenterol 2022;15(5):841-858. [CrossRef]
4. Dietrich CF, Săftoiu A, Jenssen C. Real time elastography endoscopic ultrasound (RTE-EUS), a comprehensive review. Eur J Radiol 2014;83(3):405-414. [CrossRef]
5. Yamamiya A, Irisawa A, Hoshi K, Yamabe A, Izawa N, Nagashima K, et al. Recent Advances in Endosonography-Elastography: Literature Review. J Clin Med 2021;10(16):3739. [CrossRef]
6. AbiMansour J, Chin JY, Kaur J, Vargas EJ, Abu Dayyeh BK, Law R, et al. Endoscopic ultrasound-based shear wave elastography for detection of advanced liver disease. J Clin Gastroenterol 2025;59(3):256-261. [CrossRef]
7. ASGE Standards of Practice Committee; Early DS, Ben-Menachem T, Decker GA, Evans JA, Fanelli RD, Fisher DA, et al. Appropriate use of GI endoscopy. Gastrointest Endosc 2012;75(6):1127-1131. [CrossRef]
8. Iglesias-Garcia J, de la Iglesia-Garcia D, Lariño-Noia J, Dominguez-Muñoz JE. Endoscopic ultrasound (EUS) guided elastography. Diagnostics (Basel) 2023;13(10):1686. [CrossRef]
9. Dietrich CF, Burmeister S, Hollerbach S, Arcidiacono PG, Braden B, Fusaroli P, et al. Do we need elastography for EUS? Endosc Ultrasound 2020;9(5):284-290. [CrossRef]
10. Wang TJ, Jirapinyo P, Shah R, Schuster K, Papke DJ, Thompson CC, et al. EUS-guided shear wave elastography for fibrosis screening in patients with obesity and metabolic dysfunction-associated steatotic liver disease: a pilot study (with video). Gastrointest Endosc 2025;101(2):456-462.e1. [CrossRef]
11. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). Obes Facts 2024;17(4):374-444. Erratum in: Obes Facts 2024;17(6):658. [CrossRef]
12. Hirooka M, Koizumi Y, Nakamura Y, Yano R, Hirooka K, Morita M, Imai Y, Tokumoto Y, Abe M, Hiasa Y. Deep attenuation transducer to measure liver stiffness in obese patients with liver disease. J Med Ultrason (2001) 2023;50(1):63-72. Erratum in: J Med Ultrason (2001) 2024;51(2):383. [CrossRef]
13. Puigvehí M, Broquetas T, Coll S, Garcia-Retortillo M, Cañete N, Fernández R, et al. Impact of anthropometric features on the applicability and accuracy of FibroScan® (M and XL) in overweight/obese patients. J Gastroenterol Hepatol 2017;32(10):1746-1753. [CrossRef]
14. Shiha GE, El-Etreby S, Bahgat M, Hamed M, El Sherbini M, Ghoneem EA, et al. Chronic hepatitis C patients with obesity: Do we need two operators for accurate evaluation of liver stiffness? Ann Hepatol 2018;17(5):795-801. [CrossRef]
15. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6:33. [CrossRef]

16. Shiha G, Soliman R, Mikhail NNH, Alswat K, Abdo A, Sanai F, et al. Development and multicenter validation of FIB-6: A novel, machine learning, simple bedside score to rule out liver cirrhosis and compensated advanced chronic liver disease in patients with chronic hepatitis C. Hepatol Res 2022;52(2):165-175. [CrossRef]
17. Domagk D, Oppong KW, Aabakken L, Czakó L, Gyökeres T, Manes G, et al. Performance measures for ERCP and endoscopic ultrasound: a European Society of Gastrointestinal Endoscopy (ESGE) Quality improvement initiative. Endoscopy 2018;50(11):1116-1127. [CrossRef]
18. Dietrich CF, Bibby E, Jenssen C, Saftoiu A, Iglesias-Garcia J, Havre RF. EUS elastography: How to do it? Endosc Ultrasound 2018;7(1):20-28. [CrossRef]
19. Schulman AR, Lin MV, Rutherford A, Chan WW, Ryou M. A prospective blinded study of endoscopic ultrasound elastography in liver disease: towards a virtual biopsy. Clin Endosc 2018;51(2):181-185. [CrossRef]
20. Robles-Medranda C, Oleas R, Puga-Tejada M, Valero M, Valle RD, Ospina J, et al. Results of liver and spleen endoscopic ultrasonographic elastography predict portal hypertension secondary to chronic liver disease. Endosc Int Open 2020;8(11):E1623-E1632. [CrossRef]
21. Yamashita Y, Kitano M. Advances in Endoscopic Ultrasonography Technology for Measurement of Tissue Elasticity. Dig Endosc 2026;38(1):e70055. [CrossRef]
22. Silva-Santisteban A, Agnihotri A, Cruz-Romero C, Nasser IA, Malvar GL, Nsubuga JP, et al. EUS imaging for the diagnosis of nonalcoholic fatty liver disease. Gastrointest Endosc 2022;95(4):711-716. [CrossRef]
23. Udompap P. 2D-SWE in MASLD: Should we utilize it more with these new cutoffs? Hepatology 2025;82(2):281-282. [CrossRef]
24. Duman DG, Alahdab YO, Demirtas CO, Yılmaz Y, Dilber F, Ozdemir FT, et al. Usefulness of endoscopic ultrasound strain elastography for measuring liver stiffness and the role of blood cytokeratin 18 levels as a surrogate marker of fibrosis. Turk J Gastroenterol 2025;36(10):692-699. [CrossRef]
25. Yang A, Nguyen M, Ju I, Brancatisano A, Ryan B, van der Poorten D. Utility of Fibroscan XL to assess the severity of non-alcoholic fatty liver disease in patients undergoing bariatric surgery. Sci Rep 2021;11(1):14006. [CrossRef]
26. Dietrich CF, Barr RG, Farrokh A, Dighe M, Hocke M, Jenssen C, et al. Strain elastography - How to do it? Ultrasound Int Open 2017;3(4):E137-E149. [CrossRef]
27. Chang P, Friedenberg F. Obesity and GERD. Gastroenterol Clin North Am 2014;43(1):161-173. [CrossRef]
28. Camilleri M, Malhi H, Acosta A. Gastrointestinal complications of obesity. Gastroenterology 2017;152(7):1656-1670. [CrossRef]
29. Zhang YN, Fowler KJ, Hamilton G, Cui JY, Sy EZ, Balanay M, Hooker JC, Szeverenyi N, Sirlin CB. Liver fat imaging-a clinical overview of ultrasound, CT, and MR imaging. Br J Radiol 2018;91(1089):20170959. [CrossRef]
30. Abd El-Kader SM, El-Den Ashmawy EM. Non-alcoholic fatty liver disease: The diagnosis and management. World J Hepatol 2015;7(6):846-858. [CrossRef]
31. Fujimoto K, Kato M, Tonomura A, Yada N, Tatsumi C, Oshita M, et al. Non-invasive evaluation method of the liver fibrosis using Real-time tissue elastography - Usefulness of judgment liver fibrosis stage by Liver fibrosis index (LF index). Kanzo 2010;51(9):539-541. [Japanese] [CrossRef]
32. Bataller R, Brenner DA. Liver fibrosis. J Clin Invest 2005;115(2):209-218. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 277–287 DOI: 10.14744/hf.2026.91757

ORIGINAL RESEARCH

Discriminative performance of non-invasive scoring systems for VCTE-defined steatosis and fibrosis in patients with psoriasis

Sehnaz Yuksel[1], Tulin Ergun[2], Osman Cavit Ozdogan[1], Yesim Ozen Alahdab[1], Veysi Yilmaz[2], Gozde Atmaca[2], Umit Kara[3], Coskun Ozer Demirtas[1,4,5]

1: Department of Gastroenterology, Marmara University School of Medicine, Istanbul, Türkiye
2: Department of Dermatology, Marmara University School of Medicine, Istanbul, Türkiye
3: Department of Anesthesiology and Reanimation, Adana City Training and Research Hospital, University of Health Sciences, Adana, Türkiye
4: Gastroenterology Institute, Marmara University, Istanbul, Türkiye
5: Section of Digestive Diseases, Yale University School of Medicine, New Haven, CT, USA

Highlights & Insights

- **Scientific Gap:** The optimal non-invasive screening strategy for VCTE-defined hepatic steatosis and fibrosis in patients with psoriasis remains uncertain.
- **Key Finding:** Fibrosis scores showed limited discrimination, although SAFE and BARD had high negative predictive values. FLI performed best for steatosis, followed by HSI and MAFLD-S.
- **Clinical Impact:** These scores may support preliminary triage, especially where VCTE is unavailable; low fibrosis scores can help rule out significant fibrosis, whereas elevated results require elastographic confirmation.

ABSTRACT

Background and Aim: Metabolic dysfunction-associated steatotic liver disease (MASLD) is more prevalent in patients with psoriasis. Reliable non-invasive tools are needed to evaluate hepatic steatosis and to identify patients at risk for significant liver fibrosis. This study aimed to assess the discriminative performance of commonly used non-invasive scoring systems for identifying patients with vibration-controlled transient elastography (VCTE)-defined significant liver fibrosis and hepatic steatosis in patients with psoriasis.

Materials and Methods: A total of 113 patients with psoriasis were prospectively enrolled. Liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) were assessed using VCTE. Significant fibrosis (F2–F4) was defined as LSM ≥8 kPa, and significant steatosis (S2–S3) as CAP ≥259 dB/m. The discriminative performance of non-invasive fibrosis and steatosis scores was evaluated using area under the receiver operating characteristic (AUROC) curves.

Results: Of the 113 patients, 76 (67%) were diagnosed with MASLD following VCTE assessment. The body mass index, aspartate aminotransferase–alanine aminotransferase ratio, and diabetes (BARD) score (AUROC=0.692) showed the highest performance in identifying significant fibrosis, while FIB-4, aspartate aminotransferase to platelet ratio index, non-alcoholic fatty liver disease fibrosis score (NFS), and steatosis-associated fibrosis estimator (SAFE) demonstrated lower predictive accuracy. Among patients with MASLD, the SAFE score (AUROC=0.776), followed by the BARD score (AUROC=0.716), yielded the highest discriminative performance. The SAFE score showed the highest negative predictive value (95%) for ruling out significant fibrosis in MASLD patients. For detecting significant steatosis, the fatty liver index (FLI) score (AUROC=0.867) provided the highest performance, while hepatic steatosis index (HSI) (AUROC=0.813) and metabolic dysfunction–associated fatty liver disease screening score (MAFLD-S) (AUROC=0.833) also demonstrated good discriminative ability.

Conclusion: In patients with psoriasis, commonly used non-invasive fibrosis scores showed limited discrimination for VCTE-defined significant fibrosis, but they may have value as rule-out tools in low-prevalence settings. In contrast, FLI, HSI, and MAFLD-S showed good discrimination for VCTE-defined significant hepatic steatosis.

Keywords: Metabolic dysfunction-associated steatotic liver disease; non-invasive scoring systems; psoriasis.

How to cite this article: Yuksel S, Ergun T, Ozdogan OC, Ozen Alahdab Y, Yilmaz V, Atmaca G, et al. Discriminative performance of non-invasive scoring systems for VCTE-defined steatosis and fibrosis in patients with psoriasis. Hepatology Forum 2026; 7(3):277–287.

Received: February 06, 2026; **Revised:** April 09, 2026; **Accepted:** May 25, 2026; **Available Online:** July 28, 2026

Corresponding author: Sehnaz Yuksel; Department of Gastroenterology, Marmara University School of Medicine, Istanbul, Türkiye; **E-mail:** sehnazakin96@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

Psoriasis is a chronic, immune-mediated inflammatory skin disease with a global prevalence ranging from 0.09% to 5.1%. It is characterized by well-demarcated, erythematous, scaly plaques typically located on the trunk, scalp, and extremities.[1,2] In recent years, psoriasis has been recognized not merely as a cutaneous disorder but as a systemic inflammatory condition associated with increased mortality and a substantial burden of comorbidities. Notably, metabolic syndrome, type 2 diabetes, obesity, dyslipidemia, and hypertension are frequently observed in conjunction with psoriasis.[3]

Metabolic dysfunction–associated steatotic liver disease (MASLD) is observed 1.5–3 times more frequently in individuals with psoriasis compared with the general population. In the literature, the reported prevalence of MASLD in patients with psoriasis ranges from 17% to 60%, and this patient group has also been shown to have a markedly higher prevalence of advanced liver fibrosis.[4] This association cannot be explained solely by shared risk factors; it has been proposed that psoriasis may increase the risk of developing hepatic steatosis and fibrosis independently of obesity.[5] Among the key mechanisms underlying this pathophysiological process are the effects of tumor necrosis factor-alpha, interleukin-6, and interleukin-17 released from psoriatic skin, which promote hepatic inflammation and insulin resistance, leading to increased triglyceride accumulation within hepatocytes.[6–8]

The management of psoriasis requires a personalized and holistic approach, taking into consideration the disease severity, phenotype, comorbidities, and the needs of the individual. Accordingly, systemic therapies are frequently employed, particularly in moderate-to-severe cases. Methotrexate (MTX) is one of the conventional systemic agents being used for the treatment of psoriasis and psoriatic arthritis. It may exert hepatotoxic effects, including elevations in liver enzymes and potential liver fibrosis with long-term use.[9] In patients with risk factors such as obesity, diabetes, and excessive alcohol consumption, this risk becomes even more pronounced. Current guidelines recommend screening for MASLD before initiating treatment in patients with moderate-to-severe psoriasis and advise a more cautious approach when considering MTX therapy.[10]

Over the past two decades, considerable effort has been devoted to developing accessible and cost-effective non-invasive diagnostic tools as alternatives to liver biopsy in MASLD. While ultrasonography remains the first-line method for assessing steatosis, the use of non-invasive scoring systems has been increasingly adopted in large population studies. Given that the stage of fibrosis is the most critical determinant of mortality in MASLD, the non-invasive detection of advanced fibrosis holds substantial clinical importance for patient management.[11] For this purpose, vibration-controlled transient elastography (VCTE) has become the most widely used and clinically useful non-invasive modality for liver fibrosis and steatosis assessment, as the best alternative to the gold standard liver biopsy.[12] In addition to radiologic methods, several clinical scoring systems – such as the Fibrosis-4 (FIB-4), aspartate aminotransferase to platelet ratio index (APRI), non-alcoholic fatty liver disease fibrosis score (NFS), body mass index, aspartate aminotransferase–alanine aminotransferase ratio, and diabetes (BARD), and the steatosis-associated fibrosis estimator (SAFE) score – have been developed and validated in various studies to assess fibrosis risk in MASLD.[13–17] Similar to non-invasive fibrosis scores, non-invasive steatosis scoring systems such as the fatty liver index (FLI), hepatic steatosis index (HSI), and the metabolic dysfunction–associated fatty liver disease screening score (MAFLD-S), which are derived from combinations of clinical features and routine laboratory parameters, have also been developed as practical tools for steatosis quantification.[18–20]

Since the data on optimal screening method for patients with psoriasis for liver fibrosis is uncertain, this study aimed to evaluate the discriminative ability of commonly used serum-based non-invasive fibrosis and steatosis scores against VCTE-defined fibrosis and steatosis in patients with psoriasis, and to explore the potential utility for identifying patients who may warrant further liver assessment.

Materials and Methods

Study Design, Patient Selection, and Data Collection

In this cross-sectional study, 117 patients diagnosed with psoriasis who presented to a tertiary dermatology outpatient clinic at Marmara University between January 2024 and December 2024 were prospectively evaluated for enrollment to the present study. Consecutive patients with psoriasis attending the dermatology clinic were evaluated, and VCTE was performed as part of the liver assessment rather than only in patients with suspected liver disease. Patients older than 18 years with a clinical diagnosis of psoriasis confirmed by an expert dermatologist were included. Patients were excluded if they had unreliable VCTE results, viral hepatitis seropositivity, previously known liver disease, significant alcohol consumption (for women >20 g/day, for men >30 g/day), or missing data required for the calculation of non-invasive scores. As a result, the final analyses were conducted with 113 patients with reliable VCTE measurement and available non-invasive scores.

Demographic and clinical data were collected through medical history and patient interviews. Body mass index (BMI) was used to classify participants as normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), or obese (≥30.0 kg/m^2). Furthermore, waist and hip circumferences were measured using standard techniques. Current alcohol and tobacco use were recorded, and patients were categorized into two groups based on MTX use. MTX use and cumulative dose were determined from patient records and monitoring charts. For patients receiving biologic therapy, treatment type and duration were documented. Comorbidities, including hypertension, type 2 diabetes, and dyslipidemia, were assessed, and MASLD was defined according to international consensus criteria based on hepatic steatosis plus the presence of metabolic risk factors assessed in routine clinical practice. Clinical and laboratory data were obtained within ±3 months of the VCTE assessment. Serum parameters (complete blood count, liver function tests, lipid profile, C-reactive protein, etc.) were measured after a 12-h fasting period. Viral hepatitis screening was

Table 1. Demographic, clinical, and laboratory findings

	Whole cohort (n=113)		Whole cohort (n=113)
Age, mean±SD, years	46.9±13.4	Biologics, n (%)	
Sex, n (%)		Risankizumab	20 (17.7)
Female	49 (43.4)	Ustekinumab	17 (15.0)
Male	64 (56.6)	Ixekizumab	17 (15.0)
Height, median (min-max), cm	169 (150–192)	Guselkumab	9 (8.0)
Weight, median (min-max), kg	79 (44–127)	Adalimumab	7 (6.2)
BMI, median (min-max), kg/m^2	28.7 (18.6–45.9)	Infliximab	6 (5.3)
Waist circumference, median (min-max), cm	99 (63–136)	Secukinumab	5 (4.4)
Hip circumference, median (min-max), cm	109 (50–153)	Certolizumab	4 (3.5)
Alcohol use, n (%)	33 (29.2)	Etanercept	1 (0.9)
Smoking, n (%)	70 (62.0)	AST, median (min-max), IU/L	22 (12–80)
MASLD, n (%)	76 (67.0)	ALT, median (min-max), IU/L	20 (6–142)
Comorbidities, n (%)		ALP, median (min-max), IU/L	69 (18–156)
Diabetes mellitus	16 (14.2)	GGT, median (min-max), IU/L	23 (7–168)
Hypertension	16 (14.2)	BUN, median (min-max), mg/dL	13 (7–23)
Dyslipidemia	23 (20.4)	Creatinine, median (min-max), mg/dL	0.8 (0.2–1.5)
Chronic kidney disease	9 (8.0)	Total bilirubin, median (min-max), mg/dL	0.6 (0.2–1.6)
Coronary artery disease	2 (1.8)	Total protein, median (min-max), g/dL	7.2 (5.7–8.5)
Congestive heart failure	0 (0.0)	Albumin, median (min-max), g/dL	4.4 (3.6–5.2)
COPD-Asthma	3 (2.7)	White blood cell count, median (min-max), /µL	8100 (5300–16000)
Malignancy	0 (0.0)	Hemoglobin, median (min-max), g/dL	14.4 (8.7–17.1)
MTX, n (%)	68 (60.2)	Platelets, median (min-max), ×1000/mm^3	258 (155–410)
Dose, median (min-max), mg	15 (5–20)	CRP, median (min-max), mg/L	2.9 (0.1–41.0)
Duration, median (min-max), months	12 (1–120)	HDL cholesterol, median (min-max), mg/dL	48 (26–172)
Cumulative dose, median (min-max), g	0.7 (0.1–7.2)	LDL cholesterol, median (min-max), mg/dL	126 (40–192)
		Total cholesterol, median (min-max), mg/dL	208 (123–301)
		Triglycerides, median (min-max), mg/dL	133 (45–637)

µL: Microliter; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; BUN: Blood urea nitrogen; cm: Centimeter; COPD: Chronic obstructive pulmonary disease; CRP: C-reactive protein; dL: Deciliter; g: Gram; GGT: Gamma-glutamyl transferase; HDL: High-density lipoprotein; IU: International unit; kg: Kilogram; kg/m^2: Kilogram per square meter; L: Liter; LDL: Low-density lipoprotein; mm^3: Cubic millimeter; MASLD: Metabolic dysfunction-associated steatotic liver disease; mg: Milligram; mL: Milliliter; MTX: Methotrexate; SD: Standard deviation.

performed for all participants using anti-hepatitis C virus, anti-hepatitis B core, and hepatitis B surface antigen assays.

VCTE Measurements

Liver stiffness measurement (LSM) and the controlled attenuation parameter (CAP) were obtained using a FibroScan 530 Compact device equipped with M and XL probes, performed by a physician trained and certified by the manufacturer.[21] All patients were instructed to fast for at least 3 h before the examination, in accordance with the manufacturer's recommendations. Probe selection was performed using the automatic probe selection tool integrated into the device software. For the examination, patients were placed in the supine position, and the probe was positioned over the right lobe of the liver in the 9th–11th intercostal spaces. Reliable VCTE measurements were defined as those with at least 10 valid acquisitions and an interquartile range (IQR)-to-median ratio ≤30%.[22]

CAP represents the mean estimation of ultrasound attenuation at 3.5 MHz and is expressed in decibel-meter (dB/m). LSM represents the mean estimation of stiffness (Young's modulus) at a shear wave frequency of 50 Hz and is expressed in kilopascal (kPa).[23] Patients with LSM values <8.0 kPa were considered to have no or mild liver fibrosis (F0–F1), while those with LSM values ≥8.0 kPa were classified as having significant fibrosis (F2–F4).[24] The presence of significant hepatic steatosis (S2–S3) was defined as CAP ≥259 dB/m.[25]

Calculation of Non-invasive Scores

Five non-invasive fibrosis scores, FIB-4, APRI, NFS, BARD, and SAFE, and three non-invasive steatosis scores, FLI, HSI, and MAFLD-S, were calculated. FIB-4, APRI, NFS, SAFE, FLI, HSI, and MAFLD-S were computed using their original formulas.[13–15,17–20] The BARD score was calculated based on the scoring of three variables.[16] FIB-4, APRI, NFS, BARD, and SAFE scores were compared with LSM (kPa), whereas FLI, HSI, and MAFLD-S results were compared with CAP (dB/m) values.

Determination of Cut-off Values

Receiver operating characteristic (ROC) curves were constructed to assess the overall accuracy of the non-invasive scoring systems and to determine optimal cut-off points. The Youden index was used to establish the optimal threshold for non-invasive scores in identifying significant fibrosis and significant steatosis. The optimal cut-off values in this study are mainly study-derived exploratory cut-off values using the Youden index. The literature established cut-off values were derived from their original publications.[13–20]

Statistical Analysis

Continuous variables were summarized as mean ± SD (normally distributed) or median (range) (non-normally distributed), and categorical variables as n (%). Between-group comparisons used the independent Student's t-test for normally distributed continuous variables, the Mann–Whitney U test for non-normally distributed continuous variables, and the χ^2 test for categorical variables. A $p<0.05$ was considered statistically significant.

The diagnostic performance of non-invasive tests was evaluated using ROC curves. The area under the ROC curve (AUROC) was used as an indicator for comparing test accuracy. In addition, true positive, true negative, false positive, and false negative values were calculated by comparing non-invasive scores with VCTE results at various cut-off points. Metrics such as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each cut-off value using MedCalc software (version 23.1.3; MedCalc Software Ltd., Ostend, Belgium). All statistical analyses were performed using Statistical Package for the Social Sciences software (version 27.0; IBM Corp., Armonk, New York, USA).

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Marmara University School of Medicine Clinical Research Ethics Committee (Approval Date: 12 January 2024; Approval No. 09.2024.115). Written informed consent was obtained from all participants.

Results

Patient Characteristics and VCTE Findings

Seventy-six patients (67%) met the diagnostic criteria for MASLD. The cohort consisted of 56.6% males, with a mean age of 46.9±13.4 years. Based on BMI distribution, 37 patients (32.7%) were obese, 49 (43.4%) were overweight, and 27 (23.9%) had normal weight. Regarding metabolic comorbidities, diabetes mellitus was present in 16 patients (14.2%), hypertension in 16 patients (14.2%), and dyslipidemia in 23 patients (20.4%). Elevated alanine aminotransferase (>45 IU/L) was observed in 10 of 113 patients (8.8%). In the entire cohort, the median MTX dose was 15 (5–20) mg, duration 12 (1–120) months, and cumulative dose 0.7 (0.1–7.2) g. Eighty-six patients (76%) were receiving biologic therapy, with risankizumab being the most commonly used agent (17.7%) (Table 1).

Table 2. Serum-based non-invasive scores and vibration-controlled transient elastography findings

	Whole cohort (n=113)
Steatosis scores	
FLI, median (min-max)	62 (1–100)
HSI, mean±SD	38.5±6.8
MAFLD-S, median (min-max)	0.3 (-12.4–6.7)
Fibrosis scores	
FIB-4, median (min-max)	0.8 (0.2–2.5)
APRI, median (min-max)	0.2 (0.1–0.9)
NFS, mean±SD	-2.4±1.3
BARD, median (min-max)	2 (0–4)
SAFE, median (min-max)	-42.3 (–260.6–360.1)
VCTE	
LSM, median (min-max), kPa	5.3 (2.5–18.0)
CAP, mean±SD, dB/m	268.0±57.4
IQR/M, mean±SD, %	13.1±4.4

APRI: Aspartate aminotransferase-to-platelet ratio index; BARD: Body mass index; aspartate aminotransferase-alanine aminotransferase ratio; and diabetes; CAP: Controlled attenuation parameter; dB/m: Decibel-meter; FIB-4: Fibrosis-4 score; FLI: Fatty liver index; HSI: Hepatic steatosis index; IQR/M: Interquartile range/median; kPa: Kilopascal; LSM: Liver stiffness measurement; MAFLD-S: Metabolic dysfunction-associated fatty liver disease screening score; NFS: Non-alcoholic fatty liver disease fibrosis score; SAFE: Steatosis-associated fibrosis estimator; VCTE: Vibration-controlled transient elastography.

Patients were divided into two groups based on MTX exposure: 68 patients (60.2%) were using MTX, while 45 (39.8%) were not. No significant differences were observed between the groups in terms of demographic characteristics (age, sex) or metabolic risk factors (type 2 diabetes, dyslipidemia, hypertension, BMI, and MASLD). There were also no statistically significant differences in liver enzyme levels between MTX users and non-users.

Among the 113 patients with reliable VCTE measurements, the mean CAP was 268.0 ± 57.4 dB/m, the median LSM was 5.3 (2.5–18.0) kPa, and the mean IQR/M was 13.1 ± 4.4%. MTX users exhibited a higher median LSM compared with non-users; however, the difference was not statistically significant (p=0.286). Based on LSM values, 12 patients (10.5%) exhibited significant fibrosis (F2–F4), and 65 patients (57%) had significant steatosis (S2–S3).

Table 3. Performance of serum-based non-invasive fibrosis scoring systems with exploratory cut-off values in detecting significant fibrosis

	FIB-4	APRI	NFS	BARD	SAFE
A. Whole cohort (n=113)					
Optimal cut-off	**0.86**	**0.25**	**-1.88**	**2.50**	**-10.83**
Sensitivity, (%)	41.7	41.7	50.0	66.7	66.7
Specificity, (%)	56.4	65.3	65.3	62.4	64.3
NPV, (%)	89.0	90.4	91.7	94.0	94.2
PPV, (%)	10.2	12.5	14.6	17.4	18.2
FPR, (%)	44/101 (43.6)	35/101 (34.7)	35/101 (34.7)	38/101 (37.6)	35/101 (34.7)
FNR, (%)	7/12 (58.3)	7/12 (58.3)	6/12 (50.0)	4/12 (33.3)	4/12 (33.3)
AUROC (95% CI)	0.535 (0.395–0.675)	0.609 (0.447–0.772)	0.631 (0.482–0.780)	0.692 (0.536–0.849)	0.678 (0.504–0.853)
B. MASLD subgroup (n=76)					
Optimal cut-off	**1.13**	**0.35**	**-1.60**	**2.50**	**-10.51**
Sensitivity, (%)	33.3	33.3	55.6	77.8	77.8
Specificity, (%)	73.1	86.6	68.7	58.2	65.7
NPV, (%)	88.9	90.6	92.0	95.1	95.7
PPV, (%)	13.6	25.0	19.2	20.0	23.3
FPR, (%)	19/67 (28.4)	9/67 (13.4)	21/67 (31.3)	28/67 (41.8)	23/67 (34.3)
FNR, (%)	6/9 (66.7)	6/9 (66.7)	4/9 (44.4)	2/9 (22.2)	2/9 (22.2)
AUROC (95% CI)	0.551 (0.380–0.721)	0.588 (0.388–0.788)	0.653 (0.535–0.897)	0.716 (0.535–0.897)	0.776 (0.635–0.917)
C. Non-MASLD subgroup (n=37)					
Optimal cut-off	**0.67**	**0.25**	**-2.76**	**2.50**	**-57.83**
Sensitivity, (%)	66.7	66.7	66.7	33.3	33.3
Specificity, (%)	47.0	67.7	61.8	70.6	64.7
NPV, (%)	94.1	95.8	95.5	92.3	91.7
PPV, (%)	10.0	15.4	13.3	9.1	7.7
FPR, (%)	18/34 (52.9)	11/34 (32.4)	13/34 (38.2)	10/34 (29.4)	12/34 (35.3)
FNR, (%)	1/3 (33.3)	1/3 (33.3)	1/3 (33.3)	2/3 (66.7)	2/3 (66.7)
AUROC (95% CI)	0.471 (0.251–0.690)	0.672 (0.414–0.930)	0.549 (0.347–0.751)	0.588 (0.303–0.873)	0.353 (0.067–0.639)
D. MTX user subgroup (n=68)					
Optimal cut-off	**0.77**	**0.35**	**-1.60**	**2.50**	**23.40**
Sensitivity, (%)	50.0	16.7	50.0	83.3	66.7
Specificity, (%)	46.8	87.1	74.2	59.7	72.6
NPV, (%)	90.6	91.5	93.9	97.4	95.7
PPV, (%)	8.3	11.1	15.8	16.7	19.1
FPR, (%)	33/62 (53.2)	8/62 (12.9)	16/62 (25.8)	25/62 (40.3)	17/62 (27.4)
FNR, (%)	3/6 (50.0)	5/6 (83.3)	3/6 (50.0)	1/6 (16.7)	2/6 (33.3)
AUROC (95% CI)	0.492 (0.288–0.695)	0.481 (0.271–0.692)	0.684 (0.482–0.887)	0.801 (0.623–0.979)	0.675 (0.418–0.931)
E. MTX non-user subgroup (n=45)					
Optimal cut-off	**0.86**	**0.25**	**-1.92**	**2.50**	**-11.83**
Sensitivity, (%)	66.7	66.7	50.0	50.0	66.7
Specificity, (%)	56.4	64.1	61.5	66.7	64.1
NPV, (%)	91.7	92.6	88.9	89.7	92.6
PPV, (%)	19.1	22.2	16.7	18.8	22.2
FPR, (%)	17/39 (43.6)	14/39 (35.9)	15/39 (38.5)	13/39 (33.3)	14/39 (35.9)
FNR, (%)	2/6 (33.3)	2/6 (33.3)	3/6 (50.0)	3/6 (50.0)	2/6 (33.3)
AUROC (95% CI)	0.577 (0.387–0.767)	0.735 (0.522–0.948)	0.551 (0.325–0.777)	0.603 (0.375–0.830)	0.667 (0.425–0.909)

APRI: Aspartate aminotransferase-to-platelet ratio index; AUROC: Area under the receiver operating characteristic curve; BARD: Body mass index; aspartate aminotransferase–alanine aminotransferase ratio; and diabetes; CI: Confidence interval; FIB-4: Fibrosis-4 score; FNR: False negative rate; FPR: False positive rate; MASLD: Metabolic dysfunction-associated steatotic liver disease; MTX: Methotrexate; NFS: Non-alcoholic fatty liver disease fibrosis score; NPV: Negative predictive value; PPV: Positive predictive value; SAFE: Steatosis-associated fibrosis estimator.

In the overall cohort, the median FIB-4 was 0.8 (0.2–2.5), median APRI was 0.2 (0.1–0.9), mean NFS was –2.4±1.3, median BARD was 2 (0–4), and median SAFE was -42.3 (-260.6–360.1). For steatosis scores, the median FLI was 62 (1–100), mean HSI 38.5±6.8, and median MAFLD-S 0.3 (-12.4–6.7) (Table 2).

Comparison of Non-invasive Fibrosis and Steatosis Scores with Exploratory Cut-off Values

In the ROC analyses in the entire cohort, the BARD score showed the highest AUROC among the evaluated scores for identifying significant fibrosis, with an AUROC of 0.692 (95% confidence interval [CI], 0.536–0.849). The performance of the other non-invasive tests was as follows: FIB-4 0.535 (95% CI, 0.395–0.675), APRI 0.609 (95% CI, 0.447–0.772), NFS 0.631 (95% CI, 0.482–0.780), and SAFE 0.678 (95% CI, 0.504–0.853). The BARD and SAFE scores showed 66.7% sensitivity and 62.4% and 64.3% specificity, respectively, for detecting significant fibrosis, while the SAFE score with an optimal cut-off of –10.83 achieved the highest NPV (94.2%) among all tests (Table 3).

In the analyses performed to predict significant steatosis (S2–S3), FLI demonstrated the highest discriminative performance in the entire cohort with an AUROC of 0.867 (95% CI, 0.799–0.935), while the HSI and MAFLD-S scores showed good discriminatory ability with AUROCs of 0.813 (95% CI, 0.732–0.894) and 0.833 (95% CI, 0.759–0.907), respectively. In the MASLD subgroup, FLI also showed the highest discriminative performance with an AUROC of 0.769, followed by the MAFLD-S and HSI scores, with AUROCs of 0.755 and 0.706, respectively (Table 4).

In exploratory subgroup analyses, we tested the performance of each non-invasive scoring system across MASLD and MTX strata. In the MASLD subgroup (n=76), when evaluating non-invasive tests for identifying significant fibrosis, the SAFE score demonstrated the highest discriminative performance with an AUROC of 0.776, followed by the BARD score with an AUROC of 0.716. The FIB-4, APRI, and NFS scores showed poor performance in the MASLD subgroup. The sensitivities of the SAFE and BARD scores were above 75%, and their specificities were 65.7% and 58.2%, respectively. The SAFE score, with an optimal cut-off of -10.51, also provided the highest NPV (95.7%) in this subgroup. Among patients without MASLD (n=37), the APRI score showed the highest discriminative performance for identifying significant fibrosis, with an AUROC of 0.672, whereas the other scores exhibited low performance. In this group, the APRI score, with an optimal cut-off of 0.25, yielded an NPV of 95.8%.

In the MTX-treated group (n=68), the BARD score showed the highest AUROC among the evaluated scores for detecting significant fibrosis, with a value of 0.801. The AUROC values the other scores were as follows: FIB-4 0.492, APRI 0.481, NFS 0.684, and SAFE 0.675. In this group, the BARD score achieved a NPV of 97.4% with an optimal cut-off of 2.50. In the group not treated with MTX (n=45), the APRI score showed the highest discriminative performance for significant fibrosis, providing an AUROC value of 0.735 and a NPV of 92.6% at the optimal cut-off of 0.25 (Table 3 and Fig. 1).

In patients using MTX, FLI exhibited the highest performance for detecting significant steatosis, with an AUROC of 0.905, while the HSI and MAFLD-S scores showed AUROCs of 0.823 and 0.844, respectively. Similarly, among patients not using MTX, FLI, HSI, and MAFLD-S demonstrated strong discriminatory ability for detecting significant steatosis, with AUROCs of 0.866, 0.841, and 0.856, respectively (Table 4 and Fig. 2).

Comparison of Non-invasive Fibrosis and Steatosis Scores with Literature Established Cut-off Values

When diagnostic performance was evaluated using established cut-off values, the NPVs were notably high and demonstrated consistency with the results obtained from study-derived exploratory thresholds (Supplementary Table 1). Due to the absence of patients categorized into the "rule-in" zone according to established cut-offs in our cohort, sensitivity and NPV values for FIB-4, APRI, and NFS could not be calculated (Supplementary Table 2, 3). Regarding steatosis scores, established cut-off values yielded higher sensitivity rates (reaching 100% for HSI in the whole cohort) compared to exploratory thresholds, while maintaining high NPVs, albeit with a relatively lower specificity (Supplementary Table 4).

Discussion

In the present study, we evaluated the diagnostic performance of commonly used non-invasive fibrosis and steatosis scores in patients with psoriasis using VCTE as the reference standard. Our findings indicate that, among fibrosis scores, BARD and SAFE scores demonstrated the highest discriminative performance for identifying significant liver fibrosis in the entire cohort and in the MASLD subgroup. In patients without MASLD, APRI score demonstrated the highest discriminative performance. Among MTX users, the BARD score again yielded the highest discriminative performance, whereas in MTX non-users, APRI demonstrated the highest discriminatory ability. These findings likely reflect the populations in which these scores were originally developed, with SAFE and BARD being MASLD-specific tools and APRI having broader applicability across chronic liver disease.

Although MTX exposure has the potential to induce liver fibrosis, we hypothesized that MTX exposure might influence the discriminative performance of the fibrosis scores. However, the limited number of patients with significant fibrosis in our cohort likely reduced our ability to detect such effects. Importantly, no significant differences in liver enzymes or fibrosis frequency were observed between MTX users and non-users.

Regarding significant steatosis prediction, FLI demonstrated the highest discriminative performance across the entire cohort and all subgroups, including MASLD patients and those with or without MTX exposure. The HSI and MAFLD-S scores also showed good discriminative ability, although consistently inferior to FLI. This study is in line with previous studies that have validated FLI and HSI in diverse populations and extends their applicability to patients with psoriasis.

Overall, non-invasive fibrosis scores showed modest diagnostic performance in this population, with AUROC values generally below 0.7. Nevertheless, BARD and SAFE scores outperformed other scoring systems in detecting significant fibrosis, consistent with

Table 4. Performance of serum-based non-invasive steatosis scoring systems with exploratory cut-off values in detecting significant steatosis

	FLI	HSI	MAFLD-S
A. Whole cohort (n=113)			
Optimal cut-off	**50.50**	**36.31**	**-0.41**
Sensitivity, (%)	86.2	78.5	80.0
Specificity, (%)	77.1	68.7	68.7
NPV, (%)	80.4	70.2	71.7
PPV, (%)	83.5	77.3	77.6
FPR, (%)	11/48 (22.9)	15/48 (31.2)	15/48 (31.2)
FNR, (%)	9/65 (13.8)	14/65 (21.5)	13/65 (20.0)
AUROC (95% CI)	0.867 (0.799–0.935)	0.813 (0.732–0.894)	0.833 (0.759–0.907)
B. MASLD subgroup (n=76)			
Optimal cut-off	**70.50**	**37.71**	**0.03**
Sensitivity, (%)	66.2	72.3	73.9
Specificity, (%)	81.8	72.7	72.7
NPV, (%)	29.0	30.8	32.0
PPV, (%)	95.6	94.0	94.1
FPR, (%)	2/11 (18.2)	3/11 (27.3)	3/11 (27.3)
FNR, (%)	22/65 (33.8)	18/65 (27.7)	17/65 (26.2)
AUROC (95% CI)	0.769 (0.617–0.920)	0.706 (0.516–0.896)	0.755 (0.587–0.924)
C. MTX user subgroup (n=68)			
Optimal cut-off	**50.50**	**36.36**	**-0.41**
Sensitivity, (%)	84.8	76.1	78.3
Specificity, (%)	86.4	77.3	72.7
NPV, (%)	73.1	60.7	61.5
PPV, (%)	92.9	87.5	85.7
FPR, (%)	3/22 (13.6)	5/22 (22.7)	6/22 (27.3)
FNR, (%)	7/46 (15.2)	11/46 (23.9)	10/46 (21.7)
AUROC (95% CI)	0.905 (0.833–0.977)	0.823 (0.725–0.921)	0.844 (0.753–0.935)
D. MTX non-user subgroup (n=45)			
Optimal cut-off	**58.50**	**39.90**	**0.63**
Sensitivity, (%)	89.5	84.2	84.2
Specificity, (%)	76.9	92.3	84.6
NPV, (%)	90.9	88.9	88.0
PPV, (%)	73.9	88.9	80.0
FPR, (%)	6/26 (23.1)	2/26 (7.7)	4/26 (15.4)
FNR, (%)	2/19 (10.5)	3/19 (15.8)	3/19 (15.8)
AUROC (95% CI)	0.866 (0.755–0.978)	0.841 (0.709–0.973)	0.856 (0.744–0.969)

AUROC: Area under the receiver operating characteristic curve; CI: Confidence interval; FLI: Fatty liver index; FNR: False negative rate; FPR: False positive rate; HSI: Hepatic steatosis index; MAFLD-S: Metabolic dysfunction–associated fatty liver disease screening score; MASLD: Metabolic dysfunction-associated steatotic liver disease; MTX: Methotrexate; NPV: Negative predictive value; PPV: Positive predictive value.

prior reports demonstrating their limited but clinically useful accuracy.[13–17] In a biopsy-proven MASLD cohort, Ruffillo et al.[26] demonstrated that both NFS and BARD scores had only modest accuracy for identifying significant fibrosis, with comparable AUROC values (0.68 and 0.67, respectively), supporting their limited discriminative performance. Importantly, the BARD score may be preferred in clinical practice due to its simplicity and the absence of indeterminate zones. In a large Asian MASLD cohort, the SAFE score demonstrated higher AUROC values than those observed in our study, in which fibrosis status was assessed histologically.[27] Differences between

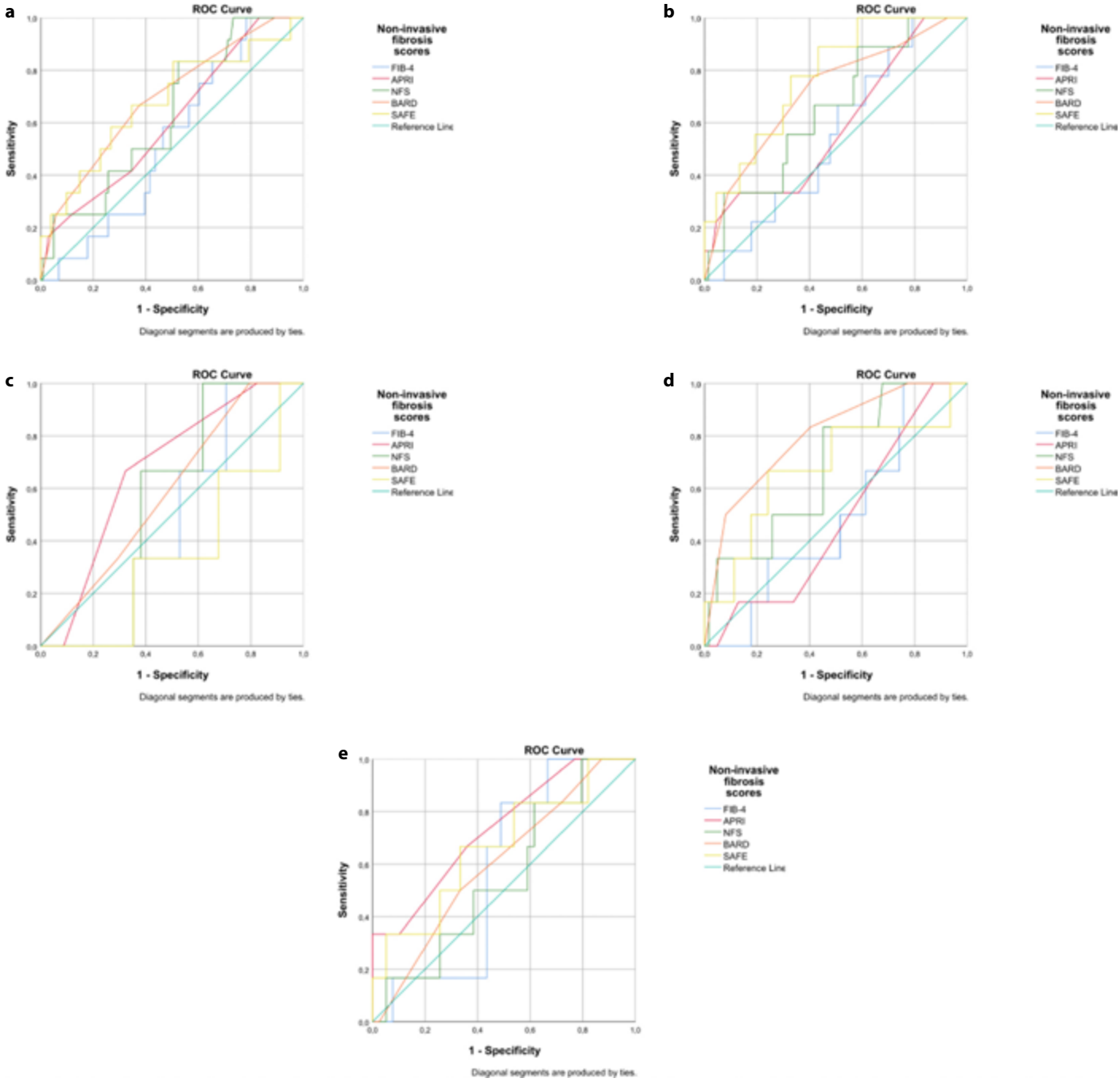


Figure 1. ROC curve analysis of serum-based fibrosis scores in detecting significant fibrosis in the whole cohort **(a)** and MASLD **(b)**, non-MASLD **(c)**, MTX user **(d)**, MTX non-user **(e)** subgroups.

APRI: Aspartate aminotransferase-to-platelet ratio index; BARD: Body mass index; aspartate aminotransferase–alanine aminotransferase ratio; and diabetes; FIB-4: Fibrosis-4 score; MASLD: Metabolic dysfunction-associated steatotic liver disease; MTX: Methotrexate; NFS: Non-alcoholic fatty liver disease fibrosis score; ROC: Receiver operating characteristic curve; SAFE: Steatosis-associated fibrosis estimator.

biopsy-based and VCTE-based reference standards likely explain this discrepancy. Despite lower AUROC values, all fibrosis scores in our study demonstrated high NPVs, supporting their clinical utility for ruling out significant fibrosis rather than confirming it. In contrast, PPVs were low, underscoring that elevated scores should prompt further evaluation rather than be considered diagnostic.

From a clinical perspective, our findings suggest that serum-based fibrosis scores may help identify patients less likely to have significant fibrosis and have a role in preliminary risk stratification among patients with psoriasis in dermatology clinics, particularly in settings with limited access to VCTE. Low SAFE or BARD scores in patients with MASLD, and low APRI scores in those without MASLD, can be considered for pre-

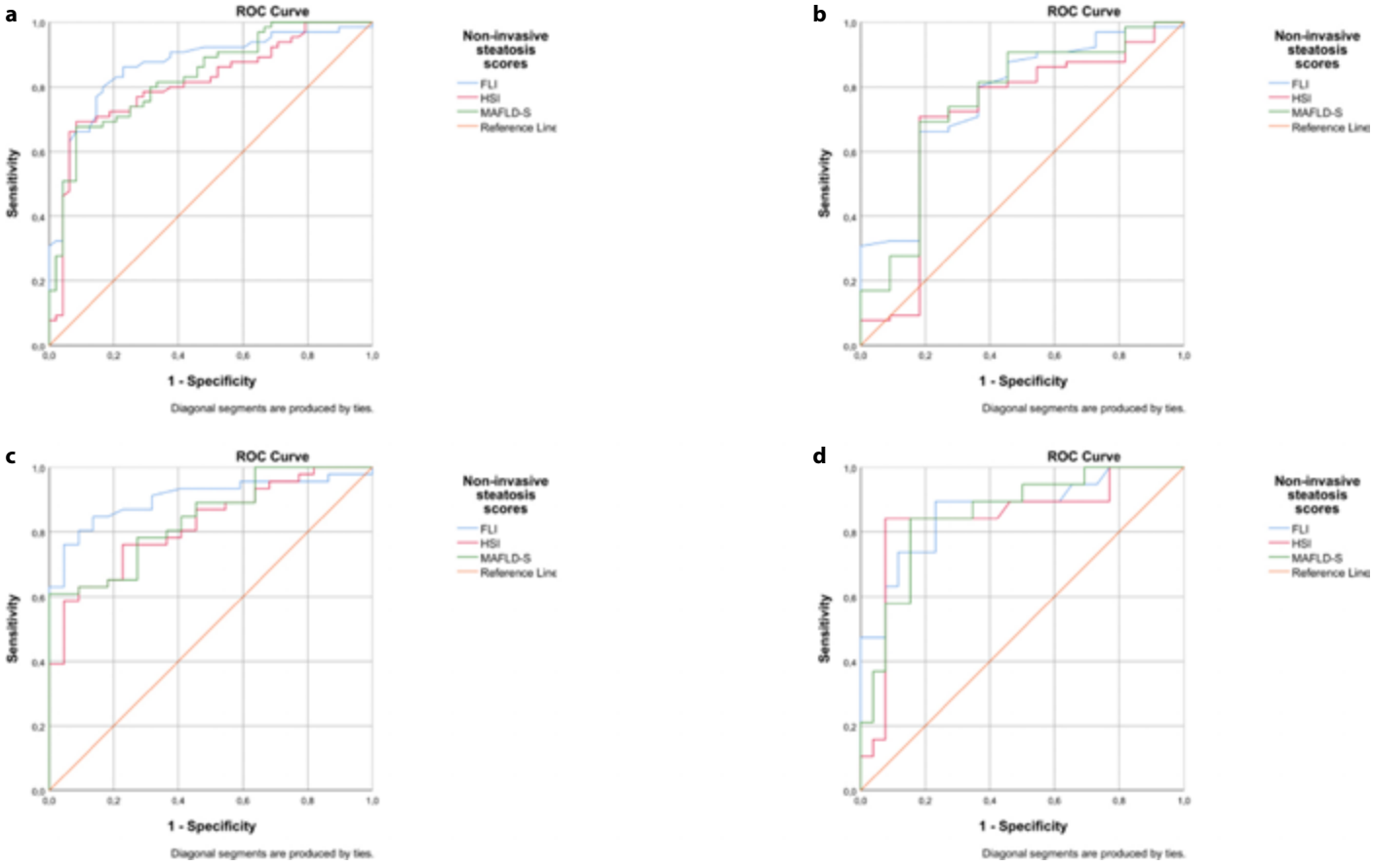


Figure 2. ROC curve analysis of serum-based steatosis scores in detecting significant steatosis in the whole cohort **(a)** and MASLD **(b)**, MTX user **(c)**, MTX non-user **(d)** subgroups.

FLI: Fatty liver index; HSI: Hepatic steatosis index; MAFLD-S: Metabolic dysfunction–associated fatty liver disease screening score; MASLD: Metabolic dysfunction–associated steatotic liver disease; MTX: Methotrexate; ROC: Receiver operating characteristic curve.

liminary triage in excluding significant fibrosis. However, these scores should not be used as standalone diagnostic tools, and abnormal/elevated results should be confirmed by elastography. The clinical utility of these non-invasive indices is further strengthened by the fact that the results obtained from established cut-off values parallel our exploratory findings, highlighting that while these tools have limited PPV, their high NPVs make them excellent preliminary triage instruments for ruling out significant fibrosis and steatosis in routine clinical practice. The steatosis scores evaluated in this study showed consistently strong performance. FLI, in particular, demonstrated excellent discriminative performance, although optimal cut-off values were higher than those reported in general populations, likely reflecting higher BMI and greater central obesity in patients with psoriasis. Data on the performance of MAFLD-S in patients with psoriasis are scarce, and our findings suggest that it may also serve as a practical screening tool in this population.

The diagnostic accuracy of serum-based NITs is known to vary significantly across different clinical settings. For instance, factors such as advanced age, type 2 diabetes, or obesity often lead to higher false-positive rates in scores like FIB-4 and NFS.[28,29] Paradoxically, despite the high prevalence of obesity (32.7%) and a high median BMI (28.7 kg/m^2) in our cohort, the study-derived exploratory cut-offs for fibrosis scores were notably lower than established values. This suggests that in patients with psoriasis, significant liver involvement may occur at lower biochemical thresholds, potentially masked by the systemic inflammatory nature of the disease. Furthermore, as highlighted in recent literature, clinicians should exercise caution when interpreting these scores in patients with varying transaminase levels, as elevated enzymes can disproportionately inflate biochemical-based indices and affect the accuracy of fibrosis assessment.[30] By considering these factors, our study underscores the importance of a personalized approach when using NITs for liver risk stratification in the psoriasis population.

In the present study, we focused on distinguishing patients with no or mild fibrosis from those with significant fibrosis (F2–F4), rather than advanced fibrosis alone. This approach is clinically relevant, as fibrosis stage F2 or higher is associated with disease progression and has direct implications for MTX discontinuation in the management of psoriasis. In addition, the limited number of patients with advanced fibrosis precluded meaningful analyses restricted to F3–F4 disease.

Several limitations should be acknowledged. First, this was a single-center study with a modest sample size, and only a small number of patients had significant fibrosis, limiting statistical precision and making subgroup analyses inherently exploratory. Notably, explor-

atory analyses for advanced fibrosis could not be performed due to the low number of events. Although NPV values were high, this should be interpreted in the context of the low prevalence of significant fibrosis in the cohort. Therefore, the observed NPV values do not necessarily indicate strong standalone test performance. Nevertheless, the prospective collection and evaluation of all clinical, biochemical, and elastographic data may have strengthened our findings compared to those obtained from retrospective studies, and low score values may still have practical triage utility as part of a stepwise assessment strategy. Second, liver biopsy was not performed in our study; therefore, this should not be interpreted as a histologically validated diagnostic study. Instead, the analyses reflect the concordance and discrimination of serum-based scores against VCTE-defined fibrosis and steatosis categories. Third, the cut-off values derived from this dataset are exploratory and should not be considered definitive or broadly generalizable without external validation. Finally, MASLD diagnosis was based on routinely available metabolic parameters, and some metabolic risk factors could not be assessed in all patients.

Conclusion

In patients with psoriasis, commonly used serum-based fibrosis scores demonstrated limited discriminative performance for detecting significant fibrosis; they represent valuable triage tools for ruling out significant fibrosis, particularly in resource-limited settings with restricted access to VCTE. In contrast, steatosis scores, particularly FLI, showed high reliability and good discrimination for detecting significant steatosis. To better elucidate their impact on clinical decision-making, large-scale, prospective, multicenter studies evaluating these scores in patients with psoriasis are warranted.

Online Appendix Link: https://file.paplino.com/hepatologyforum/files/1785246202-appendix-en.pdf

Ethical Committee Approval: The study was initiated after obtaining approval from the Marmara University School of Medicine Clinical Research Ethics Committee (Approval Date: 12 January 2024; Approval No. 09.2024.115).

Informed Consent: Written informed consent was obtained from all participants.

Conflict of Interest: The authors declare that they have no competing interests.

Financial Disclosure: The authors declare that they have no financial disclosures.

Use of AI for Writing Assistance: The authors declare that no artificial intelligence (AI)–assisted technologies (including large language models, chatbots, or image generators) were used in the preparation of this manuscript.

Author Contributions: Concept: SY, COD; Design: SY, COD; Supervision: TE, OCO, YOA, COD; Funding: SY, UK, COD; Materials: SY; Data Collection and/or Processing: SY, TE, VY, GA, UK; Analysis and/or Interpretation: SY, UK, COD; Literature Review: SY, COD; Writing: SY; Critical Review: SY, TE, OCO, YOA, COD.

Peer-review: Externally peer-reviewed.

References

1. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm 2005;2005(5):273-279. [CrossRef]
2. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol 2017;31(2):205-212. [CrossRef]
3. Korman NJ. Management of psoriasis as a systemic disease: what is the evidence? Br J Dermatol 2020;182(4):840-848. [CrossRef]
4. Gisondi P, Targher G, Zoppini G, Girolomoni G. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol 2009;51(4):758-764. [CrossRef]
5. Gau SY, Huang KH, Lee CH, Kuan YH, Tsai TH, Lee CY. Bidirectional association between psoriasis and nonalcoholic fatty liver disease: Real-world evidence from two longitudinal cohort studies. Front Immunol 2022;13:840106. [CrossRef]
6. Candia R, Ruiz A, Torres-Robles R, Chávez-Tapia N, Méndez-Sánchez N, Arrese M. Risk of non-alcoholic fatty liver disease in patients with psoriasis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2015;29(4):656-662. [CrossRef]
7. Kunz M, Simon JC, Saalbach A. Psoriasis: Obesity and Fatty Acids. Front Immunol 2019;10:1807. [CrossRef]
8. Prussick RB, Miele L. Nonalcoholic fatty liver disease in patients with psoriasis: a consequence of systemic inflammatory burden? Br J Dermatol 2018;179(1):16-29. [CrossRef]
9. Ezhilarasan D. Hepatotoxic potentials of methotrexate: Understanding the possible toxicological molecular mechanisms. Toxicology 2021;458:152840. [CrossRef]
10. Azzam A, Jiyad Z, O'Beirne J. Is methotrexate hepatotoxicity associated with cumulative dose? A systematic review and meta-analysis. Australas J Dermatol 2021;62(2):130-140. [CrossRef]
11. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389-397.e10. [CrossRef]
12. Tsai E, Lee TP. Diagnosis and evaluation of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis, including noninvasive biomarkers and transient elastography. Clin Liver Dis 2018;22(1):73-92. [CrossRef]
13. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology 2007;45(4):846-854. [CrossRef]
14. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43(6):1317-1325. [CrossRef]
15. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38(2):518-526. [CrossRef]
16. Harrison SA, Oliver D, Arnold HL, Gogia S, Neuschwander-Tetri BA. Development and validation of a simple NAFLD clinical scoring system for identifying patients without advanced disease. Gut 2008;57(10):1441-1447. [CrossRef]

17. Sripongpun P, Kim WR, Mannalithara A, Charu V, Vidovszky A, Asch S, et al. The steatosis-associated fibrosis estimator (SAFE) score: A tool to detect low-risk NAFLD in primary care. Hepatology 2023;77(1):256-267. [CrossRef]
18. Lee JH, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, et al. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. Dig Liver Dis 2010;42(7):503-508. [CrossRef]
19. Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol 2006;6:33. [CrossRef]
20. Ruiz-Manriquez J, Olivas-Martinez A, Chávez-García LC, Fernández-Ramírez A, Moctezuma-Velazquez C, Kauffman-Ortega E, et al. Prevalence of metabolic-associated fatty liver disease in Mexico and development of a screening tool: The MAFLD-S Score. Gastro Hep Adv 2022;1(3):352-358. [CrossRef]
21. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol 2003;29(12):1705-1713. [CrossRef]
22. Bilgin BO, Sunbul M, Kani HT, Demirtas CO, Keklikkiran C, Yilmaz Y. Arterial stiffness is associated independently with liver stiffness in biopsy-proven nonalcoholic fatty liver disease: a transient elastography study. Eur J Gastroenterol Hepatol 2020;32(1):54-57. [CrossRef]
23. Newsome PN, Sasso M, Deeks JJ, Paredes A, Boursier J, Chan WK, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol 2020;5(4):362-373. [CrossRef]
24. Kamali L, Adibi A, Ebrahimian S, Jafari F, Sharifi M. Diagnostic Performance of Ultrasonography in Detecting Fatty Liver Disease in Comparison with Fibroscan in People Suspected of Fatty Liver. Adv Biomed Res 2019;8:69. [CrossRef]
25. Mikolasevic I, Orlic L, Franjic N, Hauser G, Stimac D, Milic S. Transient elastography (FibroScan(®)) with controlled attenuation parameter in the assessment of liver steatosis and fibrosis in patients with nonalcoholic fatty liver disease - Where do we stand? World J Gastroenterol 2016;22(32):7236-7251. [CrossRef]
26. Ruffillo G, Fassio E, Alvarez E, Landeira G, Longo C, Domínguez N, et al. Comparison of NAFLD fibrosis score and BARD score in predicting fibrosis in nonalcoholic fatty liver disease. J Hepatol 2011;54(1):160-163. [CrossRef]
27. Li G, Lin H, Sripongpun P, Liang LY, Zhang X, Wong VWS, et al. Diagnostic and prognostic performance of the SAFE score in non-alcoholic fatty liver disease. Liver Int 2024;44(1):15-26. [CrossRef]
28. Singh A, Gosai F, Siddiqui MT, Gupta M, Lopez R, Lawitz E, et al. Accuracy of noninvasive fibrosis scores to detect advanced fibrosis in patients with type-2 Diabetes With biopsy-proven nonalcoholic fatty liver disease. J Clin Gastroenterol 2020;54:891-897. [CrossRef]
29. Alkayyali T, Qutranji L, Kaya E, Bakir A, Yilmaz Y. Clinical utility of noninvasive scores in assessing advanced hepatic fibrosis in patients with type 2 diabetes mellitus: a study in biopsy-proven non-alcoholic fatty liver disease. Acta Diabetol 2020;57(5):613-618. [CrossRef]
30. Kaya E, Bakir A, Eren F, Yilmaz Y. The utility of noninvasive scores in non-alcoholic fatty liver disease patients with normal and elevated serum transaminases. Hepatol Forum 2020;1(1):8-13. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 288–291 DOI: 10.14744/hf.2025.36953

CASE REPORT

Acute on chronic liver failure in erythropoietic protoporphyria: A case report and review of the literature

Amith Viswanath[1], Rohan T Thomas[2], Santosh Kumar E[2], Uday George Zachariah[2], Sheethal K Jose[3], Meera Thomas[4], Thomas Alex Kodiatte[4]

1: Department of Medical Gastroenterology, Christian Medical College Vellore, India
2: Department of Hepatology, Christian Medical College Vellore, India
3: Department of Dermatology, Christian Medical College Vellore, India
4: Department of Pathology, Christian Medical College Vellore, India

Clinical Pearls

- **Unique Features of the Case:** A 29-year-old woman with erythropoietic protoporphyria (EPP) presented with fever, jaundice, and pancytopenia. She had photosensitivity since childhood. Skin biopsy suggested lipoid proteinosis but was later confirmed as EPP with genetic testing.
- **Primary Lesson for Clinicians:** This case highlights the need for early EPP diagnosis in photosensitive patients. Distinguishing EPP from other conditions like lipoid proteinosis requires specialized tests. Timely intervention is crucial to prevent rapid progression to ACLF.

ABSTRACT

Erythropoietic protoporphyria (EPP) is a disease caused by an inborn error of heme biosynthesis. It manifests as painful photosensitivity in childhood. Liver disease occurs due to the deposition of protoporphyrin. Cholestasis due to protoporphyrin leads to a vicious cycle of worsening, which can lead to liver failure. A 29-year-old woman presented with a three-month history of intermittent low-grade fever and a one-month history of jaundice. She had a history of painful blisters over the skin in childhood that started at two years of age and progressed to multiple contractures from healed ulcers by five years of age. She also had splenomegaly on examination. Her blood tests showed pancytopenia, hyperbilirubinemia, and elevated liver enzymes. Tropical fever workup was negative. Autoimmune hepatitis was considered, as antinuclear antibodies (ANA) were positive with elevated immunoglobulin G (IgG). Skin biopsy showed features suggestive of lipoid proteinosis. However, on review with Periodic Acid-Schiff-diastase (PAS-D) staining, a close mimic, EPP was considered a possibility. Liver biopsy showed features of EPP with infiltration with refractile brown pigment showing bright-red birefringence on polarizing microscopy. Next-generation sequencing (NGS) confirmed EPP with a ferrochelatase enzyme coding gene mutation. The patient developed pneumonia during hospitalization and developed acute on chronic liver failure (ACLF) grade 3a, as defined by the European Association for the Study of the Liver (EASL), with ascites and encephalopathy. She was treated with photoprotective measures, ursodeoxycholic acid, antibiotics, and supportive care. The family was counseled regarding options for sequential hepatic and bone marrow transplants. She was managed with the best supportive care.

Keywords: Acute-on-chronic liver failure, erythropoietic protoporphyria.

How to cite this article: Viswanath A, Thomas RT, Kumar ES, Zachariah UG, Jose SK, Thomas M, Kodiatte TA. Acute on chronic liver failure in erythropoietic protoporphyria: A case report and review of the literature. Hepatology Forum 2026; 7(3):288–291.

Received: November 29, 2024; **Revised:** May 22, 2025; **Accepted:** July 03, 2025; **Available Online:** September 25, 2025

Corresponding author: Amith Viswanath; Department of Medical Gastroenterology, Christian Medical College Vellore Ranipet Campus, India; **E-mail:** amithsvati@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

Erythropoietic protoporphyria (EPP) (Online Mendelian Inheritance in Man [OMIM], 177000) is a disorder recognized first in 1961, caused by an inborn error of heme biosynthesis due to mutations in the gene encoding the mitochondrial enzyme ferrochelatase (FECH). The clinical presentation of EPP is variable, with a common manifestation of early childhood painful photosensitivity.[1] Liver disease develops in EPP in 1–4% of cases. The clinical spectrum of liver involvement includes mild elevations in liver enzymes, progressive fibrosis, cirrhosis, and, rarely, acute liver failure. Portal hypertension is a common feature of advanced disease. Early recognition of liver involvement is critical, as progression can be rapid and potentially fatal without timely intervention.[2]

Case Report

A 29-year-old lady from India, born to a non-consanguineous marriage, presented with a history of fever for three months and jaundice for one month. There was a history of developing vesicles on the body in childhood, predominantly on sun exposure. Lesions began at two years, initially on the face and scalp, and gradually progressed to involve all the photo-exposed areas. They ruptured spontaneously to form erosions and ulcers. They were associated with pain and a burning sensation and later healed with scarring. By five years of age, she also developed multiple contractures from the healed ulcers but did not develop any new lesions after that. Despite these photosensitivity symptoms since childhood, she had never received a diagnosis for her condition prior to the current admission. She was married with two children, and there was no similar illness in her family. On general examination, there was pallor and icterus. Cutaneous examination revealed generalized atrophic vermicular scarring on the face. Perioral furrowing, a restricted mouth opening, and tongue protrusion were present. Atrophic scars were noted on the dorsa of the hands and legs. There was fibrotic scarring with contractures of the left ring and little fingers, while linear contracted scars were seen on the legs, extending from the right great toe to the knee with areas of depigmentation and crusting (Fig. 1). Hyperkeratotic papules coalescing to form plaques were also noted on the dorsa of the fingers. She had moderate splenomegaly on palpation. The differentials considered were tropical diseases (malaria, Brucella, Leishmaniasis), infective endocarditis, tuberculosis, and lymphoma. Causes of portal hypertension were considered, including pre-hepatic (vascular thrombosis), hepatic (advanced liver disease of various etiologies), and post-hepatic (Budd-Chiari disease) mechanisms. The possibility of lipoid proteinosis, erythropoietic protoporphyria, dystrophic epidermolysis bullosa, and Kindler's syndrome were considered for skin disease.

On investigation, she had pancytopenia (hemoglobin: 8.8 grams per deciliter (g/dL) [normal range: 11–15 g/dL for women]; leucocyte counts of 2.1×10^9/L [normal range: $4.0–12.0\times10^9$/L]; and platelet counts of 119×10^9/L [normal range: $150–450\times10^9$/L]). Peripheral smear showed a normocytic normochromic picture.



Figure 1. Atrophic scars over dorsum of left hand, hyperkeratotic papules and plaques on the dorsal aspect of fingers with fibrotic scarring and contractures of left ring & little fingers.

She was evaluated with a rapid diagnostic test for visceral leishmaniasis rK39 (antibody detection against recombinant K39), immunoglobulin M (IgM) for Brucella, enzyme-linked immunosorbent assay (ELISA) for IgM Leptospirosis, and TPHA (Treponema pallidum hemagglutination assay) for syphilis, which were negative. Echocardiogram ruled out infective endocarditis. She had hyperbilirubinemia (total bilirubin: 3.28 milligrams per deciliter (mg/dL) [normal range: <1.2 mg/dL]; direct bilirubin: 2.49 mg/dL) with elevated liver enzymes (aspartate aminotransferase: 202 international units per liter (IU/L) [normal range: <40 IU/L]; alanine aminotransferase: 61 IU/L [normal range: <41 IU/L]; alkaline phosphatase: 151 IU/L [normal range: 40–125 IU/L]) and prolonged prothrombin time with an international normalized ratio (INR) of 1.4 (normal range: <1.2). Antinuclear antibodies (ANA) were positive, 1+ at 1:80 dilution, and immunoglobulin G was 3724 mg/dL (normal range: 700–1600 mg/dL). Viral markers (hepatitis B surface antigen and anti-hepatitis C) and autoimmune markers (anti-smooth muscle antibody, anti-liver kidney microsome type 1, antimitochondrial antibody, and anti-soluble liver antigen antibody) were negative. Serum ceruloplasmin was 574 U/L (normal range: 200–1100 U/L). Ultrasound of the liver showed mild coarse echotexture with normal size; the portal vein was normal, and the spleen was enlarged and measured 17.5 cm in the largest dimension. Noninvasive liver stiffness measurement with Acoustic Radiation Force Impulse (ARFI) was in the cirrhotic range (4.6 meters/second (m/s)).

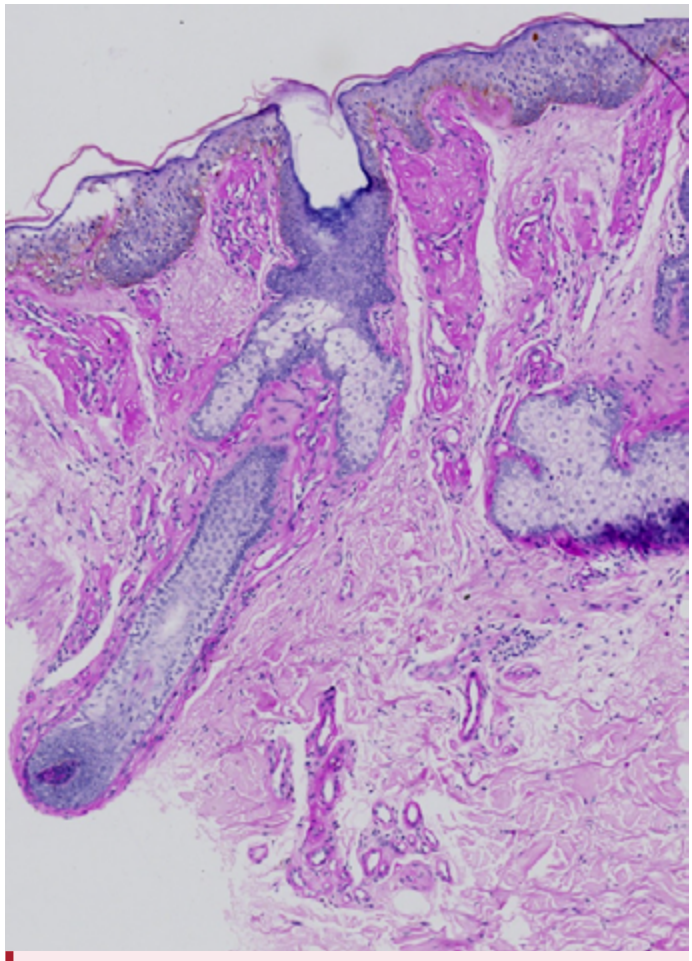


Figure 2. Skin biopsy with abundant eosinophilic material around superficial dermal vessels which is PAS positive and PASD resistant, H & E, 100x.

The skin lesions were biopsied and showed benign papillomatous lesions with eosinophilic material around superficial dermal blood vessels and sweat gland complexes. The initial interpretation was lipoid proteinosis. A literature review found a case report of lipoid proteinosis mimicking erythropoietic protoporphyria.[3] The skin biopsy was then reviewed with special Periodic Acid-Schiff (PAS) and Periodic Acid-Schiff-diastase (PAS-D) stains. The eosinophilic material around the blood vessels was found to be PAS-positive and diastase-resistant, but it was not seen around the sweat gland complexes. The diagnosis of EPP was considered (Fig. 2).

A transjugular liver biopsy was done, and lobular parenchyma showed diffuse ballooning of hepatocytes, some containing a coarse brown granular pigment. Some of the Kupffer cells and canaliculi also contained coarse brown refractile pigment. The refractile brown pigment showed bright-red birefringence with a centrally located, dark Maltese cross on polarizing microscopy (Fig. 3). The features were suggestive of porphyria, particularly erythropoietic protoporphyria. Next-generation sequencing (NGS) for porphyria and related disorders showed a homozygous mutation in the ferrochelatase enzyme coding gene (FECH:c.1153G>A), confirming the diagnosis of EPP.

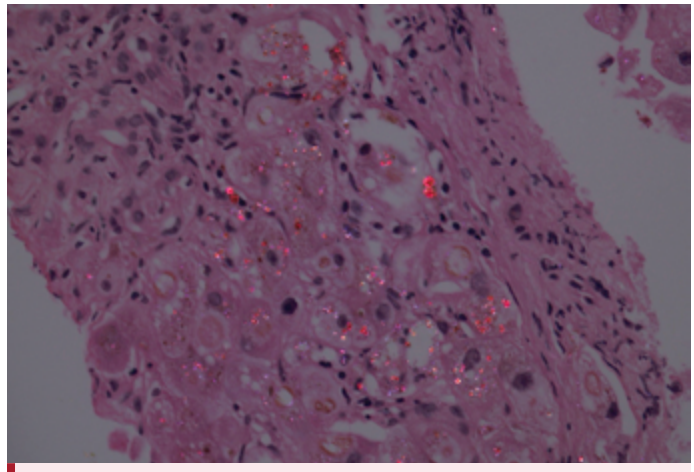


Figure 3. Photomicrograph displaying red birefringence and clusters of brilliantly illuminated granules seen in the deposits within the hepatocytes, bile ducts and canaliculi, in a Maltese cross appearance, H&E, 20x.

She developed pneumonia during the hospital stay. Within a week, she developed acute-on-chronic liver failure (ACLF) as defined by the European Association for the Study of the Liver - Chronic Liver Failure-Sequential Organ Failure Assessment (EASL-CLIF), with ascites and encephalopathy. Her jaundice worsened, with a total bilirubin of 16.1 mg/dL, direct bilirubin of 13.8 mg/dL, and elevated liver enzymes (aspartate aminotransferase: 266 IU/L; alanine aminotransferase: 76 IU/L; alkaline phosphatase: 127 IU/L). Her EASL-CLIF grade was 3a with three organ failures (liver, cerebral, and respiratory). She was managed with photoprotective measures, ursodeoxycholic acid, intravenous antibiotics, and standard treatment for hepatic encephalopathy. The family was counseled regarding treatment options, including transplants. She was managed with the best supportive care and succumbed to her illness after discharge from the hospital.

Discussion

Porphyria cutanea tarda (PCT) and erythropoietic protoporphyria (EPP) are the two forms of porphyria known to cause liver disease. The liver disease precedes the onset of skin disease in PCT and vice versa in EPP.[4] It has been recently discovered that EPP is usually inherited in an autosomal recessive manner.[5] EPP is typically characterized by painful photosensitivity in childhood. The estimated prevalence of the disease in Europe was previously determined to be 1 in 109,000. However, recent data from exome databases suggest a prevalence of approximately 1 in 17,000 among Caucasians.[6]

The FECH gene, located on chromosome 18, encodes the FECH enzyme. FECH is responsible for catalyzing the insertion of iron into a protoporphyrin ring to produce heme, the end product. A partial decrease in FECH activity results in the accumulation of protoporphyrin. Protoporphyrin builds up in the development of red blood cells during hematopoiesis. Upon entering circulation, free protoporphyrin diffuses across the red blood cell membrane and binds to plasma proteins. Cutaneous lesions occur due to the presence of protoporphyrin in erythrocytes and plasma in skin vasculature.

Hyaline PAS-positive perivascular material deposits can be found, with extensive fine fibrillar material and reduplication of blood vessel walls and epidermal basal lamina upon histological examination.[1]

The liver retrieves protoporphyrin from the plasma, where most of it is excreted in its original form via bile. At the same time, the remaining amount is converted to heme through liver ferrochelatase metabolism. Protoporphyrin deposition in the liver presents as dark brown deposits exhibiting a Maltese-cross appearance upon polarizing microscopy.[4] The hepatobiliary system clears protoporphyrin, which has a concentration-dependent hepatotoxic effect. Cholestasis caused by protoporphyrin results in additional protoporphyrin accumulation, initiating a vicious cycle of escalating cholestasis and decreased protoporphyrin excretion. Severe liver disease is fatal in the absence of liver transplantation.[4] Biochemical screening for EPP involves testing for total erythrocyte protoporphyrin levels, followed by fractionation into metal-free and zinc protoporphyrin. The diagnosis of EPP is confirmed by demonstrating an increase in total erythrocyte protoporphyrin levels (>3–4 times the upper limit of normal), with predominantly (>85%) metal-free protoporphyrin.[6]

Various treatment options for erythropoietic protoporphyria (EPP) have been reported, including ursodeoxycholic acid (UDCA), haematin infusion, plasmapheresis, hemodialysis, exchange transfusions, and intravenous vitamin E therapy.[4] Liver transplantation is an option for restoring normal liver function, with nearly 100 cases of liver transplantation for EPP documented.[5] It does not address the underlying deficiency of the FECH enzyme, leading to a high rate of recurrent EPP. A study found that 11 out of 17 patients (65%) who survived for more than two months after liver transplantation experienced a recurrence.[7] Sequential liver transplantation followed by bone marrow transplantation has also been reported as a success.[8] Givosiran, a small interfering ribonucleic acid (RNA) that prevents the accumulation of delta-aminolevulinic acid and porphobilinogen, has been recently approved for acute hepatic porphyrias. However, its role in EPP is not yet defined.[9] Another drug, afamelanotide, an α-melanocyte-stimulating hormone analog, is approved for photoprotection in EPP.[10]

The significance of this case lies in its demonstration of the rare but devastating progression to ACLF in a patient with long-undiagnosed EPP. Despite classic photosensitivity symptoms since childhood, the diagnosis remained elusive until advanced liver disease developed, highlighting the importance of early recognition. The diagnostic challenges in EPP, particularly when mimicking other conditions like lipoid proteinosis, emphasize the utility of specialized staining techniques and genetic testing for confirmation. The rapid deterioration following infection and the potentially fatal outcome also reinforce the need for research into novel therapeutic approaches, as current interventions remain largely supportive.

Conclusion

EPP is a rare disease characterized by photosensitivity, skin lesions, and liver disease. ACLF due to EPP is a rare entity with high mortality. Sequential hepatic and bone marrow transplantation is considered for severe cases of EPP with hepatic involvement.

Informed Consent: The patient provided written informed consent for the publication of this case report, including the use of medical images, and their personal details were anonymized in accordance with privacy guidelines.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: Not declared.

Author Contributions: Concept: AV, RTT, SKE; Design: AV, RTT, SKE; Supervision: SKE, UGZ, MT, SKJ, TAK; Funding: SKE, UGZ; Materials: AV, RTT, SKE, MT, SKJ, TAK; Data Collection and/or Processing: AV, RTT, SKJ, MT, TAK; Analysis and/or Interpretation: AV, RTT, MT, SKJ, TAK; Literature Search: AV, RTT, SKJ; Writing: AV, SKE, UGZ; Critical Reviews: AV, RTT, SKE, UGZ, MT, SKJ, TAK.

Peer-review: Externally peer-reviewed.

References

1. Lecha M, Puy H, Deybach JC. Erythropoietic protoporphyria. Orphanet J Rare Dis 2009;4:19. [CrossRef]
2. Holme SA, Anstey AV, Finlay AY, Elder GH, Badminton MN: Erythropoietic protoporphyria in the U.K.: clinical features and effect on quality of life. Br J Dermatol 2006;155(3):574-581. [CrossRef]
3. Bloomer JR, Hill HD, Kools AM, Straka JG: Heme synthesis in protoporphyria. Curr Probl Dermatol 1991;20:135-147. [CrossRef]
4. Anstey AV, Hift RJ: Liver disease in erythropoietic protoporphyria: insights and implications for management. Gut 2007;56(7):1009-18.
5. Gou EW, Balwani M, Bissell DM, Bloomer JR, Bonkovsky HL, Desnick RJ, et al. Pitfalls in erythrocyte protoporphyrin measurement for diagnosis and monitoring of protoporphyrias. Clin Chem 2015;61(12):1453-1456. [CrossRef]
6. Dickey AK, Naik H, Keel SB, Levy C, Beaven SW, Elmariah SB, et al; Porphyrias Consortium of the Rare Diseases Clinical Research Network. Evidence-based consensus guidelines for the diagnosis and management of erythropoietic protoporphyria and X-linked protoporphyria. J Am Acad Dermatol 2023;89(6):1227-1237.
7. McGuire BM, Bonkovsky HL, Carithers RL Jr, Chung RT, Goldstein LI, Lake JR, et al. Liver transplantation for erythropoietic protoporphyria liver disease. Liver Transpl 2005;11(12):1590-1596. [CrossRef]
8. Rand EB, Bunin N, Cochran W, Ruchelli E, Olthoff KM, Bloomer JR. Sequential liver and bone marrow transplantation for treatment of erythropoietic protoporphyria. Pediatrics 2006;118(6):e1896-e1899. [CrossRef]
9. Ventura P, Bonkovsky HL, Gouya L, Aguilera-Peiró P, Montgomery Bissell D, Stein PE, et al; ENVISION Investigators. Efficacy and safety of givosiran for acute hepatic porphyria: 24-month interim analysis of the randomized phase 3 ENVISION study. Liver Int 2022;42(1):161-172. [CrossRef]
10. Langendonk JG, Balwani M, Anderson KE, Bonkovsky HL, Anstey AV, Bissell DM, et al. Afamelanotide for erythropoietic protoporphyria. N Engl J Med 2015;373(1):48-59. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 292–295 DOI: 10.14744/hf.2025.99427

CASE REPORT

A fructose-intolerant patient with acute liver injury: Not only the active ingredient, but also excipients matter

Eda Kaya[1], Aleko Zedginidze[1], Djawid Baraksei[1], Ali Canbay[1], Andrea Tannapfel[2], Oliver Goetze[1]

1: Department of Medicine, Universitätsklinikum Knappschaftskrankenhaus Bochum, Ruhr University Bochum, Bochum, Germany
2: Institute of Pathology, Ruhr University Bochum, Bochum, Germany

Clinical Pearls

- **Unique Features of the Case:** The patient's cholestatic liver injury was caused by undiagnosed hereditary fructose intolerance (aldolase B mutation). Symptoms worsened by fructose-containing medications resolved after switching to fructose-free treatment.
- **Primary Lesson for Clinicians:** Clinicians should consider hereditary fructose intolerance in unexplained liver injury, especially with a lifelong aversion to sweets or fruit. A thorough review of both diet and medications for hidden fructose excipients is essential, as their removal leads to rapid recovery.

ABSTRACT

We report the case of an 18-year-old female with cholestatic hepatopathy of unknown origin, presenting with therapy-resistant jaundice and pruritus following oral contraceptive use and gastrointestinal infections. In another hospital, drug-induced autoimmune hepatitis (DILI-AIH) was suspected, and corticosteroid therapy was initiated but remained unresponsive. Initiation of colestyramine led to a worsening of symptoms and increasing liver transaminases. After referral to our centre, a mini-laparoscopic liver biopsy was performed, and histopathology revealed cholestatic DILI and mild fibrosis, with no signs of AIH. After a repeated precise history from the mother, a hereditary fructose intolerance was highly suggestive, and genetic testing confirmed a homozygous mutation in the aldolase B gene (A149P). Additionally, no pathogenic mutations in genes encoding bile acid and phospholipid transporters were detected. The treatment was adjusted to sugar-free colestyramine, leading to complete resolution of symptoms. In the management of hereditary fructose intolerance, not only dietary ingredients but also the supplements and medications may contain fructose excipients that could exacerbate and aggravate liver injuries.

Keywords: Acute liver injury, aldolase B, fructose, liver fibrosis.

How to cite this article: Kaya E, Zedginidze A, Baraksei D, Canbay A, Tannapfel A, Goetze O. A fructose-intolerant patient with acute liver injury: Not only the active ingredient, but also excipients matter. Hepatology Forum 2026; 7(3):292–295.

Received: April 01, 2025; **Revised:** August 12, 2025; **Accepted:** August 18, 2025; **Available Online:** April 10, 2026

Corresponding author: Ali Canbay; Department of Medicine, Universitätsklinikum Knappschaftskrankenhaus Bochum, Ruhr University Bochum, Bochum, Germany;
E-mail: ali.canbay@rub.de

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

Hereditary fructose intolerance (HFI) is a rare autosomal recessive disorder caused by mutations in the ALDOB gene encoding aldolase B, located on chromosome 9q22.3. This enzyme deficiency leads to the accumulation of fructose-1-phosphate, which inhibits gluconeogenesis. HFI is typically diagnosed in childhood, with common symptoms including vomiting, hypoglycemia, and faintness starting after weaning from breast milk. These symptoms often result in a natural avoidance of fructose-containing foods.[1] Herein, we present a case of multifactorial liver injury based on HFI diagnosed late in adulthood and the presence of non-pathogenic mutations in bile acid and phospholipid transporters, which predispose to cholestatic liver diseases.

Case Report

An 18-year-old patient was referred initially to an external clinic following oral contraceptive use and diverse infections. The patient complained of fatigue and pruritus on the hands and feet, which was treated with cetirizine. On physical examination, no other signs were noted apart from icterus and scratch marks related to pruritus. There was no history of substantial alcohol, drug, or herbal mixture intake. The total bilirubin was 4.6 mg/dL, direct bilirubin 3.76 mg/dL, indirect bilirubin 1.04 mg/dL, alanine transaminase (ALT) 253 U/L, aspartate transaminase (AST) 375 U/L, alkaline phosphatase (ALP) 129 U/L, and γ-glutamyl-transferase (GGT) 23 U/L. Serological tests for viral hepatitis, including hepatitis A, B, C, and E, were negative. Viral infections, including Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, and adenovirus, were ruled out. The autoantibodies, including antinuclear antibody, anti-mitochondrial antibody, liver-kidney microsomal antibody, myeloperoxidase antibody, proteinase 3 antibody, and immunoglobulin G and M concentrations, were within the normal range. Hepatic magnetic resonance imaging and cholangiopancreatography revealed no sign of tumor, inflammation, or biliary obstruction. The liver biopsy showed signs of drug-induced liver injury (DILI) without signs of autoimmune hepatitis. Oral contraceptives, which she used over 6 months, and cetirizine, which was prescribed due to pruritus, were stopped immediately. Initially, steroid therapy resulted in a decrease in ALP and bilirubin levels. The patient was prescribed colestyramine and ursodeoxycholic acid and followed up in ambulatory settings. Due to worsening of the symptoms and increase in liver transaminases, including ALT and AST, the patient was referred to our tertiary care center. During the extended anamnesis, the patient and her mother reported experiencing nausea and vomiting after consuming fruits since childhood, which resulted in avoiding fructose-containing foods. There was no documented history of abnormal liver test results in childhood. Subsequently, we performed a mini-laparoscopic hepatic biopsy, which yielded macroscopically a cholestatic green liver without organomegaly (Fig. 1). Liver histology showed a DILI with cholestasis accompanied by mild fibrosis without signs of autoimmune hepatitis, which indicated a worsening of liver fibrosis. Subsequently, we checked the additives of the prescribed colestyramine and determined that the preparation contained sucrose and replaced it with a sugar-free preparation. We finally performed a genetic analysis, which confirmed a homozygous mutation for the aldolase B gene (A149P, homozygous) and mutations of bile acid and phospholipid transporters, which predispose to cholestatic liver diseases (ABCB4 c.504T>C and c.711A>T, homozygous; ABCB11 p.A44V, heterozygous; ABCB11 p.D482G, heterozygous). Following the therapeutic change to a sugar-free colestyramine, after 4 weeks the patient was presented in our outpatient clinic with complete regression of icterus and pruritus. The patient was referred to a dietician. The change in the liver transaminases over time is depicted in Figure 2. Informed consent was taken from the patient. We did not use any artificial intelligence–assisted technology in preparation of this case report.

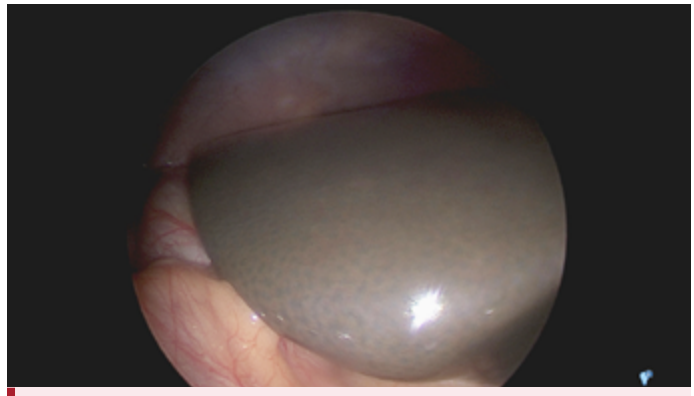


Figure 1. Cholestatic green liver detected in mini-laparoscopic examination.

Discussion

In the case report, we presented a young female with multifactorial liver injury due to the presence of HFI and non-pathogenic mutations in bile acid and phospholipid transporters, predisposing to cholestatic liver disease. The patient did not report any similar cholestasis episodes previously due to a strict self-avoidance of fructose and no history of medication use, which resulted in a late diagnosis in adulthood. The acute injury was caused by oral contraceptives, gastrointestinal infections, cetirizine, and exacerbated with the unfortunate treatment of pruritus with sorbitol-containing excipients of colestyramine. In Figure 3, we depicted the liver histopathology indicating the deficient aldolase B expression with less staining compared to the normal liver. To the best of our knowledge, this is the first laparoscopic and histological visualization of the liver in a patient with hereditary fructose intolerance and severe cholestasis.

A fructose-restricted diet constitutes the backbone of HFI. Besides, medications should also be strictly chosen to avoid sucrose and sorbitol.[2] In the literature, there are reported cases of fatal outcomes following the infusion of fructose-containing solutions after an appendectomy or abortion in otherwise healthy young adults.[3,4] Therefore, fructose-containing solutions are abandoned due to the lethal complications and absence of reported advantages over glucose.[3] To prevent such exposures, mobile applications have been proposed to help identify and eliminate foods and medications containing intolerable ingredients, and they should be encouraged.[5]

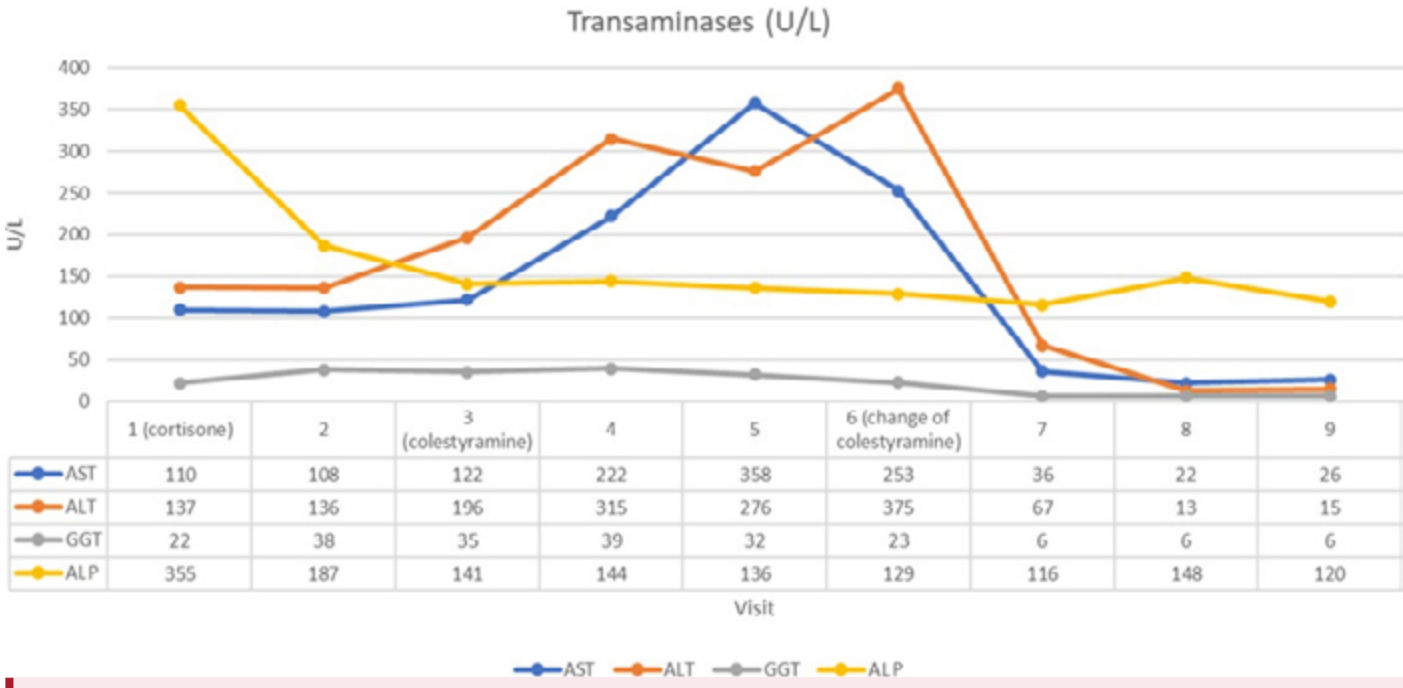


Figure 2. Change of liver transaminases during the visits.

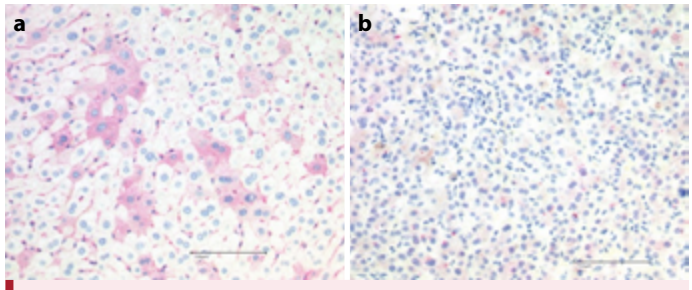


Figure 3. Comparison of normal liver tissue with the patient with aldolase B deficiency. **(a)** Normal liver **(b)** Patient with aldolase B deficiency.

Moreover, strict adherence to a diet that eliminates fructose, sucrose, and sorbitol (FSS) is linked to an excellent prognosis and a normal life expectancy.[6] Also in our case, cessation of fructose-containing medications resulted in immediate improvement of the liver injury. On the other hand, in some cases, small amounts of fructose consumption—less than 40 mg/kg/day or 1.5 g/day—seemed to be tolerable.[7] Furthermore, in an Italian cohort with long-term follow-up over 10 years, even minimal fructose exposure was associated with hepatic steatosis on liver ultrasound (93%). Elevated transaminase levels were reported in 75% of the patients. There was no sign of growth retardation.[7] Therefore, the safe level of fructose exposure remains controversial. Moreover, adhering to a strict diet can sometimes be challenging. As an alternative to the strict FSS diet, PF-06835919—an oral ketohexokinase inhibitor that suppresses hepatic fructose metabolism—was recently investigated in three patients with HFI. The authors administered different doses of fructose and observed a successful suppression of hepatic fructose metabolism.[8] Such a medical approach should certainly be investigated in clinical trials but represents a promising therapeutic option.

When fructose intolerance is suspected, it should be confirmed through genetic testing rather than histological confirmation via liver or kidney biopsy, due to the invasive nature of the latter.[9] A fructose tolerance test should be avoided due to a possible lethal complication. In our case, we performed mini-laparoscopy due to an atypical and prolonged period of liver injury, which began with the use of oral contraceptives and persisted with infections and cetirizine. Therefore, we had the opportunity to stain the liver tissue for aldolase B activity.

Here, aside from identifying aldolase B deficiency, we identified mutations in bile acid and phospholipid transporters that contribute to a predisposition for cholestatic liver disease. ABC transporters play a crucial role in transporting bile salts from hepatocytes to the bile canalicular lumen. Among these, ABCB11 has been linked to progressive familial intrahepatic cholestasis (PFIC) type 2—a condition characterized by severe cholestasis and intense pruritus. This disorder is marked by significantly elevated serum bile acids and normal serum γ-glutamyl-transferase activity. ABCB4 is known to be involved in a large spectrum of diseases, including PFIC type 3, intrahepatic cholestasis of pregnancy, low-phospholipid-associated cholelithiasis, and primary biliary cirrhosis.[10] Although we did not find any mutations indicating PFIC in our case, the heterozygous mutations may predispose to cholestatic liver disease following drug-induced liver injury.

In summary, this case represents a multifactorial liver injury with contributing factors including gastrointestinal infections, DILI associated with contraceptive use, and fructose ingestion in a patient with HFI. Consequently, attributing the liver injury to a single cause is challenging. However, we believe that the primary challenge was the undiagnosed HFI, which proved decisive for treatment decisions, particularly in the choice of medication.

Conclusion

In conclusion, the management of HFI includes lifetime monitoring and the engagement of medical and dietary counsellors, including hepatological follow-up. Not only the dietary ingredients, but also the supplements and medications, should be meticulously investigated.

Informed Consent: Informed consent was taken from the patient.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Use of AI for Writing Assistance: We did not use any artificial intelligence-assisted technologies in the preparation of this manuscript.

Author Contributions: Concept: AC, OG; Supervision: AC, AT, OG; Materials: EK, AC, AT, OG; Funding: AC; Data Collection and/or Processing: EK, AZ, DB, OG; Analysis and/or Interpretation: EK, AZ, DB, OG; Literature Search: EK, AZ, DB, OG; Writing: AC, AT, OG; Critical Reviews: AC, AT, OG.

Peer-review: Externally peer-reviewed.

References

1. Singh SK, Sarma MS. Hereditary fructose intolerance: A comprehensive review. World J Clin Pediatr 2022;11(4):321-329. [CrossRef]
2. Kim MS, Moon JS, Kim MJ, Seong MW, Park SS, Ko JS. Hereditary fructose intolerance diagnosed in adulthood. Gut Liver 2021;15(1):142-145. [CrossRef]
3. Collins J. Metabolic disease. Time for fructose solutions to go. Lancet 1993;341(8845):600. [CrossRef]
4. Schulte MJ, Lenz W. Fatal sorbitol infusion in patient with fructose-sorbitol intolerance. Lancet 1977;2(8030):188. [CrossRef]
5. Izquierdo-García E, Lázaro-Cebas A, Montero Pastor B, Such Díaz A, Álvaro-Alonso EA, López Guerra L, et al. Design of mobile and website health application devices for drug tolerability in hereditary fructose intolerance. Orphanet J Rare Dis 2024;19(1):12. [CrossRef]
6. Simons N, Debray FG, Schaper NC, Kooi ME, Feskens EJM, Hollak CEM, et al. Patients with aldolase B deficiency are characterized by increased intrahepatic triglyceride content. J Clin Endocrinol Metab 2019;104(11):5056-5064. [CrossRef]
7. Di Dato F, Spadarella S, Puoti MG, Caprio MG, Pagliardini S, Zuppaldi C, et al. Daily fructose traces intake and liver injury in children with hereditary fructose intolerance. Nutrients 2019;11(10):2397. [CrossRef]
8. Koene EJ, Buziau AM, Cassiman D, Cox TM, Bons J, Scheijen JL, et al. Safety and efficacy of pharmacological inhibition of ketohexokinase in hereditary fructose intolerance. J Clin Invest 2025;135(6):e187376. [CrossRef]
9. Douillard C, Mention K, Dobbelaere D, Wemeau JL, Saudubray JM, Vantyghem MC. Hypoglycaemia related to inherited metabolic diseases in adults. Orphanet J Rare Dis 2012;7:26. [CrossRef]
10. Morita SY, Terada T. Molecular mechanisms for biliary phospholipid and drug efflux mediated by ABCB4 and bile salts. Biomed Res Int 2014;2014:954781. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 296–301 DOI: 10.14744/hf.2025.05779

CASE REPORT

A rare but lethal hepatic infection: Emphysematous hepatitis – Case report and literature review

Gokalp Okut, Mehmet Alperen Ugur, Halil Yildiz, Halil Takci, Sait Murat Dogan

Department of General Surgery and Organ Transplantation, Izmir City Hospital, Izmir, Türkiye

Clinical Pearls

- **Unique Features of the Case:** A rare, rapidly fatal case of emphysematous hepatitis in a 67-year-old man with poorly controlled type 2 diabetes. CT showed extensive intrahepatic gas without a drainable abscess, and cultures grew *E. coli* and *Enterobacter hormaechei*.
- **Primary Lesson for Clinicians:** In diabetic patients with sepsis and intrahepatic gas on CT, emphysematous hepatitis should be considered. Early diagnosis, broad-spectrum antibiotics, glycemic control, and urgent drainage or surgery are essential.

ABSTRACT

Emphysematous hepatitis (EH) is a rare and often fatal liver infection characterized by gas within the hepatic parenchyma without abscess formation. Diabetes mellitus and gastrointestinal malignancies are the main predisposing factors. Prompt diagnosis and aggressive treatment are essential due to its fulminant course. A 67-year-old male with uncontrolled type 2 diabetes and a long smoking history presented with abdominal pain, nausea, vomiting, dyspnea, and altered consciousness. Laboratory tests revealed elevated liver enzymes, hyperbilirubinemia, severe hyperglycemia, and increased inflammatory markers. Abdominal CT showed a gas-containing lesion in the left hepatic lobe without fluid collection. Due to rapid clinical deterioration, emergency surgical resection was performed. Despite postoperative intensive care and meropenem therapy, the patient died six hours after surgery. Cultures grew *E. coli* and *Enterobacter hormaechei*. Only 19 EH cases have been reported to date. Most patients are elderly and have diabetes. Diagnosis relies on CT imaging, which reveals intrahepatic gas without abscess. Pathogenesis may involve anaerobic bacterial fermentation and microcirculatory impairment in diabetic patients. Despite antibiotics and drainage, mortality remains high. EH should be considered in diabetic patients with sepsis and intrahepatic gas on CT. Early diagnosis and immediate intervention—including antimicrobial therapy and drainage—are critical to improving survival.

Keywords: Acute hepatitis, emphysematous hepatitis, liver failure.

How to cite this article: Okut G, Ugur MA, Yildiz H, Takci H, Dogan SM. A rare but lethal hepatic infection: Emphysematous hepatitis – Case report and literature review. Hepatology Forum 2026; 7(3):296–301.

Received: May 29, 2025; **Revised:** October 31, 2025; **Accepted:** November 10, 2025; **Available Online:** June 30, 2026

Corresponding author: Gokalp Okut; Department of General Surgery and Organ Transplantation, Izmir City Hospital, Izmir, Türkiye; **E-mail:** gokalp.okut@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

Emphysematous hepatitis (EH) is a rare and often fulminant infection of the liver parenchyma characterized by gas formation in the absence of liquefied abscesses.[1] Among the most well-established predisposing factors are diabetes mellitus and gastrointestinal malignancies.[2,3] Computed tomography (CT) is the gold standard imaging modality for diagnosis. Since the first case was reported, only a limited number of cases have been described in the literature (Table 1).[1–19] Given its rapid progression and potential to cause sepsis and multiorgan failure, prompt diagnosis and treatment are crucial. In this report, we aim to present a case of EH, outlining its etiology, diagnostic process, and treatment in the context of previously reported cases.

Case Report

A 67-year-old male presented to the emergency department with a two-day history of abdominal pain, nausea, and vomiting. In the last six hours prior to admission, he had developed shortness of breath and altered mental status.

His medical history was notable for poorly controlled type 2 diabetes mellitus, and he had a 40-year history of smoking one pack of cigarettes per day. His daily medications included short- and long-acting subcutaneous insulin.

On arrival, his vital signs were as follows: body temperature 39°C (N: 36.5–37.5°C), blood pressure 110/70 mmHg (N: 120/80), heart rate 132 beats per minute (N: 60–100), respiratory rate 22 breaths per minute (N: 12–20), and oxygen saturation of 95% on room air. Physical examination revealed diffuse abdominal tenderness on palpation.

Initial laboratory findings were as follows: white blood cell count 5,700/mm^3 (reference: 3,900–10,500), C-reactive protein 323 mg/L (reference: <5.0), creatinine 1.58 mg/dL (reference: 0.70–1.20), alanine aminotransferase 394 U/L (reference: <41), aspartate aminotransferase 1,056 U/L (reference: <50), total bilirubin 2.4 mg/dL (reference: <1.20), conjugated bilirubin 1.81 mg/dL (reference: <0.30), and blood glucose 511 mg/dL (reference: 82–115). Arterial blood gas analysis revealed a pH of 7.21, a base excess of –12.8 mmol/L, and a lactate level of 6.7 mmol/L. The Sequential Organ Failure Assessment (SOFA) score was calculated as 8.

Contrast-enhanced abdominal CT revealed a gas-forming lesion in the left hepatic lobe, almost completely replacing the lobe and partially extending to segments 5–8, without a fluid-filled abscess component (Fig. 1). The patient had no known history of hepatobiliary disease or prior abdominal surgery.

Although percutaneous drainage was initially considered, due to the rapid progression of his septic condition, surgical intervention was deemed more appropriate. The patient was started on empirical antibiotic therapy consisting of ceftriaxone 1 g and metronidazole 500 mg and was subsequently prepared for exploratory surgery and liver resection/drainage under intensive care monitoring.

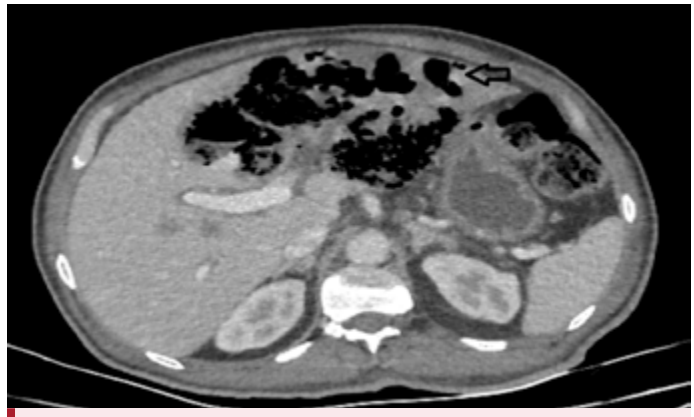


Figure 1. Contrast-enhanced abdominal computed tomography revealed a gas-forming lesion in the left hepatic lobe, without a fluid-filled abscess component.

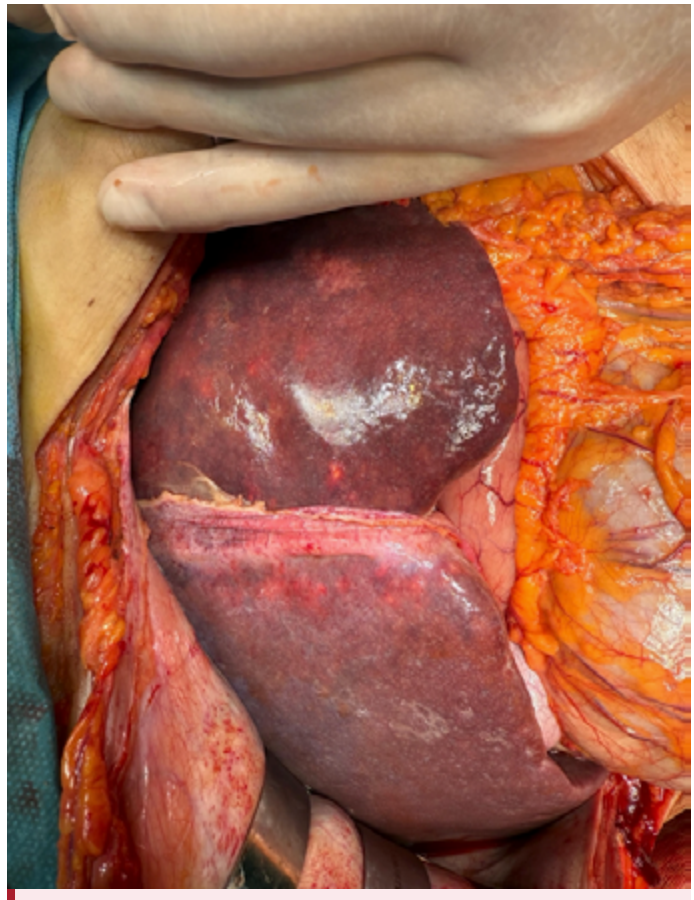


Figure 2. The affected hepatic tissue appeared darker in color compared to normal parenchyma.

A Makuuchi incision was performed to access the abdominal cavity, revealing approximately 500 mL of serous fluid. A sample was taken for microbiological analysis. For better visualization, cholecystectomy and mobilization of the left hepatic lobe were performed.

Intraoperatively, the affected hepatic tissue appeared darker in color compared to normal parenchyma (Fig. 2). During transection,

Table 1. Summary of reported cases of emphysematous hepatitis in the literature, including demographic characteristics, comorbidities, imaging findings, associated malignancies, treatment modalities, isolated pathogens, and clinical outcomes

References	Year	Sex	Age	DM	Imaging	Presence of malignancy	Treatment	Pathogen(s)	Outcome
Blachar[1]	2002	F	43	Yes	CT: Right hepatic lobe involvement	No	Antibiotics, CT-guided drainage	*Klebsiella pneumoniae*	Died
Letourneau Guillon[2]	2010	M	53	No	CT: 8-cm, air-filled cavity located in the right lobe of the liver, centered on segment VIII	HC	Antibiotics	*Enterobacter cloacae and Clostridium perfringens*	Died
Chauhan[3]	2012	M	77	Yes	CT: Segments VI and VII of liver	No	Antibiotics, CT-guided drainage	n/a	Died
Kim[4]	2012	F	80	No	CT: Hepatic parenchymal emphysema measuring 6.3×4.4 cm in the segment 7-8 of the right liver	HC	Antibiotics, CT-guided drainage	*Clostridium perfringens, Escherichia coli*	Died
Nada[5]	2017	M	73	No	CT: Mottled gas opacity throughout the parenchyma of the right hepatic lobe	Pancreatic carcinoma liver and lung metastasis	Antibiotics	*Streptococcus mutans, Enterococcus faecalis*	Died
Ghosn[6]	2019	F	38	Yes	CT: Mixed collection containing air and debris spreading at the posterior aspect of the left lobe of the liver	No	Antibiotics, surgical drainage, percutaneous drainage	*Escherichia coli, Enterococcus faecium*	Survived
Azri[7]	2020	F	75	No	CT: Left lobe involvement	HC	Na	*Klebsiella pneumoniae, Escherichia coli, Enterococcus faecalis, Clostridium perfringens, Aeromonas ichthiosmia*	Died
Calderon[8]	2020	F	80	Yes	CT: A large amount of air within the liver parenchyma	No	Antibiotics	*Clostridium perfringens*	Died
Miranda[9]	2020	M	74	No	CT: An extensive area with gas within the right lobe of the liver (9.3cm)	No	Antibiotics	*Escherichia coli*	Died
Bofill[10]	2021	M	82	Yes	CT: A large area of gas in the right hepatic lobe	No	Antibiotics, CT-guided drainage	*Klebsiella pneumoniae*	Died
Estébanez-Ferrero[11]	2021	F	67	No	CT: A hypoattenuated area in the right hepatic lobe with abundant air in the hepatic parenchyma	No	Antibiotics, surgical drainage, percutaneous drainage	*Escherichia coli*	Survived
Francois[12]	2022	F	70	Yes	CT: A large (9 cm) air-filled cavity in the right liver lobe	No	Antibiotics, CT-guided drainage	*Escherichia coli, Streptococcus anginosus* and *Klebsiella oxytoca*	Survived
Porez[13]	2023	M	59	Yes	CT: Limited area in the liver containing multiple gas bubbles without enhancement wall nor collection, located in the right anterior segment dome (5.8x5 cm)	No	Antibiotics, USG-guided drainage, surgical drainage	*Klebsiella pneumoniae*	Survived
Bayerl[14]	2023	M	79	Yes	CT: Periportal gas collection in liver segment 6 from 3-4 to 4 cm in diameter with well-described margins	No	Antibiotics, surgery	*Clostridium perfringens, Enterococcus faecium*	Survived

Table 1 (cont). Summary of reported cases of emphysematous hepatitis in the literature, including demographic characteristics, comorbidities, imaging findings, associated malignancies, treatment modalities, isolated pathogens, and clinical outcomes

References	Year	Sex	Age	DM	Imaging	Presence of malignancy	Treatment	Pathogen(s)	Outcome
Pan[15]	2023	M	48	Yes	CT: 6.6 × 5.5 × 5.3 cm air collection with some remaining parenchyma debris in the left liver lobe	No	Antibiotics, USG-guided drainage	*Klebsiella oxytoca*	Survived
Ayoub[16]	2024	F	77	Yes	CT: Multiple gas bubbles without enhancement wall nor collection, measuring 12 × 11.3 cm	No	Antibiotics	*Multidrug-resistant Escherichia coli*	Died
Tekinhatun[17]	2024	F	80	No	CT: Aerial views of the liver parenchyma covering approximately 50% of the right lobe	No	Antibiotics	*Escherichia coli*	Died
Al Khatib[18]	2025	F	70	No	CT: Pneumoperitoneum and transformation into emphysematous hepatitis at the metastatic site	Colon tumor, liver metastasis	Antibiotics, ileocecal resection and ileocolostomy, CT-guided drainage	*Clostridium septicum*	Died
Chen[19]	2025	M	57	Yes	CT: 8.6 cm by 6.5 cm area of gas in the right hepatic lobe, pneumoperitoneum	No	Antibiotics, CT-guided drainage	*Klebsiella pneumoniae and carbapenem-resistant Enterobacteriaceae*	Survived

HC: Hilar cholangiocarcinoma; DM: Diabetes mellitus; CT: Computed tomography.

the diseased tissue was noted to be spongy and hypoperfused. A non-anatomic liver resection was performed until healthy tissue margins were achieved. A tissue sample was taken from the necrotic liver parenchyma for microbiological analysis. Postoperatively, the patient was returned to the ICU intubated for stabilization.

Meropenem (3×1000 mg/day) was initiated postoperatively. Despite aggressive management, the patient succumbed to refractory acidosis and hypotension in the sixth postoperative hour.

Blood cultures grew *Escherichia coli*, tissue cultures yielded *Enterobacter hormaechei*, and abdominal fluid cultures demonstrated high levels of *Enterobacter hormaechei*. Both isolates exhibited resistance to amoxicillin-clavulanate and ampicillin, while remaining susceptible to ampicillin-sulbactam, cefazolin, ceftazidime, ceftolozane-tazobactam, ceftriaxone, cefuroxime, ciprofloxacin, gentamicin, imipenem, meropenem, piperacillin-tazobactam, and trimethoprim-sulfamethoxazole.

Discussion

EH is a rare condition characterized by gas collection in the liver parenchyma in the absence of a defined abscess cavity. Including the present case, only 20 cases have been reported to date.[1–19] Early diagnosis and prompt intervention are essential to reduce the high mortality rate associated with its fulminant course.

Among the reported cases, 10 patients were male (50%), and 12 had diabetes mellitus. The age range was 38–82 years, with 70% of patients older than 60. Thirteen patients experienced a fatal outcome. Our patient was a 67-year-old male with a history of diabetes who died due to rapidly progressive refractory septic shock despite antibiotic therapy and surgical drainage.

The pathogenesis of EH remains unclear. Given the high prevalence of type 2 diabetes mellitus among reported cases, a plausible hypothesis involves anaerobic bacterial fermentation—producing gas composed of nitrogen (60%), hydrogen (15%), carbon dioxide (5%), and oxygen (5%) in a host with impaired immunity and altered microcirculation due to hyperglycemia.[13] Diabetes-related microangiopathy may hinder the clearance of catabolic products, facilitating gas accumulation.

Another noteworthy observation is the presence of malignancies in approximately 25% of patients. This association appears to be multifactorial. Patients with malignant disease frequently exhibit impaired host immunity due to tumor-related metabolic stress, chemotherapy, corticosteroid exposure, or malnutrition, which may predispose to opportunistic hepatic infections. Moreover, hepatobiliary and metastatic tumors can cause ductal obstruction, microvascular compromise, and tumor necrosis, resulting in a hypoxic and glucose-rich microenvironment that facilitates anaerobic fermentation and gas production by organisms such as *Clostridium perfringens*, *Klebsiella pneumoniae*, and *Escherichia coli*.[2,4,5,7,13] In addition, invasive procedures commonly performed in

patients with hepatobiliary malignancies (e.g., ERCP, biliary stenting, percutaneous drainage) may promote bacterial translocation into hepatic parenchyma.[13] Of note, *C. perfringens* is particularly associated with malignancy-related cases, and its alpha toxin and perfringolysin O have been shown to impair neutrophil maturation, increase oxidative injury, and promote extensive tissue necrosis, thereby accelerating disease progression and contributing to the fulminant clinical course.[20,21]

The clinical presentation of EH is often nonspecific, with fever and abdominal pain being the most common symptoms.[5,10] Laboratory results typically show elevated inflammatory markers, liver enzymes, and bilirubin levels.[2]

CT is the most reliable imaging modality for EH diagnosis, as it reveals the characteristic radiological features of the disease. CT not only helps define the localization and extent of the infection but also aids in excluding other intra-abdominal causes of pain and sepsis. In addition, it is crucial to distinguish hepatic gas from gas in other liver structures, such as bile ducts (e.g., post-ERCP), portal venous gas (e.g., bowel infarction), hepatic infarction secondary to hepatic artery thrombosis (e.g., after liver transplantation), or pyogenic liver abscesses.[12]

Although mortality remains high, early diagnosis significantly improves outcomes. Surviving patients received aggressive treatment including antibiotics, percutaneous drainage, and/or surgical intervention. Three cases were treated with percutaneous drainage alone,[12,15,19] one with surgery alone,[14] and three with both surgical and percutaneous drainage.[6,11,13] Although the absence of a drainable fluid collection may lead to the initial assumption that percutaneous drainage would be inadequate, recent reports suggest that early percutaneous drainage may be sufficient in selected cases, potentially avoiding surgery altogether.

In our case, however, due to the rapid clinical deterioration and the absence of a condition favorable for evaluation by interventional radiology or a reasonable expectation of success with percutaneous treatment, surgical drainage was prioritized as a faster and more definitive solution. Although recent literature suggests favorable outcomes with percutaneous drainage, surgical approaches are generally preferred in patients with impaired consciousness and unstable vital signs, as they are more likely to provide definitive results. Given the extreme rarity of emphysematous hepatitis and the limited number of reported cases, there are no well-defined criteria to guide the decision-making process between surgical and percutaneous drainage.

Conclusion

EH is a life-threatening condition if not diagnosed and treated promptly. CT is the gold standard imaging modality for diagnosis. Diabetes mellitus is a major predisposing factor, and optimal management involves a combination of broad-spectrum antibiotics, percutaneous or surgical drainage, and strict glycemic control.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written informed consent for publication of this case report and accompanying images was obtained from the patient's next of kin, as the patient was unable to provide consent due to his clinical condition and subsequently died during the postoperative period.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: This study received no funding.

Use of AI for Writing Assistance: The study did not use any artificial intelligence (AI)-based technologies (such as Large Language Models [LLMs], chatbots or image generators, including ChatGPT).

Author Contributions: Concept: GO, HT; Design: GO; Supervision: SMD, HT; Funding: HY; Materials: MAU; Data Collection and/or Processing: GO, HY, MAU; Analysis and/or Interpretation: SMD, GO; Literature Search: MAU, HY, HT; Writing: GO; Critical Review: SMD.

Peer-review: Externally peer-reviewed.

References

1. Blachar A, Federle MP, Brancatelli G. Acute fulminant hepatic infection causing fatal "emphysematous hepatitis": case report. Abdom Imaging 2002;27(2):188-190. [CrossRef]
2. Létourneau-Guillon L, Audet P, Plasse M, Lepanto L. Answer to Case of the Month #162: Emphysematous Infection of the Liver Parenchyma. Can Assoc Radiol J 2010;61(2):117-119. [CrossRef]
3. Chauhan U, Prabhu SM, Shetty GS, Solanki RS, Udiya AK, Singh A. Emphysematous hepatitis-a fatal infection in diabetic patients: case report. Clin Res Hepatol Gastroenterol 2012;36(6):e114-e116. [CrossRef]
4. Kim JH, Jung ES, Jeong SH, Kim JS, Ku YS, Hahm KB, et al. A case of emphysematous hepatitis with spontaneous pneumoperitoneum in a patient with hilar cholangiocarcinoma. Korean J Hepatol. 2012;18(1):94-97. [CrossRef]
5. Nada KM, El Husseini I, Abu Hishmeh ME, Shah NS, Ibragimova N, Basir R. A rare case of septic shock secondary to emphysematous hepatitis. Case Rep Crit Care 2017;2017:3020845. [CrossRef]
6. Ghosn Y, Abdallah A, Hussein Kamareddine M, Geahchan A, Baghdadi A, El-Rassi Z, et al. Gas-forming liver abscess versus emphysematous hepatitis: a radiologic diagnostic dilemma-A case report and review of the literature. Case Rep Hepatol 2019;2019:5274525. [CrossRef]
7. Azri A, Pichon J, Fartoukh M, Djibré M. Fatal emphysematous hepatitis with spontaneous pneumoperitoneum. Liver Int 2020;40(5):1224. [CrossRef]
8. Calderon H, Serfin J. 13-Hour progression of emphysematous hepatitis as depicted on repeat computerized tomography. J Surg Case Rep 2020;2020(4):rjaa089. [CrossRef]
9. Miranda G, Dionísio AC, Azevedo C, Carvalho E, Semião M, Branco V, et al. Fulminant emphysematous hepatitis-a rare cause of septic shock. Eur J Case Rep Intern Med 2020;7(5):001539. [CrossRef]
10. Bofill A, Marco F. Emphysematous Hepatitis. N Engl J Med. 2021;385(17):e58. [CrossRef]

11. Estébanez-Ferrero B, Fuentes-Porcel O, Lorenzo-Liñán MÁ, Rico-Morales MDM. Emphysematous hepatitis: a very rare entity with a poor prognosis. Rev Esp Enferm Dig 2021;113(8):612-614. [CrossRef]
12. Francois S, Aerts M, Reynaert H, Van Lancker R, Van Laethem J, Kunda R, et al. Step-up approach in emphysematous hepatitis: a case report. World J Hepatol 2022;14:464-470. [CrossRef]
13. Porez D, Kallel H, Dobian S, Gerbert-Ferrendier T, Nacher M, Djossou F, et al. Diagnostic and management of emphysematous hepatitis with emphasis on biopathology. Microorganisms 2023;11(9):2137. [CrossRef]
14. Bayerl C, Berg AK, Angermair S, Kim D, Hamm B, Beyer K, et al. First successful treatment of Clostridium perfringens-associated emphysematous hepatitis: a case report. Front Med (Lausanne) 2023;10:1164466. [CrossRef]
15. Pan N, Wang S, Miao Z. Emphysematous hepatitis with successful treatments: a rare case report. Medicine (Baltimore) 2023;102(4):e32530. [CrossRef]
16. Ayoub C, Oula A, Nabila E, Asmae OA, Siham AR. Emphysematous hepatitis: A case report and review of literature. Radiol Case Rep 2024;19(12):6629-6632. [CrossRef]
17. Tekinhatun M, Yavaş HG. Emphysematous hepatitis: A rare fatal case. J Clin Ultrasound 2024;52(8):1235-1239. [CrossRef]
18. Al Khatib A, Duboc H, Soliman H. Emphysematous Hepatitis Due to Clostridium septicum. Clin Gastroenterol Hepatol 2025;23(4):A32. [CrossRef]
19. Chen M, Chen J, Zhuang Z, He X, Wang Y, Liang J, et al. Septic shock caused by emphysematous hepatitis complicated with intracranial infection. IDCases 2025;39:e02159. [CrossRef]
20. Takehara M, Takagishi T, Seike S, Ohtani K, Kobayashi K, Miyamoto K, et al. Clostridium perfringens α-toxin impairs innate immunity via inhibition of neutrophil differentiation. Sci Rep 2016;6:28192. [CrossRef]
21. Awad MM, Ellemor DM, Boyd RL, Emmins JJ, Rood JI. Synergistic effects of alpha-toxin and perfringolysin O in clostridium perfringens -mediated gas gangrene. Infect Immun 2001;69(12):7904-7910. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 302–305 DOI: 10.14744/hf.2026.08929

CASE REPORT

Suspected azathioprine-induced hypersensitivity pneumonitis in a patient with autoimmune hepatitis: A rare case report

Yusuf Bunyamin Ketenci, Hakan Demiroz, Mehmet Akca, Ufuk Avcioglu

Department of Gastroenterology, Ondokuz Mayis University School of Medicine, Samsun, Türkiye

Clinical Pearls

- **Unique Features of the Case:** This case describes a rare delayed pulmonary hypersensitivity reaction occurring after 3 years of azathioprine treatment for autoimmune hepatitis in a young woman.
- **Primary Lesson for Clinicians:** Clinicians should consider azathioprine-induced hypersensitivity pneumonitis in patients receiving azathioprine who develop unexplained respiratory symptoms, as early recognition and drug discontinuation can lead to full recovery.

ABSTRACT

Azathioprine (AZA) is a widely prescribed immunosuppressive agent in the long-term management of autoimmune hepatitis (AIH), valued for its steroid-sparing properties and efficacy in maintaining disease remission. While its common adverse effects – such as myelosuppression, hepatotoxicity, and gastrointestinal intolerance – are well-recognized and routinely monitored, hypersensitivity pneumonitis (HP) remains an exceptionally rare but potentially life-threatening complication. Herein, we describe a 21-year-old female patient with AIH diagnosed at age 18. Who developed possible AZA-induced HP during the 3rd year of continuous therapy. We discuss the potential immunopathogenic mechanisms, review the limited literature on AZA-related pulmonary toxicity, and emphasize the importance of early recognition to prevent irreversible lung injury and optimize patient outcomes.

Keywords: Autoimmune hepatitis, azathioprine, drug-induced lung injury, hypersensitivity pneumonitis.

How to cite this article: Ketenci YB, Demiroz H, Akca M, Avcioglu U. Suspected azathioprine-induced hypersensitivity pneumonitis in a patient with autoimmune hepatitis: A rare case report. Hepatology Forum 2026; 7(3):302–305.

Received: August 11, 2025; **Revised:** November 16, 2025; **Accepted:** December 22, 2025; **Available Online:** July 08, 2026

Corresponding author: Yusuf Bunyamin Ketenci; Department of Gastroenterology, Ondokuz Mayis University School of Medicine, Samsun, Türkiye; **E-mail:** bketenci@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Introduction

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease requiring immunosuppressive therapy to control immune-mediated hepatic injury. Azathioprine (AZA), a purine analog immunosuppressant, remains a cornerstone of the maintenance therapy of AIH due to its efficacy and generally manageable side effect profile. Common adverse effects include myelosuppression, hepatotoxicity, gastrointestinal intolerance, and infection risk. However, AZA can rarely cause severe hypersensitivity reactions, including pulmonary toxicity such as hypersensitivity pneumonitis (HP).

HP is an immune-mediated interstitial lung disease characterized by an exaggerated inflammatory response to inhaled or systemic antigens. Drug-induced HP, especially due to AZA, is an underrecognized entity but has been reported mainly in patients treated for inflammatory bowel disease, organ transplantation, and vasculitis. In contrast, AZA-induced HP in patients with AIH is exceedingly rare, with very few documented cases, making the recognition of this adverse event clinically important. Early diagnosis is crucial since withdrawal of AZA generally leads to resolution, whereas delayed recognition can result in serious morbidity or mortality.

We herein provide a detailed overview of the pathophysiology, clinical presentation, diagnostic workup, and management of AZA-induced HP, emphasizing its rarity in AIH and the importance of clinician awareness of this life-threatening but reversible complication.

Case Report

An 18-year-old Caucasian, female taekwondo athlete was being followed up for known hereditary spherocytosis.

When she applied to the emergency room with complaints of jaundice in the eyes and skin, it was seen that aspartate transaminase: 1148 U/L, alanine aminotransferase: 1833 U/L, Gamma Glutamyl Transpeptidase: 106 U/L, alkaline phosphatase: 49 U/L, total bilirubin: 4.56 mg/dL, direct bilirubin: 4.26 mg/dL. Viral hepatitis was excluded, and her history confirmed no herbal or drug use. Vascular systems were normal on portal Doppler ultrasound; the liver size was 187 mm, and the spleen size was 146 mm. Antinuclear antibody (ANA) was positive with a 1/1000 titer. Antimitochondrial antibody and anti-smooth muscle antibody were negative. Immunoglobulin G: 22.5 g/L. Liver biopsy was done. The biopsy revealed that AIH with mononuclear inflammatory cell infiltration, interface hepatitis, necroinflammatory foci, and pseudo-rosette formation. The diagnosis of AIH was made when the revised original score for AIH was 22 (definite AIH). Methylprednisolone 30 mg orally was initiated. After 2 weeks, the steroid tapering regimen was continued, whereas 50 mg AZA was added. Remission was observed in the 6th month of treatment. In the 3rd year of AZA treatment and the 2nd year of discontinuation of steroid treatment, when she was 21 year old, she presented to the chest diseases clinic with a history of pneumonia-like bronchitis that had been continuing for 3 months. Saturation (room air) and heart rate were normal. There was no pathology in respiratory function tests and echocardiography. Blood count, serum biochemistry values, and C-reactive protein were normal. A high-resolution computed tomography scan of the chest revealed bronchiectasis and atelectasis. Although the radiologic findings were not entirely typical for HP, the exclusion of infectious, cardiac, autoimmune, and environmental causes, together with the marked clinical improvement after AZA withdrawal, supported the diagnosis of AZA-induced pulmonary hypersensitivity (Fig. 1).

To exclude other possible causes of the pulmonary findings, a detailed differential diagnostic workup was performed. Infectious etiologies, including bacterial pneumonia, tuberculosis, viral infections, and fungal diseases, were ruled out based on negative blood cultures, sputum analysis, and serological testing. Cardiac causes such as congestive heart failure were excluded with a normal echocardiographic evaluation and absence of elevated natriuretic peptide levels. Autoimmune and rheumatologic conditions (including systemic lupus erythematosus, sarcoidosis, and vasculitis) were excluded by negative autoimmune serologies (antineutrophil cytoplasmic antibodies, and rheumatoid factor) and absence of compatible clinical features. Environmental and occupational exposures were also carefully questioned and excluded by patient history. Importantly, following the discontinuation of AZA, the patient's respiratory symptoms improved significantly, which strongly supported the diagnosis of AZA-induced HP. Bronchoalveolar lavage and lung biopsy were not performed due to clinical stability and rapid response to AZA withdrawal.

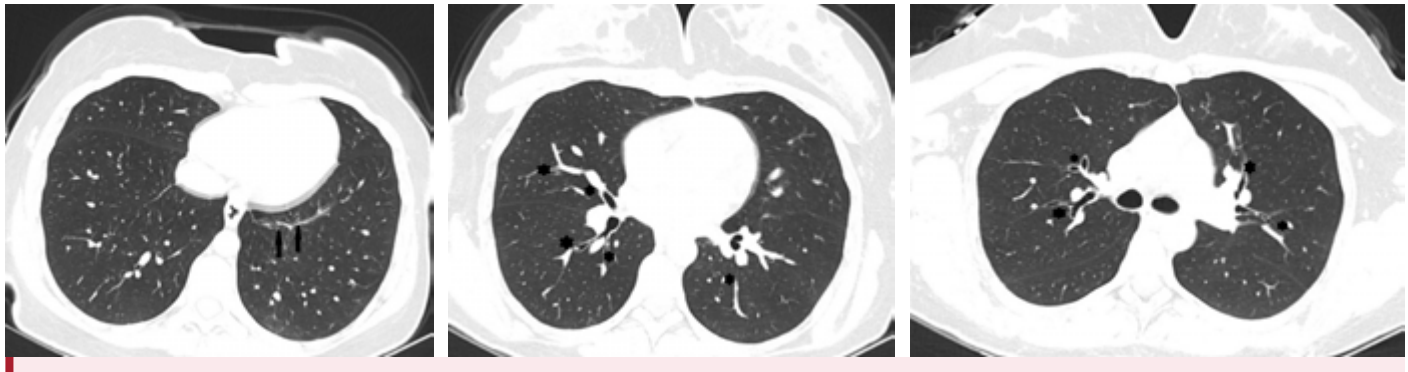


Figure 1. Bronchiectasis and atelectasis on high-resolution thoracic tomography (Bronchiectasis is shown with asterisks. Atelectasis is shown with arrows).

After other causes were excluded, the patient's symptoms began to decrease 10 days after discontinuing AZA, suggesting AZA-related hypersensitivity. One month later, her symptoms had almost completely disappeared. During this period, she started on 500 mg twice daily of mycophenolate mofetil. Transaminase levels remained normal during the 1st year of mycophenolate mofetil treatment. She has no respiratory symptoms now. Informed written consent was obtained from the patient.

Discussion

AZA is metabolized primarily in the liver to 6-mercaptopurine and to active thioguanine nucleotides, suppressing purine synthesis and lymphocyte proliferation. While dose-dependent toxicities such as myelosuppression and hepatotoxicity are well-characterized, hypersensitivity reactions are thought to be immune-mediated and idiosyncratic.[1] The imidazole moiety of AZA can act as a hapten, triggering delayed hypersensitivity reactions manifesting as fever, rash, arthralgia, and notably, pulmonary involvement, including HP.[1,2]

Pulmonary toxicity associated with AZA therapy is rare but documented in various systemic illnesses.[2,3] To our knowledge, there are few case reports and series showing azathioprine-related hypersensitivity pneumonia.[2,3] The median time to onset ranged from weeks to months after initiation of AZA, consistent with immune sensitization.[1] Notably, only a minority exhibited leukopenia, distinguishing hypersensitivity reactions from dose-dependent bone marrow toxicity.[3]

In clinical practice, patients typically develop respiratory symptoms such as cough, dyspnea, fever, and malaise, alongside radiologic findings including bilateral ground-glass opacities and centrilobular nodules on high-resolution computed tomography of the chest, consistent with an HP pattern.[1,2] This clinical condition can develop within the 1st month of starting the drug or may develop later. Initial use of steroids along with AZA can mask this condition.[4] Systemic corticosteroids can temporarily suppress the T-cell–mediated alveolar inflammation characteristic of HP, resulting in partial clinical and radiologic improvement and potentially masking early disease manifestations. This effect has been described in prior reviews and guideline discussions of HP management.[5]

If the patient's history and imaging are inadequate to diagnose the hypersensitivity pneumonitis, bronchoalveolar lavage, lung biopsy, and special antibodies can be studied.[5] Bronchoalveolar lavage often reveals lymphocytic alveolitis, and lung biopsy may demonstrate non-necrotizing granulomas, confirming the diagnosis.[1]

The differential diagnosis includes infection, relapse of underlying autoimmune disease, and other drug-induced pulmonary injuries; thus, it is imperative to exclude these causes with appropriate microbiologic testing and disease activity markers.[1,2] Rechallenge with AZA is contraindicated due to the risk of severe reactions.[2,3]

Management involves prompt discontinuation of AZA, which in reported cases resulted in rapid symptomatic and radiological improvement within days to weeks.[2,3] Systemic corticosteroids may be necessary in severe disease, but are not always required.[1] Alternative immunosuppressive agents such as mycophenolate mofetil can be considered for AIH maintenance to avoid recurrence.[2]

Despite its rarity, recognition of AZA-induced HP is critical, especially in AIH, where respiratory symptoms might be mistakenly attributed to infection or AIH progression. Documentation and publication of such cases contribute valuable knowledge to the literature and aid clinicians in the early identification and optimal management of this serious adverse event.[2,3]

This report has several limitations. First, bronchoalveolar lavage, lung histology, and drug rechallenge were not performed, so the diagnosis of AZA-induced HP could not be confirmed and remains probable rather than definitive. Second, the radiological pattern was atypical for HP, with bronchiectasis and atelectasis rather than the more classical ground-glass opacities and centrilobular nodules; alternative or structural explanations, including pre-existing or coincidental bronchiectasis, cannot be entirely excluded and may have contributed to the imaging findings. Third, mycophenolate mofetil was introduced during the same period in which respiratory symptoms improved, so its potential confounding contribution to the observed clinical course cannot be fully disentangled from the effect of AZA withdrawal alone.

Conclusion

In conclusion, AZA-induced HP represents a rare but clinically significant complication, particularly in patients with AIH, where respiratory symptoms may easily be overlooked or misattributed to infectious or autoimmune etiologies. This case highlights the need to consider AZA-induced pulmonary toxicity in patients receiving AZA who develop unexplained respiratory symptoms, even after long-term treatment. Early recognition and prompt discontinuation of AZA are paramount to prevent potentially irreversible pulmonary damage and to facilitate rapid recovery, as demonstrated by previous reports.

Although the pathophysiological mechanisms underpinning AZA-induced hypersensitivity reactions remain incompletely elucidated, the immune-mediated nature of the injury highlights the importance of comprehensive diagnostic evaluation and exclusion of alternative causes. Given the paucity of cases documented in the literature, further reporting and study of such adverse events are vital for advancing clinician awareness, informing guidelines for risk stratification, and optimizing therapeutic decision-making in managing AIH. The publication of rare presentations like this case contributes meaningfully to the collective understanding of AZA safety profiles and underscores the continuous need for vigilance in immunosuppressive drug monitoring.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Informed written consent was obtained from the patient.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: There is no financial support.

Use of AI for Writing Assistance: This article used Grammarly for grammar and semantic corrections, and Perplexity for formatting corrections.

Author Contributions: Concept: UA; Design: UA; Supervision: UA; Funding: YBK; Materials: HD; Data Collection and/or Processing: HD; Analysis and/or Interpretation: YBK; Literature Review: MA; Writing: YBK; Critical Review: MA.

Peer-review: Externally peer-reviewed.

References

1. Yi ES. Hypersensitivity pneumonitis. Crit Rev Clin Lab Sci 2002;39(6):581-629. [CrossRef]
2. Lee I, Kang GW, Kim KC. Hypersensitivity pneumonitis associated with azathioprine therapy in a patient with granulomatosis with polyangiitis. Rheumatol Int 2016;36(7):1027-1032. [CrossRef]
3. Carmichael DJ, Hamilton DV, Evans DB, Stovin PG, Calne RY. Interstitial pneumonitis secondary to azathioprine in a renal transplant patient. Thorax 1983;38(12):951-952. [CrossRef]
4. Ananthakrishnan AN, Attila T, Otterson MF, Lipchik RJ, Massey BT, Komorowski RA, et al. Severe pulmonary toxicity after azathioprine/6-mercaptopurine initiation for the treatment of inflammatory bowel disease. J Clin Gastroenterol 2007;41(7):682-688. [CrossRef]
5. Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, et al. Diagnosis of Hypersensitivity Pneumonitis in Adults. An Official ATS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2020;202(3):e36-e69. Erratum in: Am J Respir Crit Care Med 2021;203(1):150-151. Erratum in: Am J Respir Crit Care Med 2022;206(4):518. [CrossRef]

HEPATOLOGY FORUM

Volume 7, Issue 3, 2026 | 306–307 DOI: 10.14744/hf.2026.21555

LETTER TO THE EDITOR

Albumin in hepatic encephalopathy: Evidence, prioritization, and the affordability gap in decompensated cirrhosis

Mohammad Saquib Alam[1], **Nagma Khatoon**[2]

1: Department of Medicine, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India
2: Department of Obstetrics and Gynecology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

To the Editor,

We read with great interest the systematic review and meta-analysis by Covre Coan et al.[1] evaluating intravenous albumin in patients with hepatic encephalopathy (HE). The authors included four randomized controlled trials involving 306 patients and reported that albumin was associated with improved HE recovery and reduced mortality, without a significant increase in adverse events.[1] Importantly, their trial sequential analysis showed that although the mortality signal crossed the boundary for benefit, the required information size was not reached, indicating that the evidence remains promising rather than definitive.[1]

This review contributes to a growing shift in how albumin is conceptualized in decompensated cirrhosis. Traditionally, albumin has been used primarily as a plasma expander, particularly after large-volume paracentesis, in spontaneous bacterial peritonitis (SBP), and in hepatorenal syndrome-acute kidney injury (HRS-AKI). However, contemporary data emphasize that albumin also has antioxidant, scavenging, endothelial-stabilizing, and immunomodulatory properties.[2,3] These non-oncotic effects are biologically relevant in HE, where ammonia toxicity, systemic inflammation, oxidative stress, endothelial dysfunction, and circulatory impairment may interact to produce neurocognitive deterioration.[1,4]

Nevertheless, the clinical question is no longer simply whether albumin can help in HE. A more difficult bedside question is how HE should be prioritized among competing albumin indications in patients with decompensated cirrhosis. Many such patients present simultaneously with tense ascites, spontaneous bacterial peritonitis, renal dysfunction, hyponatremia, and HE. In well-resourced systems, practice recommendations may be interpreted as additive. In resource-limited settings, however, albumin availability and affordability often force clinicians to prioritize.

Current practice guidance supports albumin for large-volume paracentesis, SBP, and AKI/HRS-related scenarios, while discouraging its routine use in uncomplicated ascites.[3] The AGA update also emphasizes careful assessment of volume status, especially during HRS-AKI therapy, because excessive albumin may contribute to pulmonary edema or respiratory complications.[3] Similarly, broader reviews conclude that albumin has established roles in large-volume paracentesis, SBP, AKI, and HRS, while its use in HE, long-term ascites management, hyponatremia, extraperitoneal infections, and acute-on-chronic liver failure remains an area of ongoing evaluation.[4]

In this context, the findings of Covre Coan et al.[1] should be interpreted as a call for better stratification rather than immediate universalization. Albumin use for HE may be most defensible when HE occurs alongside other albumin-supported indications, such as SBP, AKI/HRS, marked circulatory dysfunction, or severe systemic inflammation. By contrast, isolated HE without renal dysfunction, infection, or other established indications may require more cautious use until larger, adequately powered trials confirm its benefit and identify the patients most likely to respond.

Future trials of albumin in HE should therefore move beyond binary efficacy endpoints. They should incorporate HE severity, the presence of AKI or infection, baseline serum albumin levels, inflammatory markers, volume status, the total albumin dose received, adverse pulmonary events, length of hospitalization, readmissions, and cost-effectiveness. In low- and middle-income settings, patient-level affordability and drug availability should also be assessed. A treatment that is cost-effective at the health-system level may still be unaffordable at the bedside when patients pay out of pocket.

Covre Coan et al.[1] have provided a timely synthesis supporting the use of albumin as a promising adjunct in HE. We agree that albumin

How to cite this article: Alam MS, Khatoon N. Albumin in hepatic encephalopathy: Evidence, prioritization, and the affordability gap in decompensated cirrhosis. Hepatology Forum 2026; 7(3):306–307.

Received: June 02, 2026; **Accepted:** July 05, 2026; **Available Online:** July 23, 2026

Corresponding author: Mohammad Saquib Alam; Department of Medicine, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India; **E-mail:** msalam109@myamu.ac.in

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

deserves further investigation in this setting. However, its expanding indications in cirrhosis make prioritization increasingly important. The future of albumin therapy should define not only where it works but also where it is most necessary, safest, and most feasible to deliver.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: No funding was received for this work.

Use of Artificial Intelligence: During the preparation of this manuscript, the authors used OpenAI's ChatGPT for language editing and structural refinement. The authors reviewed and approved the final content.

Author Contributions: Concept – MSA, NK; Design – MSA; Writing – MSA, NK; Critical Review – MSA, NK.

Peer-review: Externally peer-reviewed.

References

1. Covre Coan AC, do Livramento Junior VA, Prata AA, Milioli NJ, Correa TL, Martins OC, et al. Use of albumin in patients with hepatic encephalopathy: A systematic review and meta-analysis of randomized controlled studies with trial sequential analysis. Hepatol Forum 2026;7(1):4-13. [CrossRef]
2. Bernardi M, Angeli P, Claria J, Moreau R, Gines P, Jalan R, et al. Albumin in decompensated cirrhosis: new concepts and perspectives. Gut 2020;69(6):1127-1138. [CrossRef]
3. Garcia-Tsao G, Abraldes JG, Rich NE, Wong VW. AGA clinical practice update on the use of vasoactive drugs and intravenous albumin in cirrhosis: Expert review. Gastroenterology 2024;166(1):202-210. [CrossRef]
4. de Mattos ÂZ, Simonetto DA, Terra C, Farias AQ, Bittencourt PL, Pase THS, et al. Albumin administration in patients with cirrhosis: Current role and novel perspectives. World J Gastroenterol 2022;28(33):4773-4786. [CrossRef]

HEPATOLOGY FORUM Volume 7, Issue 3, 2026 | 308–309 DOI: 10.14744/hf.2026.65364

REPLY TO THE LETTER TO THE EDITOR

Reply to the Letter to the Editor: "Albumin in hepatic encephalopathy: Evidence, prioritization, and the affordability gap in decompensated cirrhosis"

Ana Carolina Covre Coan[1], Vanio Antunes do Livramento Junior[2], Alonzo Armani Prata[1], Natália Junkes Milioli[3], Tulio L. Correa[4], Otávio Cosendey Martins[5], Pedro Romeiro[7], Elísio Santos Bulhões Júnior[8], André Milani Reis[6], Matheus Vanzin Fernandes[2]

1: Federal University of Espírito Santo, School of Medicine, Vitória, Brazil
2: Porto Alegre Health Sciences Federal University School of Medicine, Porto Alegre, Brazil
3: Pontifical Catholic University of Rio Grande do Sul School of Medicine, Porto Alegre, Brazil
4: University of Pittsburgh Medical Center School of Medicine, Pittsburgh, Pennsylvania, United States
5: Federal University of Juiz de Fora School of Medicine, Juiz de Fora, Minas Gerais, Brazil
6: State University of Campinas School of Medicine, Campinas, Brazil
7: Department of Medicine, University Center of Maceió, Maceió, Brazil
8: College of Higher Education of the United Amazon, Redenção, Pará, Brazil

To the Editor,

We thank the authors of the letter entitled "Albumin in Hepatic Encephalopathy: Evidence, Prioritization, and the Affordability Gap in Decompensated Cirrhosis" for their interest in our recent systematic review and meta-analysis and for their thoughtful comments.

We agree that the role of albumin in cirrhosis has evolved substantially beyond its traditional use as a plasma expander. As emphasized in our review, the rationale for albumin administration in hepatic encephalopathy (HE) is not limited to ammonia metabolism but also includes its antioxidant, immunomodulatory, and endothelial-stabilizing properties, which may influence several pathways involved in the pathogenesis of HE.[1,2]

The authors appropriately emphasize the challenge of prioritizing albumin use in patients with decompensated cirrhosis, who frequently present with multiple concurrent complications. We agree that, in real-world practice, particularly in resource-limited settings, clinicians may face difficult decisions regarding albumin allocation. However, it is important to note that our study was designed to evaluate the efficacy and safety of albumin in patients with HE rather than to compare or rank albumin-supported indications. Therefore, questions regarding prioritization among competing clinical scenarios remain beyond the scope of the available randomized evidence included in our analysis.

We also concur that the findings should not be interpreted as definitive evidence supporting universal albumin administration for all patients with HE. As discussed in our manuscript, the trial sequential analysis demonstrated that although the mortality benefit crossed the boundary for statistical significance, the required information size was not reached, indicating that additional adequately powered randomized trials are necessary before definitive conclusions can be established.[3]

Furthermore, we agree that future investigations should focus on identifying the patient populations most likely to benefit from albumin therapy. Factors such as HE severity, baseline serum albumin concentration, systemic inflammation, renal dysfunction, infection status, and concomitant cirrhosis-related complications may all influence treatment response. Similarly, the incorporation of clinically relevant outcomes, such as hospitalization, readmission rates, adverse pulmonary events, and cost-effectiveness analyses, would provide valuable information for clinical decision-making.[3]

Finally, we appreciate the authors' emphasis on affordability and accessibility. These considerations are particularly relevant in low- and middle-income countries and deserve greater attention in future clinical trials and health policy discussions.

We thank the authors for their insightful comments and welcome further research aimed at refining the role of albumin therapy in hepatic encephalopathy and identifying the clinical settings in which its use provides the greatest benefit.

How to cite this article: Covre Coan AC, Antunes do Livramento Junior V, Prata AA, Milioli NJ, Correa TL, Martins OC, et al. Reply to the Letter to the Editor: "Albumin in hepatic encephalopathy: Evidence, prioritization, and the affordability gap in decompensated cirrhosis". Hepatology Forum 2026; 7(3):308–309.

Received: July 02, 2026; **Accepted:** July 02, 2026; **Available Online:** July 24, 2026

Corresponding author: Ana Carolina Covre Coan; Federal University of Espírito Santo, School of Medicine, Vitória, Brazil; **E-mail:** anaccovre@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

Conflicts of Interest: The authors declare no conflicts of interest.

Financial Disclosure: The authors declared that this study received no financial support.

Use of Artificial Intelligence: Artificial intelligence was not used in the preparation of the article.

Author Responsibility Statement: All authors take responsibility for all aspects of the work and for the accuracy and integrity of the content and its interpretation.

Peer-review: Externally peer-reviewed.

References

1. Arroyo V, García-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. J Hepatol 2014;61(2):396-407. [CrossRef]
2. Shawcross DL, Wright G, Olde Damink SWM, Jalan R. Role of ammonia and inflammation in minimal hepatic encephalopathy. Metab Brain Dis 2007;22(1):125-138. [CrossRef]
3. Covre Coan AC, Antunes do Livramento Junior V, Prata AA, Milioli NJ, Correa TL, Martins OC, et al. Use of albumin in patients with hepatic encephalopathy: A systematic review and meta-analysis of randomized controlled studies with trial sequential analysis. Hepatology Forum 2026;7(1):4-13. [CrossRef]

HEPATOLOGY FORUM Volume 7, Issue 3, 2026 | 310 DOI: 10.14744/hf.2026.58657

LETTER TO THE EDITOR

Effects of rifaximin in fructose-induced steatohepatitis in rats

Mevlut Kiyak

Department of Gastroenterology, Kolan Hospital, Istanbul Health and Technology University, Istanbul, Türkiye

To the Editor,

I read with interest the recently published article titled "Effects of rifaximin in fructose-induced steatohepatitis in rats." The article discusses how rifaximin may protect against early liver damage caused by fructose. The researchers showed that rifaximin helps reduce certain biochemical markers and promote healing in inflamed tissue, providing insight into the interaction between the gut and liver in fatty liver disease, which plays a role in metabolic disorders. These results support the idea that rifaximin may help alleviate liver inflammation and oxidative stress caused by excess fructose in the early stages of fatty liver disease, also known as metabolic dysfunction-associated steatotic liver disease (MASLD).[1]

Although this study provides important information, I believe that further interpretation is required in a few areas. While fructose consumption over 8 weeks triggered early liver inflammation, no fibrosis was observed in the studied groups. Therefore, these research findings may be most applicable to the early stages of MASLD. Longer-term treatment with rifaximin, beyond 8 weeks, may be useful in determining its effects in more advanced stages of MASLD.[2]

Second, the dosage regimen of rifaximin requires clarification. The rationale for administering rifaximin once or three times per week was not fully explained. Any pharmacological or evidence-based justification for this dosage regimen should be clarified. This research supports the idea that rifaximin may help reduce inflammation and oxidative stress that can contribute to fatty liver disease in animals exposed to high fructose levels. Therefore, the authors' study provides a valuable contribution to the expanding knowledge of gut-liver axis therapies.

I congratulate the authors on their valuable contribution and hope that these comments will support ongoing scientific discussion.

Conflicts of Interest: The author declares no conflicts of interest.

Financial Disclosure: No financial support was received for this article/letter.

Use of Artificial Intelligence: The author declared that they did not use artificial intelligence (AI)–assisted technologies.

Peer-review: Externally peer-reviewed.

References

1. Cabuk Celik N, Yilmaz Goc R, Bahcecioglu IH, Ozercan IH, Tuzcu M, Ilhan N, et al. Effects of rifaximin in fructose-induced steatohepatitis in rats. Hepatol Forum 2025;6(4):160-165. [CrossRef]
2. Oliveira-Cordeiro B, Fernandes-DA-Silva A, Silva-Veiga FM, Miranda CS, Martins FF, Souza-Mello V. Long-term hepatic damage in high-fructose-fed C57BL/6 mice: hepatic fibrogenesis, endoplasmic reticulum stress markers, and fibrosis. An Acad Bras Cienc 2023;95(Suppl 2):e20220784. [CrossRef]

How to cite this article: Kiyak M. Effects of rifaximin in fructose-induced steatohepatitis in rats. Hepatology Forum 2026; 7(3):310.

Received: May 17, 2026; **Accepted:** May 20, 2026; **Available Online:** July 27, 2026

Corresponding author: Mevlut Kiyak; Department of Gastroenterology, Kolan Hospital, Istanbul Health and Technology University, Istanbul, Türkiye; **E-mail:** drmkiyak@gmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

HEPATOLOGY FORUM Volume 7, Issue 3, 2026 | 311 DOI: 10.14744/hf.2026.21462

REPLY TO THE LETTER TO THE EDITOR

Reply to the Letter to the Editor: "Effects of rifaximin in fructose-induced steatohepatitis in rats"

Nese Cabuk Celik[1], Rumeysa Yilmaz Goc[2], Ibrahim Halil Bahcecioglu[3], I. Hanifi Ozercan[4], Mehmet Tuzcu[5], Necip Ilhan[6], Kazim Sahin[7]

1: Department of Rheumatology, Sivas Cumhuriyet University Faculty of Medicine, Sivas, Türkiye
2: Department of Histology and Embryology, Sivas Cumhuriyet University Faculty of Medicine, Sivas, Türkiye
3: Department of Gastroenterology, Firat University Faculty of Medicine, Elazig, Türkiye
4: Department of Pathology, Firat University Faculty of Medicine, Elazig, Türkiye
5: Department of Molecular Biology, Firat University Faculty of Science, Elazig, Türkiye
6: Department of Biochemistry, Firat University Faculty of Medicine, Elazig, Türkiye
7: Department of Animal Nutrition, Firat University Faculty of Veterinary Science, Elazig, Türkiye

To the Editor,

We would like to thank the author for their thoughtful comments and interest in our study.[1,2]

Regarding the first point, we fully agree that the absence of fibrosis limits the interpretation of our findings to early-stage disease. Although the absence of fibrosis was acknowledged as a limitation in our original study, we would also note that this early-stage model allowed for a less confounded assessment of rifaximin's anti-inflammatory and antioxidant effects before the onset of established fibrotic changes. This stage may, in fact, represent the most clinically relevant window for therapeutic intervention. Nevertheless, we agree that longer-duration models will be essential to determine whether these effects extend to fibrogenesis, as also highlighted by prior experimental evidence.[3]

Regarding the second point, the rifaximin dosing regimens, once weekly versus three times weekly, were selected to explore whether different administration frequencies could yield differential biological effects within the same experimental framework. Although both regimens demonstrated beneficial effects, no clear superiority of one frequency over the other was observed. This pattern suggests a degree of flexibility in rifaximin's dosing frequency within this model, a finding that, although preliminary, may have practical relevance for future therapeutic protocols. Further pharmacokinetic and dose–response studies are nevertheless warranted to better define the optimal strategy.

We appreciate the author's constructive remarks and agree that future studies incorporating longer experimental durations and refined dosing strategies will be important to further elucidate the therapeutic potential of rifaximin across different stages of MASLD.

Our findings identify the early inflammatory window of fructose-induced steatohepatitis as a tractable target for gut-directed intervention. Given its established safety profile and gut selectivity, rifaximin represents a compelling candidate for further investigation along this axis.

Conflicts of Interest: The authors declare that they have no conflicts of interest.

Financial Disclosure: The authors declare that this study received no financial support.

Use of Artificial Intelligence: Artificial intelligence was not used in the preparation of the article.

Peer-review: Externally peer-reviewed.

References

1. Kiyak M. Letter to the Editor: Effects of rifaximin in fructose-induced steatohepatitis in rats. Hepatology Forum 2026;7(3):310.
2. Cabuk Celik N, Yilmaz Goc R, Bahcecioglu IH, Ozercan IH, Tuzcu M, Ilhan N, Sahin K. Effects of rifaximin in fructose-induced steatohepatitis in rats. Hepatol Forum 2025;6(4):160-165. [CrossRef]
3. Oliveira-Cordeiro B, Fernandes-DA-Silva A, Silva-Veiga FM, Miranda CS, Martins FF, Souza-Mello V. Long-term hepatic damage in high-fructose-fed C57BL/6 mice: hepatic fibrogenesis, endoplasmic reticulum stress markers, and fibrosis. An Acad Bras Cienc 2023;95(Suppl 2):e20220784. [CrossRef]

How to cite this article: Cabuk Celik N, Yilmaz Goc R, Bahcecioglu IH, Ozercan IH, Tuzcu M, Ilhan N, Sahin K. Reply to the Letter to the Editor: "Effects of rifaximin in fructose-induced steatohepatitis in rats". Hepatology Forum 2026; 7(3):311.

Received: June 22, 2026; **Accepted:** June 22, 2026; **Available Online:** July 23, 2026

Corresponding author: Rumeysa Yilmaz Goc; Department of Histology and Embryology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas, Türkiye;
E-mail: rumeysayilmaz99@hotmail.com

This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.