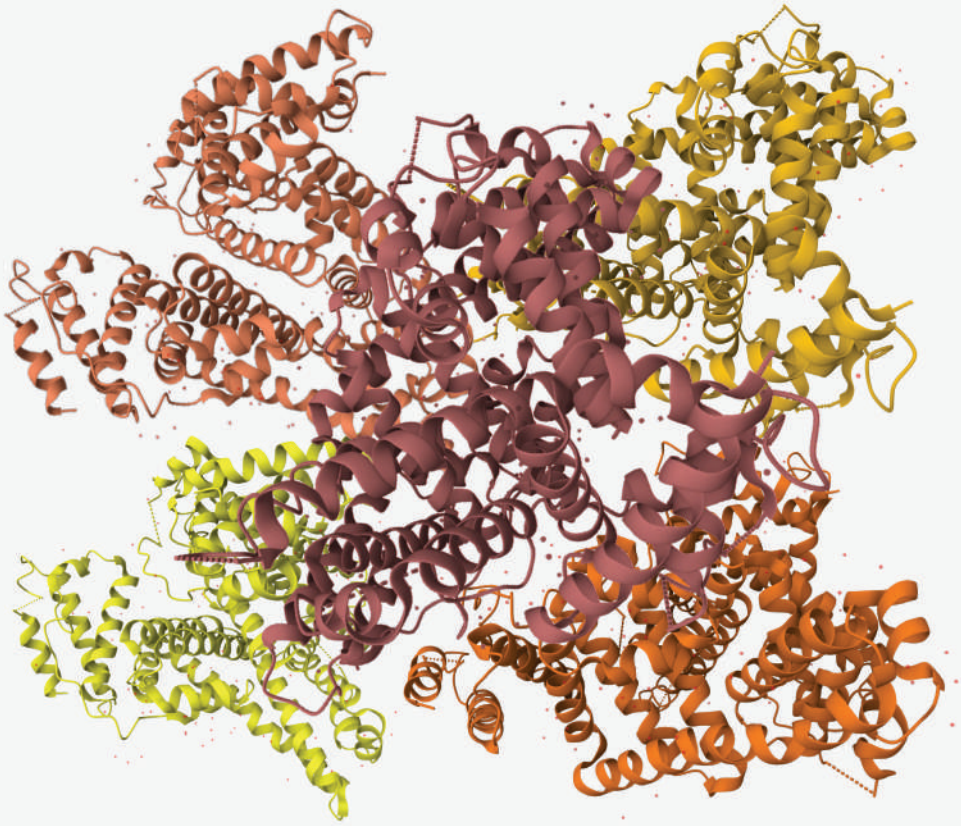
E-ISSN 2757-7392

2026 Vol 7 Issue 1

HEPATOLOGY FORUM

Official Journal of the Turkish Association for the Study of the Liver



Use of Albumin for Hepatic Encephalopathy Systematic review & Meta-analysis

Hepatosteatosis and HBV seroclearance

Statins and liver enzymes in MASLD

Sarcopenia predicts TIPS outcomes in cirrhosis

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

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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/Turkiye
Phone: +90 212 244 30 71
Fax: +90 212 234 19 60
Web: www.tasl.org.tr
E-mail: tasl@tasl.org.tr

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Address: Goztepe Mahallesi, Fahrettin Kerim Gokay Caddesi, No: 200, Daire: 2, Kadikoy, Istanbul/Turkiye
Phone: +90 216 550 61 11
Fax: +90 216 550 61 12
Web: www.karepb.com
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Volume 7 Issue 1 January 2026

Content

Editorial

HBV in the era of metabolic liver disease

HEPATOLOGY FORUM

doi: 10.14744/hf.2026.86483

When viral quiescence meets metabolic injury: Rethinking risk and treatment at the intersection of MASLD and chronic hepatitis B

Dilara Turan Gokce[1], Ulus Salih Akarca[2]

[1]Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkiye; [2]Editor in Chief, Hepatology Forum, Izmir, Turkiye

The past three decades have transformed the landscape of chronic liver disease. Universal hepatitis B virus (HBV) vaccination programs and the widespread use of potent nucleos(t)ide analogues have dramatically reduced the incidence of HBV-related cirrhosis and hepatocellular carcinoma (HCC). In parallel, the advent of curative direct-acting antivirals for hepatitis C virus (HCV) has reshaped expectations for viral hepatitis elimination. Yet, despite these achievements, liver-related morbidity and mortality remain unacceptably high worldwide, accounting for nearly two million deaths annually. This gap between virological success and clinical outcomes has led to a rethinking of the factors driving liver disease progression today.

Increasingly, the answer lies not in viral hepatitis alone, but in its convergence with metabolic dysfunction-associated steatotic liver disease (MASLD). Rather than replacing viral hepatitis, MASLD is overlapping with it, creating a dual-etiology state in which metabolic and viral insults interact within the same liver. This emerging reality challenges long-standing disease constructs and exposes important gaps in current clinical algorithms. In the era of MASLD, virological inactivity can no longer be equated with clinical safety.

In this context, the two studies published in the January 2026 issue of Hepatology Forum—the narrative review by Ejaz and colleagues[1] and the original cohort study by Bodakci and colleagues[2]—provide complementary and timely insights into this evolving paradigm. Together, they highlight not only the scale of the MASLD–viral hepatitis overlap, but also the clinical ambiguities that arise when traditional virological definitions are applied to metabolically injured livers.

The Expanding Overlap of MASLD and Viral Hepatitis

Ejaz et al. comprehensively describe the growing epidemiological convergence between MASLD and chronic viral hepatitis. MASLD now affects approximately 30% of the global adult population, with substantially higher prevalence among individuals with diabetes mellitus, hypertension, and obesity.[3] However, like viral hepatitis, MASLD exhibits marked geographic heterogeneity, with substantial variation across and within regions, as highlighted by Ejaz et al.[1] At the same time, hundreds of millions of people still live with chronic HBV or HCV. These epidemics increasingly overlap, especially in regions long affected by viral hepatitis, such as East and South Asia and sub-Saharan Africa.

Several forces underpin this convergence. First, antiviral therapies have converted HBV and HCV into chronic, manageable conditions, allowing affected populations to age and accumulate metabolic comorbidities. Second, rapid urbanization and westernization of dietary patterns have accelerated the rise of obesity and insulin resistance in HBV-endemic regions. As a result, an increasing proportion of patients now present with dual pathology, in which viral persistence coexists with metabolic lipotoxicity.

Importantly, this overlap is not benign. Epidemiological studies consistently demonstrate that MASLD amplifies the risk of fibrosis progression, cirrhosis, and HCC in patients with viral hepatitis, even when viral replication is low or suppressed.[4] These observations suggest that metabolic injury may lower the threshold at which viral signals translate into clinically meaningful liver damage.

Steatosis in Chronic HBV: Friend, Foe, or Both?

While Ejaz et al.[1] frame the problem at a population level, Bodakci et al.[2] illuminate its clinical complexity. In their long-term, biopsy-based cohort of patients with chronic HBV infection, hepatic steatosis was independently associated with higher rates of hepatitis B surface antigen (HBsAg) seroclearance, an outcome often regarded as a functional cure of HBV. Paradoxically, the same patients exhibited greater fibrosis progression and higher liver stiffness over time.

This apparent contradiction encapsulates the central dilemma of MASLD–HBV coexistence. On the one hand, metabolic inflammation may enhance certain immune pathways that facilitate viral antigen clearance. On the other hand, lipotoxicity, oxidative stress, and chronic low-grade inflammation promote fibrogenesis and structural liver injury. This discordance between virological control and histological progression indicates that a favorable viral response does not always translate into long-term clinical improvement.

How to cite this article: Turan Gokce D, Akarca US. When viral quiescence meets metabolic injury: Rethinking risk and treatment at the intersection of MASLD and chronic hepatitis B. Hepatology Forum 2026; 7(1):1–3.

Received: January 13, 2026; **Accepted:** January 14, 2026; **Available online:** January 00, 2026

Corresponding author: Ulus Salih Akarca; Editor in Chief, Hepatology Forum, Izmir, Turkiye
Phone: +90 532 644 66 20; **e-mail:** ulus.salih.akarca@ege.edu.tr

Hepatology Forum - Available online at www.hepatologyforum.org

Crucially, Bodakci et al.[2] demonstrate that this paradox is not theoretical. Even in patients who achieve HBsAg loss, advanced fibrosis may continue to evolve, underscoring that functional cure does not equate to biological quiescence when metabolic injury persists.

Mechanistic Convergence: Beyond Additive Risk

From a biological standpoint, the coexistence of MASLD and chronic viral hepatitis likely creates a permissive milieu for synergistic liver injury.[5,6] Chronic viral infection establishes a background of immune dysregulation and low-grade inflammatory signaling, while metabolic dysfunction introduces lipotoxicity, oxidative stress, and mitochondrial injury.[7] When these processes converge, hepatocytes and non-parenchymal cells may be exposed to parallel profibrotic and pro-oncogenic stimuli. Importantly, metabolic inflammation may lower the threshold at which residual viral signals become biologically relevant, even in the setting of virological quiescence.[8] This integrated framework provides a plausible mechanistic explanation for clinical observations in which favorable virological endpoints coexist with ongoing fibrosis progression and persistent hepatocellular carcinoma risk in patients with concomitant MASLD.[9]

Diagnostic Challenges

Beyond management, the coexistence of MASLD and chronic viral hepatitis introduces important diagnostic challenges. Non-invasive fibrosis assessments, including liver stiffness measurements, may reflect the cumulative impact of metabolic inflammation and viral injury, making it difficult to attribute fibrosis progression to a single etiology. Normal aminotransferase levels may provide false reassurance in this setting, as significant fibrotic remodeling can occur in the absence of biochemical activity.[10] Similarly, commonly used non-invasive scores were largely derived from single-etiology populations and may have reduced specificity in dual-etiology disease. Consequently, discordance between virological markers, biochemical indices, and fibrosis assessments is common, and liver biopsy may still play a role in selected cases to clarify disease drivers and inform risk stratification.

The Clinical Blind Spot: Inactive HBV in a Metabolically Injured Liver

Perhaps the most pressing implication of this dual-etiology framework emerges in daily clinical practice. Consider the increasingly common patient with chronic HBV infection who meets virological criteria for an inactive carrier state—low HBV DNA levels and normal aminotransferases—yet demonstrates advanced fibrosis in the setting of concomitant MASLD. Non-invasive stiffness measurements or liver biopsy may reveal significant fibrotic remodeling, while existing HBV treatment algorithms provide little practical guidance.

Current international guidelines anchor treatment decisions primarily in viral replication thresholds and biochemical activity, whereas MASLD guidelines often exclude patients with chronic viral hepatitis altogether.[11,12] The result is a growing population of patients who fall into a guideline blind spot: virologically "inactive," metabolically high-risk, and histologically advanced.

In such cases, the clinical question is no longer whether antiviral therapy is indicated by classical HBV criteria alone, but whether persistent viral signaling can be safely ignored in a metabolically primed, fibrotic liver. Emerging observational data suggest that MASLD may amplify the fibrogenic and oncogenic consequences of even low-grade viral persistence,[6,13] raising the possibility that traditional HBV DNA cutoffs, largely derived from metabolically healthier populations, may be biologically insufficient in this context.

While antiviral therapy does not treat MASLD per se, it may reduce the background viral "noise" that contributes to immune activation and long-term oncogenic risk. In the absence of prospective trials, available evidence supports a more individualized, risk-based approach, particularly in patients with advanced fibrosis, where the margin for error is small.[12,14] Antiviral treatment alone, however, is unlikely to sufficiently mitigate long-term risk and should be complemented by aggressive lifestyle modification and evidence-based metabolic pharmacotherapy. Importantly, management decisions should integrate fibrosis stage, metabolic risk profile, and patient-specific factors, rather than relying solely on traditional virological thresholds.

Implications for Guidelines and Future Research

The convergence of MASLD and viral hepatitis exposes fundamental limitations in current disease frameworks. Single-etiology thinking no longer reflects clinical reality. Risk stratification tools that rely exclusively on viral or metabolic parameters in isolation fail to capture the integrated nature of liver injury. Strict adherence to current HBV treatment algorithms may inadvertently delay intervention in a growing subgroup of high-risk patients.

Future guidelines must move toward dual-risk assessment models that account for both viral persistence and metabolic dysfunction. Prospective studies are urgently needed to determine whether antiviral therapy confers incremental benefit in metabolically driven fibrosis, even in the setting of low-level viremia. Equally important is the development of integrated management strategies that address metabolic risk factors alongside viral suppression.

Conclusion: Toward a Dual-Etiology Paradigm in Hepatology

The studies by Ejaz et al.[1] and Bodakci et al.[2] mark an important step in reframing chronic liver disease for the modern era. They remind us that virological quiescence does not equate to biological inactivity, and that metabolic injury fundamentally alters the risk landscape of viral hepatitis. As MASLD and viral hepatitis increasingly converge, hepatology must evolve beyond siloed disease constructs toward an integrated, patient-centered paradigm. For clinicians, this means moving beyond viral replication and aminotransferase thresholds alone and incorporating fibrosis burden and metabolic risk into routine decision-making. For guideline committees, this underscores the need to revisit treatment algorithms that were developed in single-etiology populations and may underestimate risk in metabolically injured livers. For future trials, priority should be given to prospective studies evaluating whether antiviral therapy provides incremental benefit in patients with MASLD-driven fibrosis, even in the setting of low-level viremia.

Key takeaways for the clinician

Clinical domain	Key insight and recommendation
Epidemiology	A substantial proportion (≈30–50%) of viral hepatitis patients have concurrent MASLD, with particularly high prevalence among individuals with diabetes and other metabolic risk factors.
Pathophysiology	Dual "hits" from virus and fat create synergistic inflammation and fibrosis. Steatosis induces ER stress which may suppress HBV replication.
Diagnosis	Normal enzymes do not rule out disease. Use CAP/FibroScan for staging but interpret LSM with caution. Biopsy remains the gold standard for discordant cases.
Prognosis	Be aware of the "steatosis paradox": a fatty liver may help clear HBsAg (functional cure), but it will accelerate fibrosis progression if metabolic factors are not controlled.
Treatment	Antiviral therapy (TDF/TAF/ETV) in virologically inactive patients with MASLD-related fibrosis should be considered but is unlikely to be sufficient as a standalone strategy. Aggressive lifestyle modification and evidence-based metabolic pharmacotherapy are essential, with careful attention to potential drug–drug interactions.

MASLD: Metabolic dysfunction-associated steatotic liver disease; ER: Endoplasmic reticulum; HBV: Hepatitis B virus; CAP: Controlled attenuation parameter; LSM: Liver stiffness measurement; TDF: Tenofovir disoproxil fumarate; TAF: Tenofovir alafenamide; ETV: Entecavir.

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 – USA; Data Collection and/or Processing – USA, DTG; Literature Search – USA, DTG; Writing – USA, DTG; Critical Reviews – USA, DTG.

Peer-review: Externally peer-reviewed.

References

1. Ejaz M, Kumar K, Sohail D, Sarfaraz I, Azam H, Yaseen F. MASLD and viral hepatitis overlap: An emerging dual burden in chronic liver disease. Hepatology Forum 2026;7(1):69-76. [CrossRef]
2. Bodakci E, Kiremitci S, Melekoglu Ellik Z, Koc O, Gumussoy M, Yilmaz V, et al. Hepatic steatosis is associated with HBsAg seroclearance in patients with chronic hepatitis B virus infection but it is also associated with disease progression. Hepatology Forum 2026;7(1):14–20. [CrossRef]
3. Younossi ZM, Kalligeros M, Henry L. Epidemiology of metabolic dysfunction-associated steatotic liver disease. Clin Mol Hepatol 2025;31(Suppl):S32-S50. [CrossRef]
4. Makuza JD, Jeong D, Binka M, Adu PA, Cua G, Yu A, et al. Impact of hepatitis B virus infection, non-alcoholic fatty liver disease, and hepatitis c virus co-infection on liver-related death among people tested for hepatitis B virus in British Columbia: Results from a large longitudinal population-based cohort study. Viruses 2022;14(11):2579. [CrossRef]
5. Negro F. Facts and fictions of HCV and comorbidities: steatosis, diabetes mellitus, and cardiovascular diseases. J Hepatol 2014;61(Suppl 1):S69-S78. [CrossRef]
6. Hasanoglu I, Rivero-Juárez A, Özkaya Şahin G, Hepatitis ESGfV. When metabolic dysfunction-associated steatotic liver disease meets viral hepatitis. J Clin Med 2025;14(10):3422. [CrossRef]
7. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018;24(7):908-922. [CrossRef]
8. Tourkochristou E, Assimakopoulos SF, Thomopoulos K, Marangos M, Triantos C. NAFLD and HBV interplay - related mechanisms underlying liver disease progression. Front Immunol 2022;13:965548. [CrossRef]
9. Kalligeros M, Henry L, Younossi ZM. Metabolic dysfunction-associated steatotic liver disease and its link to cancer. Metabolism 2024;160:156004. [CrossRef]
10. Moyana TN. Metabolic dysfunction-associated steatotic liver disease: The question of long-term high-normal alanine aminotransferase as a screening test. World J Gastroenterol 2024;30(42):4576-4582. [CrossRef]
11. Cornberg M, Sandmann L, Jaroszewicz J, Kennedy P, Lampertico P, Lemoine M, et al. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2025;83(2):502-583. [CrossRef]
12. Ghany MG, Pan CQ, Lok AS, Feld JJ, Lim JK, Wang SH, et al. AASLD/IDSA Practice Guideline on treatment of chronic hepatitis B. Hepatology 2025. [Epub ahead of print]. doi: 10.1016/j.metabol.2024.156004 [CrossRef]
13. Kalafateli M, Forlano R, Barnes E, Martinez-Gili L, Lacey M, Sigon G, et al. Risk factors of metabolic dysfunction-associated steatotic liver disease in a cohort of patients with chronic hepatitis B. Clin Gastroenterol Hepatol 2025;S1542-3565(25)00533-6. [Epub ahead of print] doi: 10.1016/j.cgh.2025.06.014 [CrossRef]
14. Tacke F, Horn P, Wai-Sun Wong V, Ratziu V, Bugianesi E, Francque S, et al. EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol 2024;81(3):492-542. [CrossRef]

HEPATOLOGY FORUM
doi: 10.14744/hf.2025.58807

Use of albumin in patients with hepatic encephalopathy: A systematic review and meta-analysis of randomized controlled studies with trial sequential analysis

Ana Carolina Covre Coan[1], Vanio Livramento Junior, Antunes[2], Alonzo Armani Prata[1], Natália Junkes Milioli[3], Tulio L Correa[4], Otavio 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, United States; [5]Federal University of Juiz de Fora, School of Medicine, 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, Brazil

Abstract

Background and Aim: Hepatic encephalopathy (HE) is a complication of cirrhosis and one of the most important manifestations of this disease. Intravenous albumin may have the potential to mitigate oxidative stress injury inherent to the pathogenesis of HE. Our study aims to evaluate the efficacy and safety of albumin for the treatment of HE.

Materials and Methods: We performed a systematic review and meta-analysis using the PubMed, Embase, and Cochrane databases. We searched for randomized controlled trials (RCTs) comparing albumin to placebo in patients with HE and decompensated cirrhosis. The outcomes were mortality and clinical improvement of HE. The odds ratio (OR) was used for binary outcomes and the mean difference (MD) for continuous outcomes with their respective 95% confidence interval (CI). Heterogeneity was assessed using the Cochran Q test and I^2 statistics. Trial sequential analysis (TSA) was performed for all outcomes.

Results: This study included four RCTs, amounting to 306 patients. There was a significant difference favoring albumin use for mortality (OR 0.44; 95% CI 0.24 to 0.79; p=0.007; I^2=0%) and for HE improvement (OR 2.41; 95% CI 1.22 to 4.75, p=0.011; I^2=34.9%) compared to placebo. There was no significant difference in ammonia levels (p=0.580), liver transplantation (p=0.732), and significant adverse events (AE) rate (p=0.586). TSA revealed that the pooled effect is statistically significant for mortality reduction with albumin use; however, regarding sample size, the result is not definitive.

Conclusion: In patients with HE, intravenous albumin leads to HE improvement and reduced mortality, without an increase in AE rates. However, the TSA indicated that further studies are required to draw precise evidence regarding the use of albumin to reduce mortality in this population.

Keywords: Albumin; cirrhosis; hepatic encephalopathy.

How to cite this article: Covre Coan AC, Antunes VLJ, Prata AA, Milioli NJ, Correa TL, Cosendey O, Romeiro P, 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.

Received: November 24, 2024; **Revised:** September 22, 2025; **Accepted:** October 21, 2025; **Available online:** January 00, 2026

Corresponding author: Ana Carolina Covre Coan, Department of Pediatric Neurology, School of Medicine, Federal University of Espírito Santo, Brazil
Phone: +55 279 990 874 77; **e-mail:** anaccovre@gmail.com

Hepatology Forum - Available online at www.hepatologyforum.org

Introduction

Hepatic encephalopathy (HE) is the most prominent neurocognitive complication of cirrhosis, represented by various manifestations of neuropsychiatric dysfunction that can be restrictive for patients' lives and their caregivers, leading to increased mortality.[1] HE is clinically characterized by a disbalance in the sleep-wake cycle, which occurs with a shift from day to night and daytime sleepiness, confusion regarding both time and space, agitation or stupor, mental confusion, and even coma.[2]

The pathogenesis of HE is not yet fully elucidated, although it is recognized that ammonia accumulation, inflammation, oxidative stress, endothelial damage, and circulatory dysfunction collectively contribute significantly.[3,4] The mediators of inflammation act by modulating the cerebral effects of ammonia in cirrhosis. Furthermore, the reduction in serum albumin concentration, due to hepatic insufficiency, results in an increase in free metabolite levels, as the blood protein's binding capacity is diminished, contributing to the precipitation of HE. The clinical neurological manifestations are associated with a sustained inflammatory response and endothelial disruption that is not suppressed by the current standard of care.[5]

In previous studies, the role of albumin has already been demonstrated for other complications of liver disease, such as in the control of ascites, spontaneous peritonitis, and hepatorenal syndrome, resulting in reduced hospitalizations and improvement in survival.[6,7] The objective of the present systematic review and meta-analysis is to evaluate the role of albumin in the management of HE.

Materials and Methods

Protocol and Registration

The systematic review and meta-analysis were conducted and structured in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[8] and the Preferred Reporting Items for Systematic Re-

views and Meta-Analyses (PRISMA)[9] recommendations (Appendix Methods 1 and 2). The study protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO)[10] under the identification number CRD 42024545137.

Ethics Approval and Consent to Participate

This study is a systematic review and meta-analysis of previously published data and did not involve direct research with human participants, animals, or any individual-level data requiring ethical approval. All procedures of the included studies were conducted in accordance with the Declaration of Helsinki.

Consent for Publication

This manuscript does not contain any individual person's data in any form; therefore, consent for publication was not required.

Eligibility Criteria and Outcomes

Inclusion in this meta-analysis was limited to studies that met all the following eligibility criteria: (i) randomized controlled trials (RCTs); (ii) enrolling patients with HE; (iii) comparing albumin to placebo; and (iv) reporting at least one of the outcomes of interest. There were no language or date restrictions. Abstracts, case reports, case series, editorials, letters to the editor, reviews, systematic reviews, and meta-analyses were excluded. The inclusion and exclusion criteria of each study are presented in Appendix Table 1.

The primary outcomes were mortality and clinical improvement in HE. Secondary outcomes were: (i) ammonia levels; (ii) liver transplantation; and (iii) significant adverse events (AE) rate. A subgroup analysis was performed in three studies to explore the impact of baseline HE severity by comparing outcomes between overt HE (oHE) and minimal HE (mHE) populations for the outcomes of HE improvement and ammonia levels.

Search Strategy and Study Selection

A systematic review of PubMed, Embase, and Cochrane Library databases was conducted on April 4, 2024. The search strategy was as follows: (albumin) AND ("hepatic encephalopathy") AND ("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR randomized [tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly [tiab] OR trial[tiab] OR groups[tiab]). The search strategy was adapted to the different databases according to support for special characters. References of eligible papers, previous systematic reviews, and meta-analyses were also searched for additional studies of interest.

Two reviewers (AC and TC) conducted the search, imported results into Rayyan software,[11] and triaged the studies. After excluding duplicates and titles/abstracts clearly unrelated to the clinical question, the eligibility of each remaining study was assessed based on a full-text review of the articles. In instances of disagreement, a third reviewer (MF) was consulted.

Data Extraction

The following data were extracted from individual studies: (i) study characteristics, including the first author, year of publication, country of origin, sample size, and duration of follow-up; (ii) patient characteristics, including the number of patients, age, and gender; and (iii) outcomes, including improvement in encephalopathy, mortality, ammonia levels, liver transplantation, and AE rates. If the included studies did not provide mean and standard deviation, their values were estimated using the reported median and range, based on the methods described by Luo et al.[12–14] and Wan et al.[15]

Statistical Analysis

Statistical analyses were conducted using R (R Foundation for Statistical Computing, Vienna, Austria) version 4.3.1. The Restricted Maximum Likelihood random effects model was employed for data synthesis. Treatment effects for dichotomous endpoints were compared using the Odds Ratio (OR) with corresponding 95% confidence intervals (CI), while continuous outcomes were assessed using the Mean Difference (MD). Statistical significance was defined as a p-value < 0.05. Heterogeneity was evaluated through I^2 statistics and Cochran's Q test. Significance for heterogeneity was determined as $p<0.10$ and $I^2>40\%$. In cases where significant heterogeneity was observed ($I^2>40\%$), sensitivity analyses were conducted to ensure the robustness and reliability of the findings. Forest plots were sorted by mean HE levels to help readers consider this variable when interpreting the results.

Trial Sequential Analysis

Trial sequential analysis (TSA) was performed using TSA software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen)[16,17]. The effect measure (OD) was used, and a random effects model using the DerSimonian–Laird method was selected. No continuity correction was applied in the case of a zero event. The required sample size was estimated based on the calculated effect size for the intervention, considering a type I error of 5% and a power of 90%; benefit, harm, and inner wedge boundaries were drawn using the O'Brien–Fleming spending function. Heterogeneity correction was performed using model variance.

Risk of Bias and Evidence Quality Assessment

Two independent authors conducted the risk of bias assessment (AC and NM). Risk of bias in selected RCTs was assessed using the second version of the Cochrane Risk of Bias assessment tool (RoB 2)[18], evaluating five domains for each outcome of the selected studies: (i) bias in the randomization process; (ii) bias due to deviations from intended interventions; (iii) bias due to missing data; (iv) bias in outcome measurement; and (v) bias in the selection of the reported results.

The overall risk of bias assessment for each specific trial outcome was derived from individual domain judgments. Disagreements were resolved through consensus after discussing the reasons for the discrepancy.

Results

Study Selection and Baseline Characteristics

As detailed in Figure 1, the initial search yielded 2,517 results. After the removal of duplicate records and ineligible studies, 25 remained and were fully reviewed. Of these, a total of 4 studies [19–22] were included (306 patients, with albumin administered to 150 and placebo to 156 patients). Baseline characteristics were described in Table 1, and the principal characteristics of the studies were reported in Table 2. Other characteristics were described in Appendix Table 2.

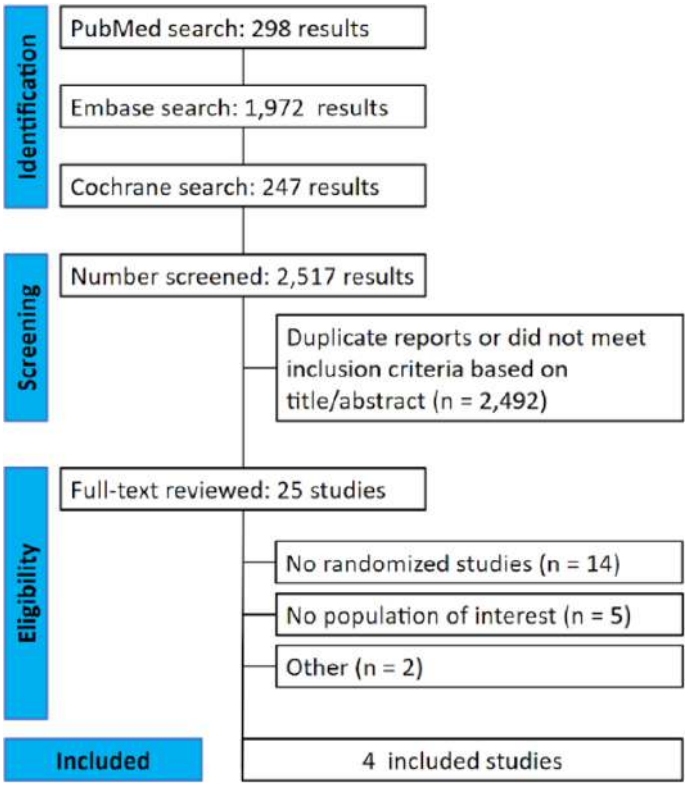

Figure 1. PRISMA flow chart for study selection.

The administration of albumin versus placebo varied slightly across the included studies. Fagan et al.[19], Simón-Talero et al.[21], and Ventura-Cots et al.[20] all administered intravenous albumin at a dose of 1.5 g/kg body weight, using placebo as the comparator. In contrast, Sharma et al.[22] provided albumin at a dose of 1.5 g/kg/day in combination with standard lactulose therapy, while the control group received lactulose alone (Table 1).

Pooled Analysis of All Studies

Primary Outcome

Mortality was reported in three studies (258 patients), and the analyses showed a significant difference favoring albumin use (OR 0.44; 95% CI 0.24 to 0.79; p=0.007; I^2=0%; Fig. 2). The clinical improvement rate of HE was reported in three studies (224 patients), and the analyses also showed a significant difference favoring albumin use (OR 2.41; 95% CI 1.22 to 4.75, p=0.011; I^2=34.9%; Fig. 3).

Secondary Outcomes

Three studies evaluated ammonia levels (219 patients), and there was no significant difference between groups (MD -1.46; 95% CI -6.62 to 3.71; p=0.58; I^2=0%; Appendix Fig. 1). Two studies evaluated the evolution to liver transplantation (138 patients), and there was no significant difference between groups (OR 0.73; 95% CI 0.12 to 4.37; p=0.732; I^2=35%; Appendix Fig. 2). Two studies evaluated the significant AE rate (202 patients), and there was also no difference between groups (OR 1.24; 95% CI 0.57 to 2.68; p=0.586; I^2=0%; Appendix Fig. 3).

Subgroup Analysis

A subgroup analysis was performed in three studies to explore the impact of baseline HE severity by comparing outcomes between oHE and mHE populations. No statistically significant difference was observed between groups in HE improvement (OR 2.41; 95% CI 1.22 to 4.75; p=0.1982; I^2=34.9%; Appendix Fig. 4) or ammonia levels (MD -1.46; 95% CI -6.62 to 3.71; p=0.2960; I^2=0%; Appendix Fig. 5). Mean HE refers to the weighted average of baseline HE grades among patients included in each study.

Trial Sequential Analysis

In the TSA for mortality, the cumulative z-line crossed the boundary for effect but did not reach the required sample size (Fig. 4). These findings suggest that, although the pooled effect is statistically significant, with regard to sample size, the result is not definitive, and future studies are necessary to be conclusive about the use of albumin to reduce mortality in this population.

In the TSA for HE improvement, the cumulative z-line lies in the zone with no statistical significance (Fig. 5). This finding implies that the sample size of the meta-analysis was too small, and it is therefore impossible to infer where the cumulative z-line will lie in future trials. No conclusions regarding the meta-analysis pooled effect for HE improvement can be made.

Risk of Bias and Evidence Quality Assessment

The studies of Simón-Talero et al.[21], Fagan et al.[19], and Ventura-Cots et al.[20] were at low risk of bias according to the RoB 2 tool (18). However, the trial by Sharma et al.[22] was at moderate risk due to the lack of blinding (Appendix Table 3).

Discussion

The results of this meta-analysis corroborated those reported in a previous one by Is et al.[23], with a statistically significant difference favoring albumin in HE improvement and reduced mortality. There were no differences in ammonia levels, evolution to liver transplantation, and AE rates of the treatment compared to the placebo group. This study has some advantages over previous meta-analyses on the topic.[23] Firstly, it included 2 new studies, Fagan et al.[19] and Ventura-Cots et al.[20], increasing the sample size by 73.8%, providing a more accurate result. Second, a TSA was performed to determine when the pooled effect is strong enough to be unlikely to be changed by more studies, helping to balance type I and II errors. Third, additional outcomes were evaluated, including serum ammonia levels, progression to liver transplantation, and AE rates.

Findings from the present meta-analysis are also in line with those reported by Bai et al.[24] in a single-center retrospective study and a meta-analysis that demonstrated albumin infusion may prevent the occurrence of oHE and improve its severity in patients with cirrhosis. A subsequent meta-analysis[25] including 42 RCTs further showed that human albumin treatment significantly improved the severity of complications in cirrhotic patients, including those with HE. Moreover, in 2023, an international position statement[26] supported the benefits of human albumin in reducing the incidence of HE, improving its severity, and lowering mortality in HE patients. However, the quality of available evidence was limited by heterogeneity in study design and subjectivity in outcome assessment. The current meta-analysis aims to address these limitations by providing greater clarity on these important findings.

doi: 10.14744/hf.2025.58807

Table 1. Baseline patient and study characteristics

Study	Follow-up (days)	Treatment	Sample size	Age (years)	Male sex	Etiology of cirrhosis					MELD-Na score	Serum albumin	previous HE
						HCV	HBV	Alcohol	NAH	Others			
Fagan et al.[19]	35	25% IV albumin (1.5 g/kg body weight)	24	63.83±6.99	22 (92)	3	–	12	7	2	11.75±3.78	3.38±0.36	–
		Placebo	24	62.21±8.59	21 (88)	4	–	10	10	0	10.46±3.36	3.20±0.38	–
Sharma et al.[22]	10	Albumin 1.5 gm/kg/day + control	60	42.5±8.7	49	5 (8.3)	12 (20)	35 (58.3)	–	8 (13.3)	26.4±5.8	2.3±0.9	27 (45)
		lactulose 30–60 ml three times a day	60	38.4±9.6	51	6 (10)	13 (21.6)	32 (53.3)	–	9 (15.0)	25.8±5.1	2.4±0.8	24 (40)
Simón-Talero et al.[21]	90	20% IV albumin (1.5 g/kg body weight)	26	63.7±11.3	19 (73.1)	9 (34.6)†		7 (26.9)	–	6 (23.1)	16.8±3.8	2.9±0.6	–
		Placebo	30	66.3±9.7	23 (76.7)	10 (33.3)†		17 (56.7)	–	2 (6.7)	16.1±5.1	3.0±0.6	–
Ventura-Cots et al.[20]	180	IV albumin (1.5 g/ kg body weight)	40	66.5 (59.9–73.6)*	29 (72.5)	6 (15)	–	19 (47.5)	–	9	17 (15–20)*	2.6 (2.41–2.93)*	26 (65)
		Placebo	42	69.1 (63.3–75.3)*	26 (61.9)	4 (9.5)	–	22 (52.3)	–	9	17 (16–20)*	2.85 (2.35–3.01)*	27 (64.3)

BInary data is displayed as number of events and percentage while continuous as mean±standard deviation unless otherwise specified. *: Median (IQR); †: Did not specify type of hepatitis virus. HCV: Hepatitis C virus; HBV: Hepatitis C virus; NAH: N-acetylheparin; MELD: Metabolic dysfunction-associated steatotic liver disease; HE: Hepatic encephalopathy.

Table 2. Principal study characteristics

Author, year	Follow-up (days)	Location; Period	Center	N	Treatment	Results (I x C)
Sharma et al.[22]	10	India; 2015–2016	Multi-centric	120	I: lactulose + albumin C: lactulose	HE recovery: 75% x 53.3% (p=0.03) Hospital stay: 6.4±3.4 days x 8.6±4.3 days (p=0.01) Mortality: 18.3%x31.6% (p=0.04) Arterial ammonia (µmol/L): 78.1±14.8 (p<0.001) x 78.9±15.2 (p=0.001) TNF alfa (pg/mL): 21.8±8.9 (p=0.001) x 30.6±9.8 (p=0.02) IL-6 (pg/mL): 18.1±6.4 (p=0.01) x 24.3±7.3 (p=0.03) IL-18 (pg/mL): 41.9±10.4 (p<0.001) x 60.0±14.4 (p=0.04) Endotoxin (EU/mL): 0.25±0.08 (p<0.001) x 0.38±0.07 (p=0.01)
Fagan et al.[19]	35	USA; 2018–2022	Uni-center	48	I: albumin C: placebo (saline)	MHE frequency: 79% (p=0.05) x 96% (p=0.96) Venous ammonia: 64.81±41.1 (p=0.20) x 78.46±41.78 (p=0.42) IL-1b (pg/ml): 0.35±0.37 (p<0.05) x 0.47±0.50 IL-6 (pg/ml): 3.18±1.73 x 4.94±7.52 TNF alfa (pg/ml): 15.06±7.94 x 16.88±7.32 IL-10 (pg/ml): 3.28±1.81 x 3.08±3.02 (p<0.05) LBP (ng/ml): 1,659.7±931.6 x 1,931.2±316.7 ICAM-1 (ng/ml): 313.1±125.6 x 343.6±125.9 (p<0.05) ADMA (IM): 0.63±0.10 (p<0.05) x 0.65±0.14 IMA (IU/ml): 1
Ventura-Cots et al.[20]	180	Spain; 2015–2019	Multi-centric	82	I: albumin C: placebo (saline)	Transplant-free survival at 90 days: 91.9% x 80.5%(p=0.3) 90-day cumulative incidence of death: 9% x 20% (p=0.1) Transplant-free survival at 180 days: 79.7% x 67.8% (p=0.2) 180-day cumulative incidence of death: 11% x 28% (p=0.09)
Simón-Talero et al.[21]	90	Spain; 2009–2012	Multi-centric	56	I: albumin C: placebo (saline)	Hospital stay: 7.0 (IQR 4.5–10.0) x 7.0 (IQR 4.8–11.0) (p=0.8) Transplant-free survival at 90 days: HR 0.37, CI 95% 0.16-0.89, p=0.02 Ammonia (µmol/L): 97 (IQR 59–134) x 113 (IQR 54–132) Renin (µIU/ml): 54.3 (IQR 14.0–226.9) x 138.2 (IQR 15.2–392.0) IL-6 (pg/ml): 275.6 (IQR 142.2–554.6) x 276.1 (IQR 157.1–642.2) IL-10 (pg/ml): 10.9 (IQR 7.2–17.2) x 13.8 (IQR 8.6–18.9) TNF (pg/ml): 45.4 (IQR 25.6–103.4) x 34.3 (IQR 26.0–68.9) MDA (nmol/ml): 2.4 (IQR 2.0–3.1) x 2.3 (IQR 2.1–3.4) sCD163 (ng/ml): 27.9 (IQR 23.7–29.6) x 24.4 (IQR 18.6–29.8)

Table 3. Demographics characteristics of the included patients

Autor, year	Clinical characteristics	Baseline HE grade 0/1/2/3/4*	Previous HE episodes n (%)
Sharma et al.[22]	Overt HE	0/0/27/57/36	51 (42.5)
Fagan et al.[19]	mHE with prior overt HE** episode	48/0/0/0/0	48 (100)
Ventura-Cots et al.[20]	Overt HE***	0/0/61/20/1	53 (64.6)
Simón-Talero et al.[21] 2013	Overt HE***	0/0/46****/10	36 (64.2)

*The severity of HE was graded according to West Haven criteria; **Grade 0; ***Grade 2 or higher; ****Grade 2 and 3.

The clinical and psychosocial burden of HE relies on the patients, the relatives, and the healthcare system.[27,28] In the US, there are no other FDA-approved therapies other than lactulose and rifaximin for this condition. (2) The idea in conducting this meta-analysis is based on the theory that HE can be caused by a sum of ammonia accumulation, inflammation, oxidative stress, and endothelial damage. In this context, it is hypothesized that albumin can act as a mediator of the inflammatory response and endothelial dysfunction in HE.[22,29]

HE refers to the broad spectrum of neuropsychiatric disturbances associated with acute or chronic liver failure, as well as portosystemic

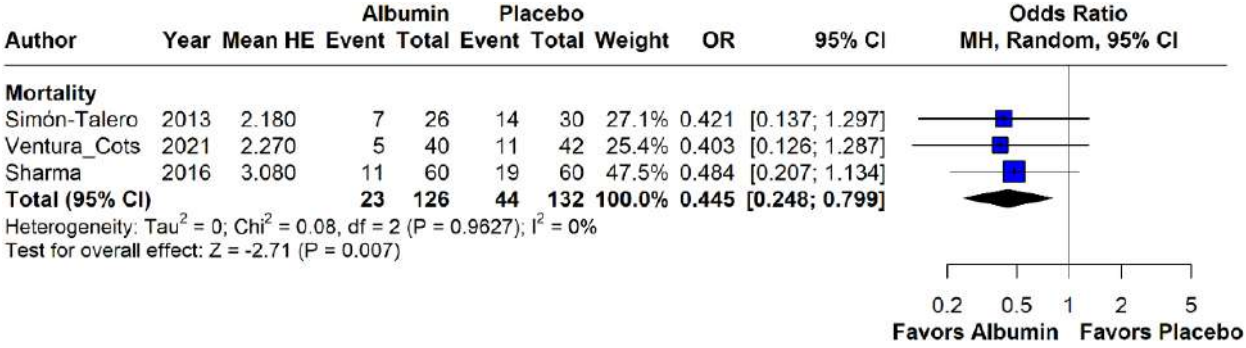

Figure 2. Forest plot of mortality. Significant difference favoring albumin use (OR 0.44; 95% CI 0.24 to 0.79; p=0.007; I^2=0%) in mortality. Mean HE refers to the weighted average of baseline HE grades among patients included in each study.

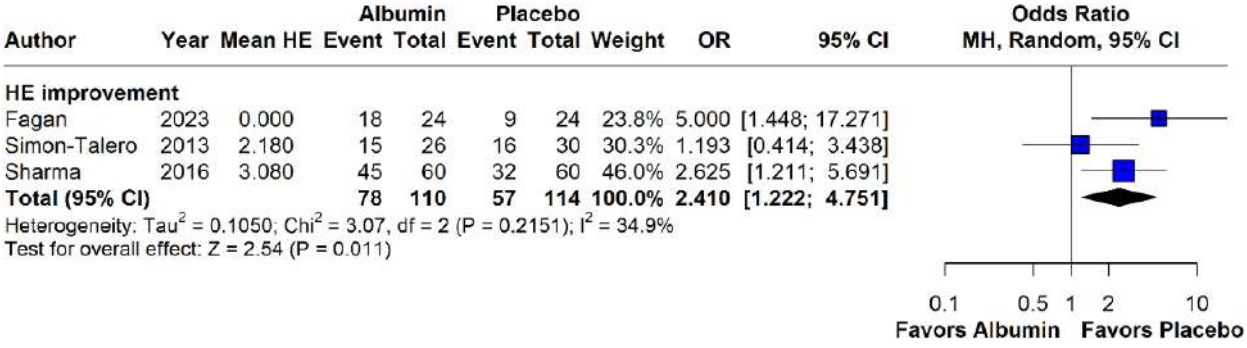

Figure 3. Forest pot of HE improvement. Significant difference favoring albumin use (OR 2.41; 95% CI 1.22 to 4.75, p=0.011; I^2=34.9%; Figure 3) in clinical improvement rate of HE. Mean HE refers to the weighted average of baseline HE grades among patients included in each study.

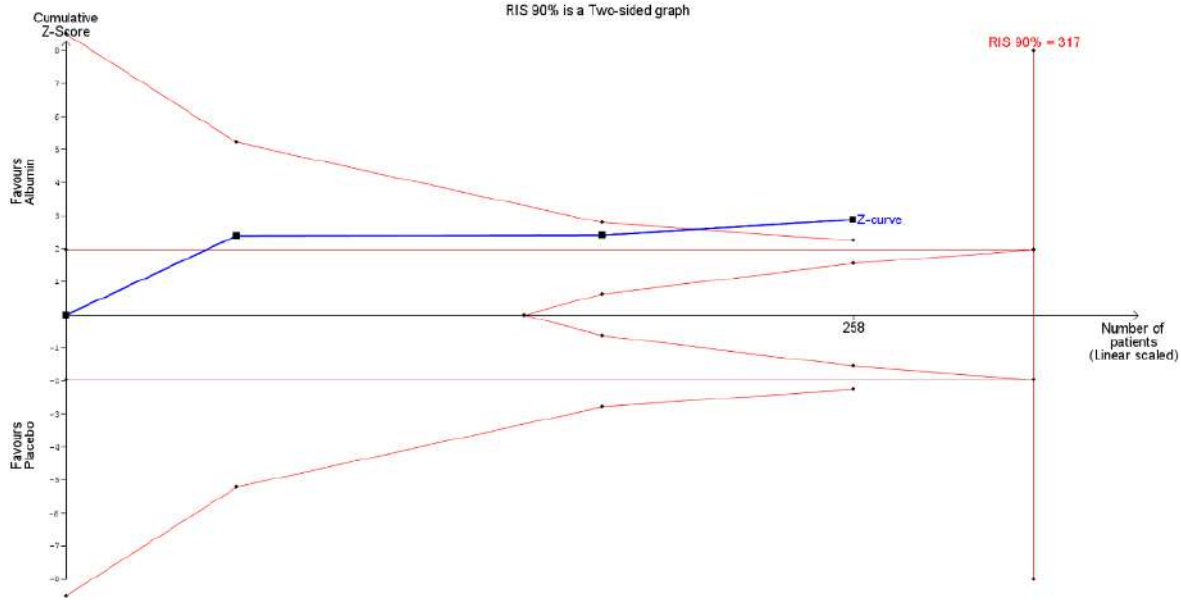

Figure 4. TSA of mortality. The cumulative z-line crossed the boundary for effect, but did not reach the required sample size.

shunting, in the absence of underlying hepatocellular disease. The pathophysiology of HE remains incompletely elucidated but is recognized as multifactorial. Nevertheless, hyperammonemia is a well-documented contributor to its development. This condition results from hepatic dysfunction and the consequent impairment of ammonia metabolism, leading to its accumulation in the bloodstream. The excess ammonia is absorbed by astrocytes in the brain, where it is converted into glutamine, leading to osmotic stress, astrocyte swelling, and subsequent brain dysfunction.[30] Despite its significant role in the development of HE, discrepancies exist in the literature regarding the direct correlation between ammonia levels and the severity of HE in patients with cirrhosis. This has contributed to the general consensus that hyperammonemia is unlikely to be the only determinant of the neurocognitive sequelae, with other contributing factors involved.

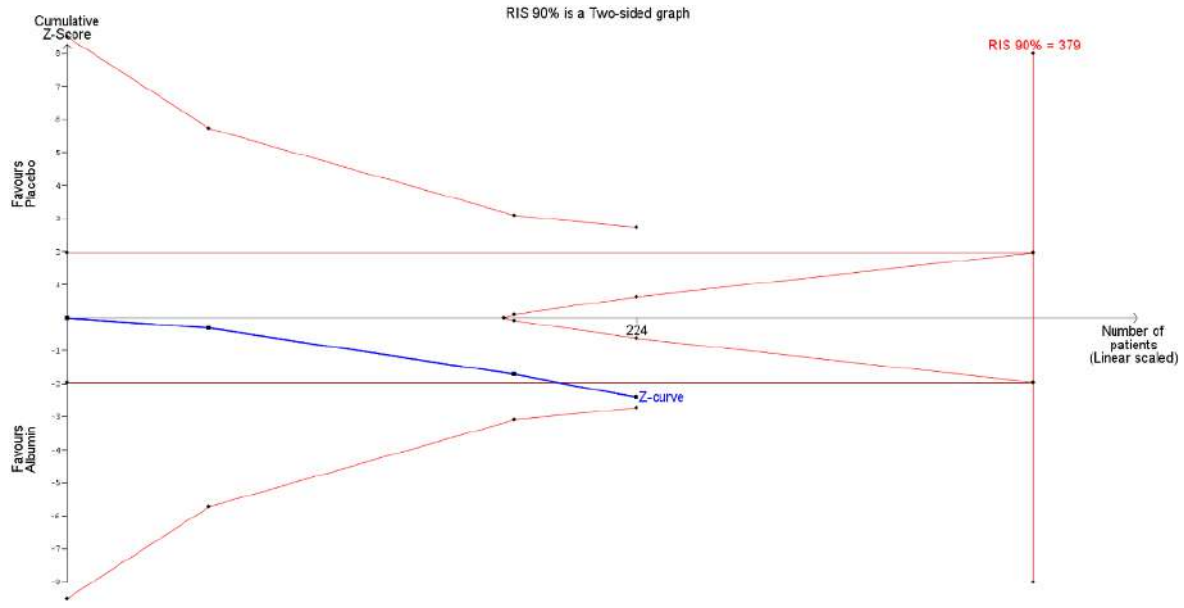

Figure 5. TSA of HE improvement. The cumulative z-line lies in the zone with no statistical significance.

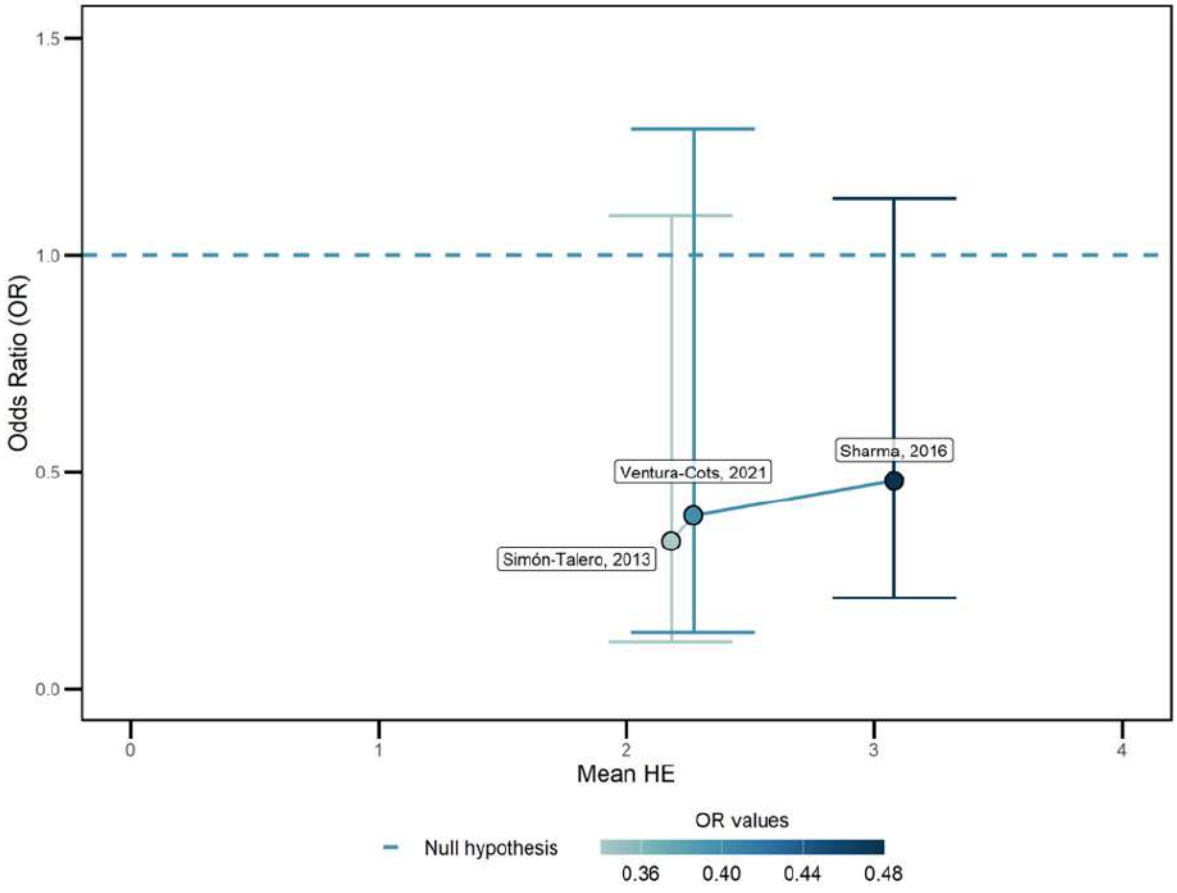

Figure 6. Difference in mortality between groups vs baseline HE. Scatter plot for the difference in mortality between groups versus baseline HE with CI and null hypothesis.

Current treatments for oHE are focused on reducing ammonia production and/or enhancing its elimination, as well as promptly correcting precipitating factors. However, there are no interventions specifically targeting the other contributing factors.[31] In this context, albumin becomes a particularly interesting option due to its effects in modulating systemic inflammation. It is known that albumin has antioxidant ef-

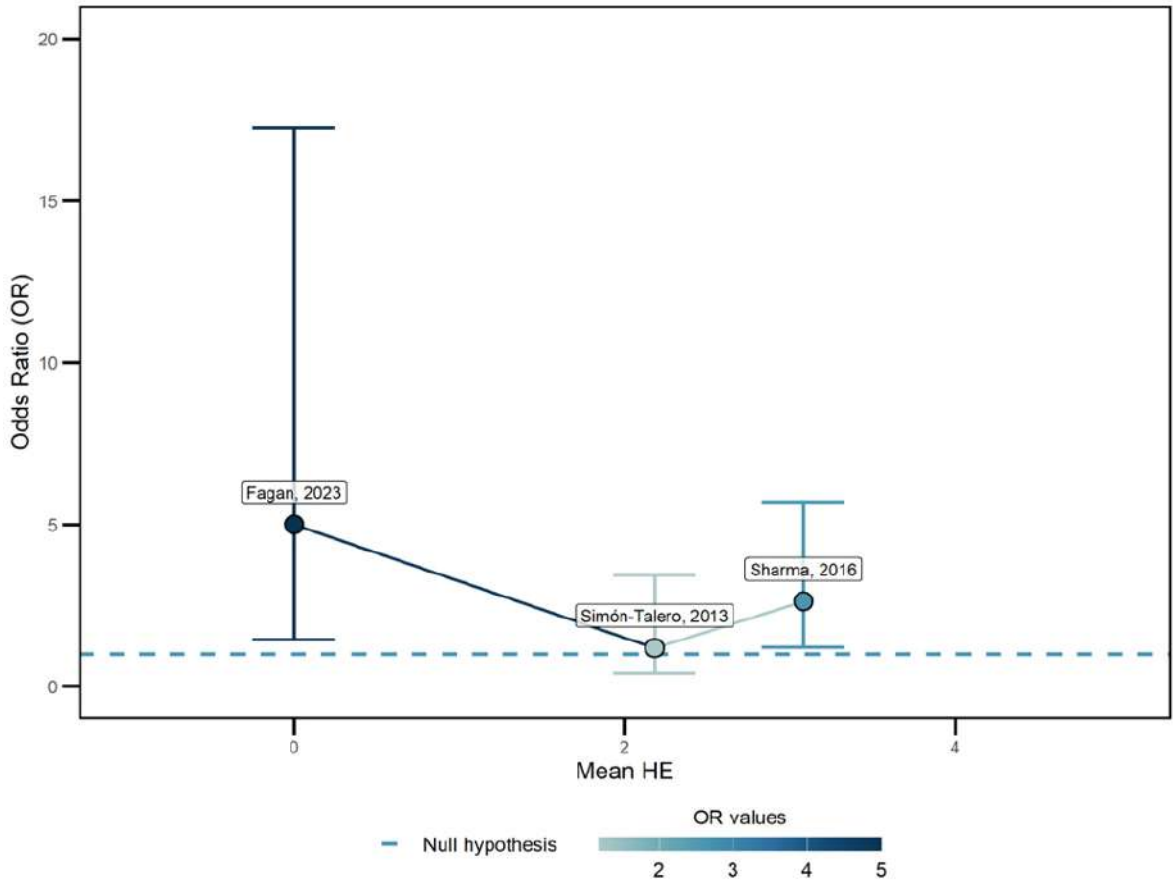

Figure 7. Difference in HE improvement between groups vs baseline HE. Scatter plot for the difference in HE improvement between groups versus baseline HE with CI and null hypothesis.

fects, due to its ability to bind free metals and capture free radicals, and bilirubin bound to albumin inhibits lipid peroxidation, representing an indirect antioxidant effect.[29]

Additionally, a notable characteristic of albumin is its ability to bind to pro-inflammatory substances and mediators of inflammation, thereby attenuating endothelial dysfunction and vasodilation.[22] Furthermore, systemic inflammation not only leads to circulatory dysfunction, which reduces cerebral perfusion[32], but also enhances the inhibitory effect of ammonia on brain function.[5] Therefore, considering the potential impact of systemic inflammation on the decompensation of cirrhosis in the presence of HE, as well as albumin's role in modulating innate immune responses and oxidative stress, it is plausible to propose that some of albumin's effects may be related to these underlying mechanisms.

This meta-analysis found no significant differences in ammonia levels or liver transplantation rates, challenging the mechanistic rationale for albumin's benefits linked to hyperammonemia pathophysiology. Furthermore, in the study by Fagan et al.[19], there was no significant change in liver disease severity or venous ammonia levels between or within groups; however, improvements were observed in systemic inflammation and endothelial dysfunction. This may account for the greater improvement in the Portosystemic Hepatic Encephalopathy Scores (PHES), which are associated with inflammation, as opposed to critical flicker frequency (CFF), a neurophysiological test that may be more closely linked to ammonia levels.[19] Simón-Talero et al.[21] investigated oHE and found no correlation between increased survival and inflammatory markers or ammonia levels, leaving an unresolved question regarding the mechanism by which albumin might reduce mortality.[21] Sharma et al.[22] examined the combined use of lactulose and albumin in oHE patients and observed a greater reduction in inflammatory markers (such as cytokines), although ammonia levels decreased equally in both treatment groups. In contrast, Ventura et al.[20] studied oHE and was unable to demonstrate a reduction in mortality and did not assess systemic inflammation.

Some non-randomized studies also reported similar results. Jalan et al.[4] evaluated patients with HE receiving albumin or not and demonstrated that the severity of HE was significantly improved in the albumin group. The single-center retrospective study by Bai et al.[24] demonstrated that albumin infusion was linked to a decreased incidence and improvement of oHE, potentially correlating with reduced in-hospital mortality among cirrhotic patients, regardless of oHE status. Furthermore, long-term albumin administration demonstrated prolonged overall survival and acted as a disease-modifying treatment for HE in the open-label RCT by Caraceni et al.[7] Additionally, it improved survival and reduced emergent hospitalizations in the non-randomized prospective study conducted by Di Pascoli et al.[6]

In terms of severity, HE is classified as covert or mHE, characterized by minor or no symptoms but with abnormalities on neuropsychological and/or neurophysiological tests, or oHE, which is defined as grades II or higher according to the West Haven criteria.[33] This study included three studies focused on populations with oHE, while one study in-

volved patients with mHE and a prior oHE event classified as grade zero. This characteristic was detailed in Table 3, which highlights the heterogeneity in patient populations across the included studies, with varying distributions of baseline HE grades and differing proportions of patients with previous HE episodes. This variability may introduce bias and influence the interpretation of outcomes.

Despite this study having a population predominantly based on oHE, mHE has been described as a condition present in up to 80% of individuals with stable cirrhosis, which predisposes them to the development of oHE.[34,35] Even after maximal treatment of symptoms of HE, most patients had not fully restored their cognitive function and remained with mHE, which is defined as a condition where patients with cirrhosis have a normal neurological examination but exhibit measurable cognitive impairments.[19] The diagnosis of mHE is currently based on abnormalities in neurophysiological, neuropsychological, or psychophysical tests.[2] It is already recognized that this subset of patients has an increase in mortality due to future HE.[35] The study by Fagan et al.[19] showed that albumin promotes the reversal of mHE, which can be another clinical benefit of albumin use in patients in this context.

Limitations

The study has limitations. First, there are only four RCTs evaluating the use of albumin in the HE population, with a pooled small sample size, which may compromise the reliability of the results. A TSA was conducted to estimate the required sample size while balancing type I error. This analysis indicated that the required sample size was not achieved, highlighting the need for future multicenter trials with larger cohorts to validate the reduction in mortality and improve statistical power. Second, one of the studies was not blinded, increasing the risk of publication bias and potentially affecting the generalizability of the findings. Finally, the populations of the included studies vary in terms of HE severity, as shown in Table 3. This variability may have influenced the results, underscoring the importance of evaluating each subgroup to determine the true effect of the treatment in specific populations.

Scatter plots (Fig. 6, 7, and Appendix Fig. 6–8) were employed to assess the impact of baseline HE on the respective outcomes: mortality, HE improvement, ammonia levels, liver transplantation, and AEs. The analysis revealed no clear evidence that baseline HE significantly influenced these outcomes. The scatter plots highlighted the heterogeneity across the studies, and no definitive conclusions could be drawn. Furthermore, a subgroup analysis was performed for the two outcomes that included studies with both oHE and mHE populations: HE improvement and ammonia levels, neither of which showed statistical significance (Appendix Fig. 4, 5). Further research with larger sample sizes and standardized methodologies is essential to better understand the effect of baseline HE on patient outcomes.

However, our study also has strengths, such as the inclusion of only RCTs, which reduces the bias of selection, and the TSA, which helps to balance type I and II errors and determines when the pooled effect is strong enough to be unlikely to be changed by more studies.

Conclusion

This meta-analysis showed that albumin infusion should be considered in the treatment of HE, as its use resulted in better clinical improvement and lower mortality rates. However, as indicated by the TSA, new RCTs with larger sample sizes, multi-center designs, and greater diversity in patient populations are necessary to reach a definitive conclusion on this topic. Future studies should aim to identify the specific HE populations that would benefit the most from this treatment, delineating subgroups for oHE and mHE, as well as addressing specific patient comorbidities.

Online Appendix Link:
https://hepatologyforum.org/storage/upload/files/1761307426-appendix-en.pdf

Ethics Committee Approval: Not applicable. This study did not involve human participants, animal subjects, or any data requiring ethical approval.

Conflict of Interest: All authors report no relationships that could be construed as a conflict of interest. and take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Financial Disclosure: Not applicable. This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Use of AI for Writing Assistance: All data generated or analysed during this study are included in this published article [and its supplementary information files]. The authors confirm that no artificial intelligence (AI)–assisted technologies, such as Large Language Models (LLMs), chatbots, or image creators, were used in the production of this work.

Author Contributions: Concept – ACC, VALJ, AAP, NJM, TLC, OCM, PR, ESBJ, AMR, MVF; Design – ACC, VALJ, AAP, NJM, TLC, OCM, PR, ESBJ, AMR, MVF; Supervision – ACC, VALJ, AAP, NJM, TLC, OCM, PR, ESBJ, AMR, MVF; Data Collection and/or Processing – ACC, VALJ, AAP, NJM, TLC, OCM, PR, ESBJ, AMR, MVF; Analysis and/or Interpretation – ACC, VALJ, AAP, TLC, MVF; Literature Review – ACC, VALJ, AAP, NJM, TLC, OCM, PR, ESBJ, AMR, MVF; Writing – ACC, MVF; Critical Review – ACC, VALJ, AAP, NJM, TLC, OCM, PR, ESBJ, AMR, MVF.

Peer-review: Externally peer-reviewed.

References

1. Bajaj JS, Wade JB, Sanyal AJ. Spectrum of neurocognitive impairment in cirrhosis: Implications for the assessment of hepatic encephalopathy. Hepatology 2009;50(6):2014-2021. [CrossRef]
2. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. J Hepatol 2014;61(3):642-659. [CrossRef]
3. Mandiga P, Kommu S, Bollu PC. Hepatic Encephalopathy. 2025 Jan 20. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025 Jan.
4. Jalan R, Kapoor D. Reversal of diuretic-induced hepatic encephalopathy with infusion of albumin but not colloid. Clin Sci (Lond) 2004;106(5):467-474. [CrossRef]
5. 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]
6. Di Pascoli M, Fasolato S, Piano S, Bolognesi M, Angeli P. Long-term administration of human albumin improves survival in patients with cirrhosis and refractory ascites. Liver Int 2019;39(1):98-105. [CrossRef]
7. Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, et al. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet 2018;391(10138):2417-2429.
8. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available at: www.training.cochrane.org/handbook Accessed on Oct 23, 2025.
9. 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]

10. PROSPERO. PROSPERO. York.ac.uk. 2019. Available at: https://www.crd.york.ac.uk/PROSPERO/ Accessed on Oct 23, 2025.
11. Rayyan OM. AI and the evolution of journalistic practices. J Inform Stud Technol 2025;2025:15. [CrossRef]
12. Shi J, Luo D, Wan X, Liu Y, Liu J, Bian Z, et al. Detecting the skewness of data from the five-number summary and its application in meta-analysis. Stat Methods Med Res 2023;32(7):1338-1360. [CrossRef]
13. Shi J, Luo D, Weng H, Zeng XT, Lin L, Chu H, et al. Optimally estimating the sample standard deviation from the five-number summary. Res Synth Methods 2020;11(5):641-654. [CrossRef]
14. Luo D, Wan X, Liu J, Tong T. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res 2018;27(6):1785-1805. [CrossRef]
15. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135. [CrossRef]
16. Chai-Adisaksopha C, Thorlund K, Iorio A. Interpreting trial sequential analysis. Transfusion 2016;56(12):2918-2922. [CrossRef]
17. De Cassai A, Tassone M, Geraldini F, Sergi M, Sella N, Boscolo A, et al. Explanation of trial sequential analysis: using a post-hoc analysis of meta-analyses published in Korean Journal of Anesthesiology. Korean J Anesthesiol 2021;74(5):383-393. [CrossRef]
18. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. [CrossRef]
19. Fagan A, Gavis EA, Gallagher ML, Mousel T, Davis B, Puri P, et al. A double-blind randomized placebo-controlled trial of albumin in outpatients with hepatic encephalopathy: HEAL study. J Hepatol 2023;78(2):312-321. [CrossRef]
20. Ventura-Cots M, Simón-Talero M, Poca M, Ariza X, Masnou H, Sanchez J, et al. Effects of albumin on survival after a hepatic encephalopathy episode: Randomized double-blind trial and meta-analysis. J Clin Med 2021;10(21):4885. [CrossRef]
21. Simón-Talero M, García-Martínez R, Torrens M, Augustin S, Gómez S, Pereira G, et al. Effects of intravenous albumin in patients with cirrhosis and episodic hepatic encephalopathy: a randomized double-blind study. J Hepatol 2013;59(6):1184-1192. [CrossRef]
22. Sharma BC, Singh J, Srivastava S, Sangam A, Mantri AK, Trehanpati N, et al. Randomized controlled trial comparing lactulose plus albumin versus lactulose alone for treatment of hepatic encephalopathy. J Gastroenterol Hepatol 2017;32(6):1234-1239. [CrossRef]
23. Is B, Bombassaro IZ, Tovo CV, de Mattos ÂZ, Ahlert M, Chiesa T, de Mattos AA. Albumin in the management of hepatic encephalopathy: A systematic review and meta-analysis. Ann Hepatol 2021;26:100541. [CrossRef]
24. Bai Z, Bernardi M, Yoshida EM, Li H, Guo X, Méndez-Sánchez N, et al. Albumin infusion may decrease the incidence and severity of overt hepatic encephalopathy in liver cirrhosis. Aging (Albany NY) 2019;11(19):8502-8525. [CrossRef]
25. Bai Z, Wang L, Wang R, Zou M, Méndez-Sánchez N, Romeiro FG, et al. Use of human albumin infusion in cirrhotic patients: a systematic review and meta-analysis of randomized controlled trials. Hepatol Int 2022;16(6):1468-1483. [CrossRef]
26. Bai Z, Méndez-Sánchez N, Romeiro FG, Mancuso A, Philips CA, Tacke F, et al; Liver Cirrhosis-related Complications (LCC)-International Special Interest Group. Use of albumin infusion for cirrhosis-related complications: An international position statement. JHEP Rep 2023;5(8):100785. [CrossRef]
27. Ufere NN, Satapathy N, Philpotts L, Lai JC, Serper M. Financial burden in adults with chronic liver disease: A scoping review. Liver Transpl 2022;28(12):1920-1935. [CrossRef]
28. Bajaj JS, Riggio O, Allampati S, Prakash R, Gioia S, Onori E, et al. Cognitive dysfunction is associated with poor socioeconomic status in patients with cirrhosis: an international multicenter study. Clin Gastroenterol Hepatol 2013;11(11):1511-1516. [CrossRef]
29. Arroyo V, García-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. J Hepatol 2014;61(2):396-407. [CrossRef]
30. Aldridge DR, Tranah EJ, Shawcross DL. Pathogenesis of hepatic encephalopathy: role of ammonia and systemic inflammation. J Clin Exp Hepatol 2015;5(Suppl 1):S7-20. [CrossRef]
31. Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60(2):715-735. [CrossRef]
32. Guevara M, Bru C, Ginès P, Fernández-Esparrach G, Sort P, Bataller R, et al. Increased cerebrovascular resistance in cirrhotic patients with ascites. Hepatology. 1998;28(1):39-44. [CrossRef]
33. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002;35(3):716-721. [CrossRef]
34. Romero-Gómez M, Boza F, García-Valdecasas MS, García E, Aguilar-Reina J. Subclinical hepatic encephalopathy predicts the development of overt hepatic encephalopathy. Am J Gastroenterol 2001;96(9):2718-27123. [CrossRef]
35. Tapper EB. Predicting overt hepatic encephalopathy for the population with cirrhosis. Hepatology 2019;70(1):403-409. [CrossRef]

Research Article

HEPATOLOGY FORUM

Hepatosteatosis and HBV seroclearance

doi: 10.14744/hf.2025.74529

Hepatic steatosis is associated with HBsAg seroclearance in patients with chronic hepatitis B virus infection but it is also associated with disease progression

Emin Bodakci[1], Saba Kiremitci[2], Zeynep Melekoglu Ellik[3], Ozge Koc[3], Mesut Gumussoy[3], Volkan Yilmaz[3], Hale Gokcan[3], Atilla Halil Erhan[4], Sevinc Tugce Guvenir[5], Ramazan Erdem Er[3], Berna Savas[2], Ramazan Idilman[3]

[1]Department of Gastroenterology, Gaziantep City Hospital, Gaziantep, Turkiye; [2]Department of Pathology, Ankara University School of Medicine, Ankara, Turkiye; [3]Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkiye; [4]Department of Biostatistics, Ankara University School of Medicine, Ankara, Turkiye; [5]Department of Gastroenterology, Batman Training and Research Hospital, Batman, Turkiye

Abstract

Background and Aim: The present study aimed to determine the effect of hepatic steatosis, as detected by liver biopsy, on Hepatitis B surface antigen (HbsAg) seroclearance and disease progression in patients infected with hepatitis B virus (HBV).

Materials and Methods: Patients with chronic HBV infection and chronic hepatitis B (CHB) from an existing cohort of HBV-infected patients were enrolled.

Results: This study included 296 patients: 186 with chronic HBV infection and 110 with CHB. Patients with chronic HBV infection were older (p=0.006), and exhibited a higher prevalence of wild-type mutants (p<0.001). At the baseline liver biopsy, 31% of the patients had hepatosteatosis. Thirty-two patients (11%) achieved HBsAg loss during the follow-up period; 72% had HBsAg seroconversion to anti-HBs. Multivariable Cox regression showed that the stage of HBV disease (chronic HBV infection vs. CHB) (Hazard ratio [HR]: 6.385, Confidence interval [CI]: 1.513–26.941, p=0.012) and grading of hepatosteatosis at baseline liver biopsy (HR: 4.699, CI: 1.662–13.286, p=0.004) were predictors of HBsAg seroclearance.

Conclusion: Hepatic steatosis was associated with a functional cure for chronic HBV infection; however, it also causes disease progression in HBV-infected patients.

Keywords: Hepatitis B virus; hepatosteatosis; HBsAg Seroclearance; metabolic dysfunction-associated steatotic liver disease.

How to cite this article: Bodakci E, Kiremitci S, Melekoglu Ellik Z, Koc O, Gumussoy M, Yilmaz V, et al. Hepatic steatosis is associated with HBsAg seroclearance in patients with chronic hepatitis B virus infection but it is also associated with disease progression. Hepatology Forum 2026; 7(1):14–20.

Received: July 10, 2025; **Revised:** August 22, 2025; **Accepted:** September 05, 2025; **Available online:** October 06, 2025

Corresponding author: Emin Bodakci; Gaziantep Sehir Hastanesi, Gastroenteroloji Klinigi, Gaziantep, Turkiye
Phone: +90 536 669 45 29; **e-mail:** doktor.emin.0903@hotmail.com

Hepatology Forum - Available online at www.hepatologyforum.org

Introduction

Hepatitis B virus (HBV) infection is a major global public health concern, affecting over 250 million individuals.[1,2] HBV accounts for most adult cases of chronic liver disease (CLD), cirrhosis, and hepatocellular carcinoma (HCC) in Turkiye.[3–5] However, its proportion has decreased over time. An epidemiological study conducted in 2009 found that the prevalence of Hepatitis B surface antigen (HBsAg) was approximately 4%, and one in three individuals over the age of 18 years has experienced HBV. This study estimated that more than 2 million adults were HBsAg-positive in Turkiye.[6] The incidence of acute HBV infection in Turkiye has decreased significantly due to a successful HBV vaccination program initiated in 1992, as well as the implementation of a Viral Hepatitis Control and Prevention program in 2018.

Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as a public concern. MASLD affects an estimated 38% of adults around the world, causing considerable hepatic and extrahepatic morbidity and mortality.[7–9] The prevalence of MASLD is rising worldwide in parallel with obesity, diabetes, and metabolic disorders, showing a 50% increase from 1990 to 2006.[7] MASLD has become the most prevalent chronic liver disease, and the proportion of MASLD-related cirrhosis among patients on liver transplantation waiting lists has increased over the last three decades.[10–12] The frequency of MASLD ranged from 48% to 60% based on screening studies in Turkiye, placing the country among those with the highest prevalence of MASLD globally.[13] The prevalence of hepatic steatosis in patients with HBV infection is similar to that of the general population.[14,15] A recent meta-analysis of 54 studies found the prevalence of hepatic steatosis in patients with chronic hepatitis B (CHB) to be 32.8%.[16] Both chronic HBV infection and MASLD are common conditions. These two conditions are common types of chronic liver disease, and both can cause cirrhosis and its complications, and HCC. Therefore, it is of great importance to investigate the relationship between hepatic steatosis and chronic HBV infection.

HBsAg seroclearance can occur spontaneously in individuals with chronic HBV infections, ranging from 0.1% to 2.4%, with a nonlinear trend increasing over time.[17] HBsAg seroclearance is associated with sustained immune control of HBV and better clinical outcomes, including a lower risk of disease progression, decompensated cirrhosis, and liver-related death.[17,18] Several factors, including age, gender, serum HBsAg and HBV DNA levels, HBeAg status, disease stage, and antiviral therapy, affect HBsAg seroclearance.[17,18] The ideal goal of

Table 1. Characteristics of 296 HBV-infected patients at baseline

	Overall (n=296)	Patients with chronic HBV infection (n=186)	Patients with CHB (n=110)	p
Age (years)	54.6±12.1; 56.9 (24–81)	56.1±11.2; 58.6 (24–80)	53.2±12.7; 53.6 (24–81)	0.006
Gender (%) (male/female)	143/153	82/104	61/ 49	0.071
BMI (kg/m^2)	28.0±4.7; 27.7 (17–54)	28.2±5.1; 27.7 (17–54)	27.5±4.2; 27.7 (17–38)	0.797
Diabetes mellitus (%)	8.5	7.0	11.0	0.282
Hypertension (%)	34.4	39.6	22.7	0.019
HBeAg positive (%)	8.4	3.2	17.3	<0.001
Serum AST (U/L)	32.5±30.3; 24 (8–296)	25.0±12.7; 22 (8–94)	49.4±49.9; 33 (14–296)	<0.001
Serum ALT (U/L)	44.6±56.5; 27 (8–499)	28.9±26.7; 21 (5–192)	69.9±69.7; 46 (8–499)	<0.001
Serum GGT (U/L)	28.0±42.9; 19 (6–560)	22.2±17.6; 17 (6–560)	34.1±47.2; 21 (6–372)	0.002
Fasting glucose (mg/dL)	91.8±28.0; 86 (53–434)	89.1±12.7; 86 (66–156)	94.1±43.5; 86 (53–434)	0.777
Triglycerides (mg/dL)	123.1±62.6; 106 (39–409)	129.1±72.8; 113 (39–409)	117.8±58.6; 103 (48–311)	0.063
Total cholesterol (mg/dL)	186.8±39.5; 185 (66–287)	187.0±40.5; 184 (66–287)	184.0±35.2; 182 (111–256)	0.111
LDL (mg/dL)	115.6±31.8; 111.5 (30–224)	115.8±32.3; 110 (30–224)	113.6±28.2; 108 (62–197)	0.307
HDL (mg/dL)	46.1±13.1; 43(25–126)	45.4±11.8; 43 (25–90)	47.2±14.9; 44 (29–126)	0.885
VLDL (mg/dL)	24.5±12.5; 21 (8–80)	25.3±13.5; 22.2 (8–80)	24.2±13.0; 20.0 (10–73)	0.151
Total bilirubin (mg/dL)	0.8±0.5; 0.7 (0.1–4.8)	0.8±0.3; 0.7 (0.2–1.9)	0.8±0.7; 0.6 (0.1–4.8)	0.354
Albumin (g/L)	43.3±5.6; 44 (28–62)	44.3±3.3; 44 (35–54)	41.2±8.2; 42 (28–62)	<0.001
Platelet count (10^3/µL)	246±64.5; 235.5 (67–498)	242±57.2; 234 (67–399)	244±67.6; 233 (100–498)	0.847
INR	1.0±0.1; 1.0 (0.6–1.4)	1.0±0.1; 1 (0.6–1.4)	1.0±0.1; 1.0 (0.9–1.3)	0.05
FIB-4 score	1.29±1.28; 1.05 (0.6)	1.25±1.1; 1.0 (0.3–11.5)	1.36±1.6; 1.1 (0.3–15.2)	
Follow-up (months)	121.1±67.8; 137 (126.7)	126.4±71.2; 146	112.2±60.9; 122	0.008

HBV: Hepatitis B virus; CHB: Chronic hepatitis B; BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; VLDL: Very low-density lipoprotein; INR: International normalised ratio. Mean±standard deviation, median (interquartile range).

antiviral treatment against HBV is the loss of HBsAg in serum. Unfortunately, with current oral antiviral treatment, HBsAg seroclearance rarely occurs after long-term therapy.[17] Data regarding the effect of hepatic steatosis on HBsAg seroclearance in patients with HBV infection are limited. Previous studies have reported that hepatic steatosis is associated with a higher rate of HBsAg seroclearance in chronic HBV infection.[19–22] However, most previous studies have relied on imaging methods to identify hepatic steatosis in HBV-infected patients. The aims of the present study were to determine the effect of hepatic steatosis, as detected by liver biopsy, on HBsAg seroclearance rates in patients with chronic HBV infection during long-term follow-up and to investigate whether the presence of hepatic steatosis is associated with disease progression in such patients.

Materials and Methods

Patients

This is a single-center, cross-sectional study. A total of 296 patients with chronic HBV infection and CHB from an existing cohort of HBV-infected patients who were seen at the Liver Diseases Outpatient Clinic were enrolled in the study. Chronic HBV infection was diagnosed based on the EASL guideline.[17] ICD-10 codes were used to identify patients with HBV infection. All patients with CHB received potent oral antiviral therapy at the physician's discretion. Data were collected from outpatient visit charts. This study was approved by the local ethical committee of Ankara University School of Medicine (2021/260). Our article was written in accordance with the Helsinki declaration.

Methods

Serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, and complete blood cell counts were measured by our central laboratory. Serological markers for viral infections (anti-HAV IgM, HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc IgG, anti-HCV, anti-HEV, anti-cytomegalovirus [CMV], anti-herpes simplex virus [HSV], and anti-Epstein-Barr virus [EBV]) were performed. Serum HBV DNA levels were determined using the Cobas Taqman assay (Roche Diagnostics, Branchburg, NJ, USA) with a lower detection limit of 20 IU/mL.

Table 2. The association between hepatosteatosis and HBsAg seroclearance

Grade of hepatosteatosis	Patients with chronic HBV infection (n=186)	Patients with CHB (n=110)	p	HBsAg seroclearance
No hepatosteatosis, <5%	69.9% (n=130)	66.4% (n=73)	0.816	6.4%
Grade 1, 5–33%	24.2% (n=45)	40.0% (n=30)		18.7%
Grade 2 and 3, >33%	5.9% (n=11)	6.4% (n=7)		27.8%

HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; CHB: Chronic hepatitis B. 0=<5%; Grade 1 =5-33%; Grade 2 =33–66%; Grade 3 =>66%.

Histological Evaluation

Two pathologists (B.S., S.K.), blinded to the clinical and biochemical data, re-evaluated all liver biopsy specimens. The histological features of the samples were interpreted using the Ishak scoring system.[23] Accordingly, fibrosis was evaluated on a scale of 0–6, ranging from no fibrosis (score 0), to fibrosis beginning in portal areas (score 1), periportal fibrosis (score 2), porto-portal fibrosis (score 3), porto-central fibrosis (score 4), marked bridging fibrosis with occasional nodules (score 5), and progression to cirrhosis (score 6). Hepatocellular steatosis was graded on a scale of 0–3 based on the percentage of hepatocytes: 0=<5%, Grade 1=5%–33%, Grade 2= 33%–66%, and Grade 3=>66%.[24]

Definitions

HBsAg seroclearance was defined as the loss of detectable HBsAg for at least six months, with or without seroconversion to anti-HBs. The primary endpoint of the study was to investigate the effect of hepatic steatosis on HBsAg seroclearance in patients with chronic HBV infection.

The secondary endpoint aimed to determine the impact of hepatic steatosis on the disease outcome in such patients.

Follow-up

During the follow-up period, patients were regularly seen in an outpatient clinic. Laboratory tests were performed during this period. HBV markers and HBV DNA levels were serially monitored every three or six months.

Hepatic steatosis and liver stiffness were measured at the end of the follow-up period using a FibroScan probe (Echosens, Paris, France) with either an M or XL probe, which catered to patients with different body build types. Patients were examined after fasting overnight. The FibroScan probe was placed in the appropriate intercostal space window on the anterior axillary line. At least ten valid measurements were obtained within 5–10 minutes. The median ratio of 10 successive measurements to the interquartile range (IQR) was less than 30%. TE simultaneously measured the CAP (dB/m) and liver stiffness (kPa). Steatosis was classified as follows: none (CAP <248 dB/m), mild (CAP 248–267 dB/m), moderate (CAP 268–279 dB/m), and severe (≥280 dB/m).[25]

Statistical Analysis

Descriptive statistics are summarized as count and percentage for categorical variables, mean and standard deviations for normally distributed continuous variables, and median and interquartile range for ordinal and non-normally distributed continuous variables. The differences in proportions between groups were compared using the Chi-square or Fisher's Exact tests, where appropriate. The Mann-Whitney U test compared two groups regarding ordinal or non-normally distributed continuous variables. The Wilcoxon signed-rank test evaluated the difference between baseline and follow-up biopsies. The survival estimations were conducted using the Kaplan-Meier method, with group comparisons made using the Log-rank test. Cox proportional hazards regression was employed for both univariable and multivariable analysis. Variables with a p-value less than 0.25 in the univariable analysis and clinically important variables were included in the multivariable model using a purposeful selection approach. A p-value less than 0.05 was considered significant.

Results

This study included 296 HBV-infected patients: 186 with chronic HBV infection and 110 with CHB. At diagnosis, 92% of them were HBeAg negative. The median age of the patients was 56.9 years, with a predominantly female gender composition (52%). The median serum AST, ALT, and GGT levels were 24 U/L, 27 U/L, and 19 U/L, respectively. Nine percent of the patients had diabetes mellitus, and 34% had hypertension. The median glucose, triglyceride, cholesterol, and low-density lipoprotein (LDL) levels were 86 mg/dL, 106 mg/dL, 185 mg/dL, and 112 mg/dL (Table 1). Patients with chronic HBV infection were older (p=0.006), had a greater incidence of hypertension (p=0.019), exhibited a higher prevalence of wild-type mutants (p<0.001), and had lower baseline serum AST (p<0.001), ALT (p<0.001), and GGT levels (p=0.002) compared to patients with CHB (Table 1).

At the baseline liver biopsy, 93 (31.4%) patients had hepatosteatosis: 81% had mild, and the remaining 19% had moderate/severe hepatosteatosis. No significant difference in hepatosteatosis was observed between patients with chronic HBV infection and those with CHB (30.1% vs. 33.6%, p=0.399) (Table 2). The median follow-up period was 137.4 months (IQR=126.7).

Thirty-two patients (11%) achieved HBsAg loss during the follow-up period; 23 (72%) had HBsAg seroconversion to anti-HBs. Thirty patients had chronic HBV infection, while only two had CHB (16.1% vs. 1.8%, p<0.001). Patients with HBsAg seroclearance were older (p=0.001), had higher BMIs (p = 0.023), and had lower baseline serum ALT levels (p=0.022) compared to patients without HBsAg seroclearance. The characteristics of HBV-infected patients with and without HBsAg seroclearance are exhibited in Table 3.

HBsAg seroclearance commonly occurred in patients with hepatosteatosis compared to patients without hepatosteatosis (19/93, 20.4% vs. 13/203, 6.4%; p=0.001) (Table 2). The grade of hepatosteatosis at baseline liver biopsy affected HBsAg loss (Table 2). Multivariable Cox regression indicated that the phase of HBV infection-related disease (chronic HBV infection vs. CHB) (Hazard Ratio [HR]: 6.385, Confidence Interval [CI]: 1.513–26.941, p=0.012) and the grading of hepatosteatosis (HR: 4.699, CI: 1.662–13.286, p=0.004) were significantly associated with HBsAg seroclearance in HBV-infected patients

Table 3. Baseline characteristics of HBV-infected patients with and without HBsAg seroclearance

	Patients with HBsAg loss (n=32)	Patients without HBsAg loss (n=264)	p
Age (years)	61.1±8.2; 61.6 (45–76)	54.3±12.0; 56.5 (24–81)	<0.001
Gender (%) (male/female)	16/916	127/137	0.854
BMI (kg/m^2)	30.4±4.7; 30.4 (22–40)	27.6±4.7; 27.6 (17–54)	0.023
Diabetes mellitus (%)	12.5	8.0	0.496
Hypertension (%)	48	32	0.101
HBeAg positive (%)	0	9.5	0.089
Serum AST (U/L)	24.7±10.8; 20 (14–54)	36.0±36.8; 25 (9–296)	0.165
Serum ALT (U/L)	29.3±26.9; 18 (5–107)	47.3±54.6; 27 (10–390)	0.022
Abnormal initial serum AST (>40 U/L) (%)	6.3	19.3	0.086
Abnormal initial serum ALT (>40 U/L) (%)	21.9	31.1	0.316
Serum GGT (U/L)	24.8±12.2; 22 (10–51)	27.3±34.9; 19 (6–372)	0.370
Fasting glucose (mg/dL)	93.4±17.0; 94 (72–138)	90.9±30.4; 86 (53–434)	0.206
Triglycerides (mg/dL)	103.9±49.2; 92 (57–241)	126.6±68.8; 106 (39–409)	0.520
Total cholesterol (mg/dL)	172.6±30.0; 162 (135–222)	187.1±38.9; 185 (66–287)	0.903
LDL (mg/dL)	107.6±27.8; 103 (71–170)	115.6±30.9; 109 (30–224)	0.757
HDL (mg/dL)	43.2±15.2; 38 (26–90)	46.4±12.9; 43 (25–126)	0.233
VLDL (mg/dL)	21.2±9.8; 19 (10–48)	25.2±13.6; 21 (8–80)	0.723
Total bilirubin (mg/dL)	0.6±0.3; 0.6 (0.2–1.5)	0.8±0.5; 0.7 (0.1–4.8)	0.054
Albumin (g/dL)	44.3±2.9; 44 (38–48)	42.9±6.2; 44 (4–62)	0.813
Platelet count (10^3/µL)	242±42; 238 (164–332)	243±63; 233 (67–498)	0.973
INR	1.1±0.1; 1.0 (0.4–1.4)	1.0±0.1; 1.0 (0.6–1.3)	0.980
Follow-up (months)	102.3±65.2; 128 (7–203)	133.8±53.4; 141 (24–2227)	0.013
Chronic HBV infection CHB	30 (16.1%); 2 (1.8%)		<0.001

HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; VLDL: Very low density lipoprotein; INR: International normalised ratio; CHB: Chronic hepatitis B.

(Table 4) (Fig.1a, b). HBsAg seroconversion to anti-HBs more commonly occurred in patients with HBV infection than in patients with CHB (11.3% vs. 1.8%, p = 0.003).

At the end of the follow-up period, the median serum AST, ALT, and GGT levels were 22 U/L, 22 U/L, and 18 U/L, respectively. The median glucose, triglyceride, cholesterol, and LDL levels were 92 mg/dL, 107 mg/dL, 185 mg/dL, and 114 mg/dL, respectively. The mean controlled attenuation parameter (CAP) and liver stiffness values using transient elastography (FibroScan) were 267.3±62.0 dB/m (median, 268 dB/m) and 6.2±2.7 kPa (median, 5.4 kPa), respectively. The mean FIB-4 score was 1.1±0.7 (median, 0.96).

Hepatic steatosis significantly affects disease progression. At the end of the follow-up period, the CAP and liver stiffness measurements detected by VCTE were significantly higher in those with hepatic steatosis compared to patients without hepatic steatosis (p=0.004 and p<0.001, respectively) (Table 5). Fibrosis progression was observed in patients with CHB who achieved virological remission under antiviral therapy. Liver stiffness was significantly increased in CHB patients with hepatic steatosis compared to those without hepatic steatosis (p<0.0001) (Table 5).

Discussion

This is the largest long-term follow-up single-center cohort study investigating the impact of biopsy-proven hepatic steatosis on HBsAg seroclearance and disease outcome in HBV-infected patients. HBsAg seroclearance is considered stable remission and a functional cure in the natural history of HBV infection. Liver biopsy is still the gold standard diagnostic method for diagnosing and assessing hepatic steatosis.[26] This study highlighted that the stage of HBV disease and hepatic steatosis significantly affect HBsAg seroclearance in patients with chronic HBV infection. Moderate and severe hepatosteatosis were more likely associated with HBsAg seroclearance.

Data regarding the mechanism by which hepatic steatosis influences HBsAg seroclearance are not well understood. Previous studies demon-

Table 4. Cox regression analysis revealed factors associated with HBsAg seroclerance

	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	P
Stage of HBV disease CHBV infection vs CHB	6.693	1.590–28.176	0.010	6.385	1.513–26.941	0.012
Age (>50 years)	9.726	1.316–71.871	0.026	7.125	0.985–53.003	0.055
Sex female vs male	1.078	0.533–2.181	0.834			
AST ≥40 U/L	2.709	0.644–11.387	0.174			
ALT ≥40 U/L	1.427	0.610–3.335	0.412			
GGT ≥50 U/L	2.100	0.286–15.423	0.466			
Hepatosteatosis			0.005			
Grade 1 vs Grade 0 (5–33% vs <5%)	2.452	1.117–5.382	0.025	2.513	1.144–5.520	0.022
Grade 2, 3 vs Grade 0 (≥34% vs <5%)	4.905	1.741–13.823	0.003	4.699	1.662–13.286	0.004

HBsAg: Hepatitis B surface antigen; HR: Hazard ratio; CI: Confidence interval; HBV: Hepatitis B virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transpeptidase; CHBV: Chronic hepatitis B virus; CHB: Chronic hepatitis B; 0=<5%, Grade 1 =5–33%, Grade 2 =33–66%, and Grade 3 =>66%.

Table 5. Hepatic steatosis affects disease outcome in patients with CHB who have achieved virological remission

	Patients with chronic HBV infection		p	Patients with CHB		p
	Hepatic steatosis	No steatosis		Hepatic steatosis	No steatosis	
FIB-4 score	1.14±0.46; 1.06 (0.5)	1.16±0.83; 0.96 (0.5)	0.458	1.14±0.46; 1.06 (0.5)	1.16±0.83; 0.96 (0.5)	0.120
Liver stiffness (kPa)	6.6±2.3; 6.1 (2.5)	5.7±2.0; 5.2 (2.4)	0.004	8.0±4.2; 6.8 (3.6)	5.9±2.9; 5.1 (1.9)	<0.0001
CAP (dB/m)	304.0±62.5; 316	257.6±61.7; 261	<0.0001	292.0±45.8; 295	247.3±55.6; 243	<0.0001

HBV: Hepatitis B virus; CHB: Chronic hepatitis B; CAP: Controlled attenuation parameter. Mean±standard deviation, median (interquartile range).

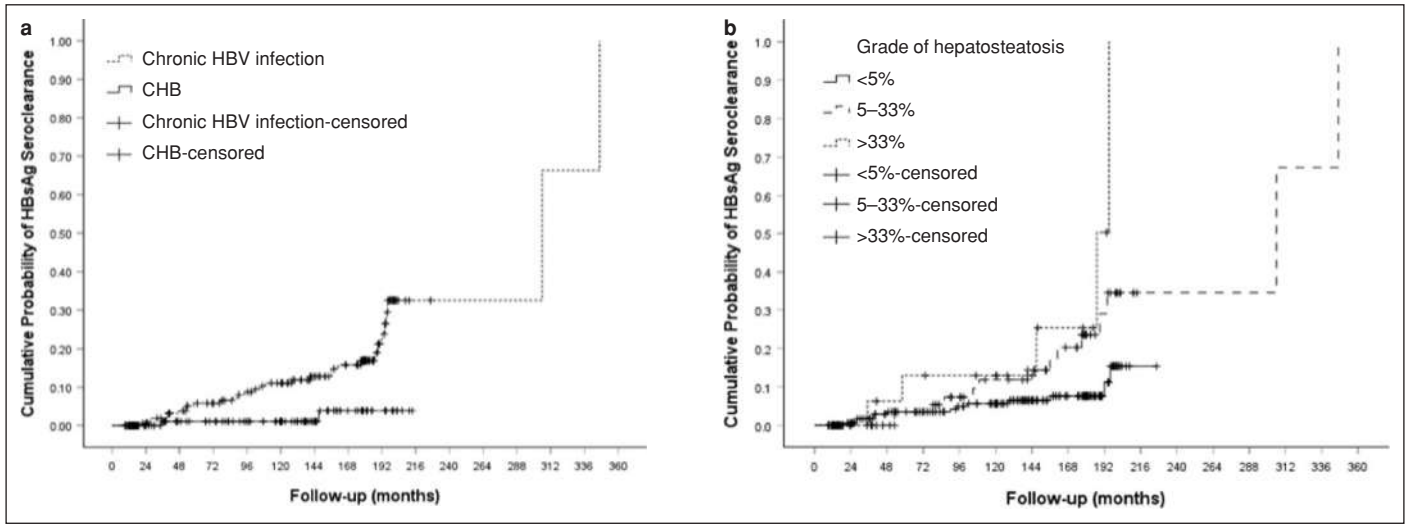

Figure 1. (a) Cumulative probability of HBsAg seroclearance in HBV-infected patients. **(b)** The grade of hepatosteatosis significantly affects HBsAg seroclerance.

strated that the presence of hepatic steatosis in patients with chronic HBV infection was associated with lower HBsAg and HBcAg levels in hepatocytes, as well as lower quantitative HBsAg levels in serum compared to those in patients with CHB.[16,19,27] A meta-analysis of six studies involving 3,870 patients with chronic HBV infection demonstrated that hepatic steatosis was significantly associated with a higher

rate of HBsAg seroclearance, with a pooled odds ratio of 2.22.[28] It was recently reported that combining low serum HBV DNA levels with hepatic steatosis led to significantly higher rates of HBsAg seroclearance.[20] It can be explained that intracellular fat alters the distribution of HBsAg in the cytoplasm of hepatocytes, leading to apoptosis, viral suppression, and ultimately HBsAg loss. Therefore, hepatic steatosis appears to be related to lower HBV replicative activity in patients with chronic HBV infection.

Chronic HBV infection is still a serious health problem and a significant cause of liver-related morbidity and mortality in the adult population of Turkiye.[4,5] Since the dramatically increasing prevalence of MASLD worldwide, chronic HBV infection and MASLD frequently coexist in Turkiye. This study confirms that over one-third of HBV-infected patients exhibited hepatosteatosis at baseline liver biopsy. Notably, there were no significant differences in hepatosteatosis prevalence between patients with chronic HBV infection and those with CHB. This prevalence is comparable to that of MASLD reported in Turkiye.[13]

The evidence regarding the impact of hepatic steatosis on HBV-related chronic liver disease, cirrhosis, and HCC is conflicting. Previous studies have shown that severe hepatic steatosis is associated with fibrosis progression, advanced fibrosis, developing cirrhosis, and HCC in patients with CHB.[19,20,29–32] However, some investigators have found no such association.[16] Dai et al.[32] recently demonstrated that chronic HBV infection with concurrent NAFLD is associated with greater severity of hepatic inflammation, ballooning, and advanced fibrosis. However, hepatic steatosis was not found to be a risk factor for significant or advanced fibrosis. The investigators concluded that hepatic steatosis could aggravate liver inflammation and fibrosis in patients with chronic HBV infection.[32] A meta-analysis reported that concomitant hepatic steatosis is associated with an increased risk of cirrhosis with a pooled OR of 1.52 and the development of HCC with a pooled OR of 1.59 in patients with CHB.[28] In a further subgroup analysis of this meta-analysis, hepatic steatosis did not affect the development of HCC in CHB patients who received antiviral treatment.[28]

Oral antiviral therapies against HBV infection cause viral suppression and reduce the risk of fibrosis progression, disease progression, and HCC development in patients with CHB.[17] In the present study, all CHB patients were treated with antiviral drugs and achieved viral suppression. Notably, fibrosis progression detected by VCTE was still observed at the end of the follow-up period in CHB patients with hepatic steatosis who were on oral antiviral therapy compared to those without hepatic steatosis. These findings indicate that concurrent hepatic steatosis contributes to the progression of hepatic fibrosis in patients with CHB who have achieved viral suppression.

In the present study, hepatic steatosis was demonstrated by liver biopsy in all participants at admission to prevent selection bias in the diagnosis of hepatic steatosis. However, in previous studies, hepatic steatosis has been diagnosed using different thresholds and various modalities, including abdominal sonography, transient elastography, computed tomography, and magnetic resonance imaging. These non-invasive diagnostic methods have different sensitivities in detecting hepatic steatosis.

The present study has several limitations. There is a lack of data on the anthropometric and detailed metabolic factors of patients, which affects the interpretation of the results. Additionally, no follow-up liver biopsies were conducted to assess the influence of hepatic steatosis on clinical outcomes in patients with CHB.

Conclusion

The stage of HBV disease and severity of hepatic steatosis contribute to HBsAg seroclearance in patients with chronic HBV infection. Hepatic steatosis can also accelerate fibrosis progression, especially in patients with CHB who have achieved virological remission under antiviral therapy.

Ethics Committee Approval: The Ankara University School of Medicine Clinical Research Ethics Committee granted approval for this study (date: 03.07.2021, number: 2021/260).

Informed Consent: Written informed consent was obtained from participants.

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 declarated.

Author Contributions: Concept – RI, EB; Design – RI, EB; Supervision – SK, OK, ZME; Data Collection and/or Processing – MG, STG, VY; Analysis and/or Interpretation – AHE, MG, REE; Literature Search – BS, AHE, VY; Writing – RI, EB; Critical Reviews –RI, EB, HG.

Peer-review: Externally peer-reviewed.

References

1. World Health Organization. Global hepatitis report 2024. Available from: http://www.who.int/hepatitis/publications/global-hepatitis-report2024/en.
2. Hsu YC, Huang DQ, Nguyen MH. Global burden of hepatitis B virus: current status, missed opportunities and call for action. Nat Rev Gastroenterol Hepatol 2023;20(8):524-537. [CrossRef]
3. Idilman R, Aydogan M, Oruncu B, 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]
4. Ucbilek E, Yildirim AE, Ellik Z, Turan İ, Haktanıyan B, Orucu B, et al. Changing trends in the etiology of cirrhosis in Turkiye: a multicenter nationwide study. Turk J Gastroenterol 2024;35(10):772-777. [CrossRef]
5. 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]
6. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect 2015;21(11):1020-1026. [CrossRef]
7. Younossi ZM, Kalligeros M, Henry L. Epidemiology of metabolic dysfunction-associated steatotic liver disease. Clin Mol Hepatol 2025;31(Suppl):S32-S50. [CrossRef]
8. 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]
9. 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.
10. Huang DQ, Terrault NA, Tackle F, Gluud LL, Arrese M, Bugianesi E, et al. Global epidemiology of cirrhosis: etiology, trends and predictions. Nat Rev Gastroenterol Hepatol 2023;20(6):388-398. [CrossRef]
11. Younossi ZM, Stepanova M, Younossi Y, Golabi P, Mishra A, Rafiq N, et al. Epidemiology of chronic liver diseases in the USA in the past three decades. Gut 2020;69(3):564-568. [CrossRef]
12. Kwong AJ, Ebel NH, Kim WR, Lake JR, Smith JM, Schladt DP, et al. OPTN/SRTR 2021 annual data report: liver. Am J Transplant 2023;23(2 Suppl 1):S178-S263. [CrossRef]

13. 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]
14. Wong VW, Wong GL, Chu WC, Chim AM, Ong A, Yeung DK, et al. Hepatitis B virus infection and fatty liver in the general population. J Hepatol 2012;56(3):533-540. [CrossRef]
15. Huang SC, Liu CJ. Chronic hepatitis B with concurrent metabolic dysfunction-associated fatty liver disease: challenges and perspectives. Clin Mol Hepatol 2023;29(2):320-331. [CrossRef]
16. Zheng Q, Zou B, Wu Y, Yeo Y, Wu H, Stave CD, et al. Systematic review with meta-analysis: prevalence of hepatic steatosis, fibrosis and associated factors in chronic hepatitis B. Aliment Pharmacol Ther 2021;54:1100-1109. [CrossRef]
17. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67(2):370-398. [CrossRef]
18. Yeo YH, Ho HJ, Yang HI, Tseng TC, Hosaka T, Trinh HN, et al. Factors associated with rates of HBsAg seroclearance in adults with chronic HBV infection: a systematic review and meta-analysis. Gastroenterology 2019;156(3):635-646.e9. [CrossRef]
19. Chu CM, Lin DY, Liaw YF. Clinical and virological characteristics post HBsAg seroclearance in hepatitis B virus carriers with hepatic steatosis versus those without. Dig Dis Sci 2013;58(1):275-281. [CrossRef]
20. Mak LY, Hui RWH, Fung J, Liu F, Wong DK, Cheung KS, et al. Diverse effects of hepatic steatosis on fibrosis progression and functional cure in virologically quiescent chronic hepatitis B. J Hepatol 2020;73(4):800-806. [CrossRef]
21. Bacaksız FG, Gokcan H, Akdogan M, Gökçe DT, Arı D, Gökbulut V,et al. Role of hepatosteatosis in HBsAg seroconversion in HBeAg-negative chronic hepatitis B patients. Int J Clin Pract 2012;75(12):e14899. [CrossRef]
22. Huang SC, Su TH, Tseng TC, Chen CL, Hsu SJ, Liu CH, et al. Metabolic dysfunction-associated steatotic liver disease facilitates hepatitis B surface antigen seroclearance and seroconversion. Clin Gastroenterol Hepatol 2024;22(3):581-590. [CrossRef]
23. Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, et al. Histological grading and staging of chronic hepatitis. J Hepatol 1995;22(6):696-699. [CrossRef]
24. Brunt EM, Kleiner DE, Carpenter DH, Rinella M, Harrison SA, Loomba R, et al. NAFLD: reporting histologic findings in clinical practice. Hepatology 2021;73(5):2028-2038. [CrossRef]
25. Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Lédinghen V, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol 2017;66(5):1022-1030. [CrossRef]
26. Bravo AA, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001;344:495-500. [CrossRef]
27. Wang MM, Wang GS, Shen F, Chen GY, Pan Q, Fan JG. Hepatic steatosis is highly prevalent in hepatitis B patients and negatively associated with virological factors. Dig Dis Sci 2014;59(10):2571-2579. [CrossRef]
28. Mao X, Cheung KS, Peng C, Mak LY, Cheng HM, Fung J, et al. Steatosis, HBV-related HCC, cirrhosis, and HBsAg seroclearance: a systematic review and meta-analysis. Hepatology 2023;77(5):1735-1745. [CrossRef]
29. Bondini S, Kallman J, Wheeler A, Prakash S, Gramlich T, Jondle DM, et al. Impact of nonalcoholic fatty liver disease on chronic hepatitis B. Liver Int 2007;27(5):607-611. [CrossRef]
30. Seto WK, Hui R, Mak LY, Fung J, Cheung KS, Liu KSH, et al. Association between hepatic steatosis measured by controlled attenuation parameter, and fibrosis burden in chronic hepatitis B. Clin Gastroenterol Hepatol 2018;16(4):575-583.e2. [CrossRef]
31. Choi HSJ, Brouwer WP, Zanjir WMR, de Man RA, Feld JJ, Hansen BE, et al. Nonalcoholic steatohepatitis is associated with liver-related outcomes and all-cause mortality in chronic hepatitis B. Hepatology 2020;71(2):539-548. [CrossRef]
32. Dai YN, Xu CF, Pan HY, Chen MJ, Yu CH. Fatty liver is associated with significant liver inflammation and increases the burden of advanced fibrosis in chronic HBV infection. BMC Infect Dis 2023;23(1):637. [CrossRef]

Research Article

HEPATOLOGY FORUM

Statins and liver enzymes in MASLD: A 12-month review

doi: 10.14744/hf.2025.02335

Impact of statins on liver transaminases in patients with metabolic dysfunction–associated steatotic liver disease: A 12-month retrospective review

Paul Jen Wui Wong[1], Sau Chyun Ng[1], Samuel George[2], Rasnaizam bin Rasdi[1]

[1]*Department of Internal Medicine, Gastroenterology Unit, Hospital Tengku Ampuan Afzan, Kuantan, Malaysia;* [2]*Klinik Kesihatan Bentong, Bentong, Malaysia*

Abstract

Background and Aim: Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most common chronic liver disease worldwide and is strongly linked to metabolic comorbidities such as diabetes mellitus, hypertension, dyslipidemia, and coronary artery disease. Despite their cardiovascular benefits, statins are historically underused in patients with MASLD because of concerns regarding hepatotoxicity. This study aimed to evaluate the impact of statins on liver transaminase levels in patients with MASLD and assess whether statin type or dose influences these outcomes.

Materials and Methods: We conducted a retrospective review of 104 patients with MASLD who attended outpatient clinics between January 2023 and December 2024. Patients on statins for ≥12 months were included, while those with viral hepatitis, autoimmune liver disease, or significant alcohol intake were excluded. The data collected included comorbidities, statin type/dose, and liver transaminase levels at baseline, 3, 6, and 12 months. Patients without baseline transaminase levels available at the time of statin initiation were excluded. Of the 104 patients recruited, only 21 underwent transient elastography, of which two had advanced chronic liver disease.

Results: The mean BMI was 34.26 kg/m². Most patients had diabetes mellitus (86%), hypertension (88.5%), and dyslipidemia (98.1%). Transaminase levels remained stable over 12 months (ALT, $\chi^2(3)=0.340$, p=0.952; AST, $\chi^2(3)=0.342$, p=0.926). Statin type and dose had no significant effects on transaminase levels.

Conclusion: Statins of different types and doses did not significantly affect transaminases in patients with MASLD, indicating that statins are safe for use in patients with MASLD who meet the criteria for lipid-lowering therapy. Further studies are warranted to explore the long-term hepatic effects of statins in patients with metabolic dysfunction-associated steatohepatitis (MASH), focusing on histological outcomes.

Keywords: Liver transaminases; MASLD; statins.

How to cite this article: Wong PJW, Ng SC, George S, Rasdi R. Impact of statins on liver transaminases in patients with metabolic dysfunction–associated steatotic liver disease: A 12-month retrospective review. Hepatology Forum 2026; 7(1):21–25.

Received: July 21, 2025; **Revised:** August 22, 2025; **Accepted:** September 05, 2025; **Available online:** September 06, 2025

Corresponding author: Paul Jen Wui Wong; Department of Internal Medicine, Gastroenterology Unit, Hospital Tengku Ampuan Afzan, Kuantan, Malaysia
Phone: +609-513 3333; **e-mail:** thejww@gmail.com

Hepatology Forum - Available online at www.hepatologyforum.org

Introduction

Metabolic dysfunction-associated fatty liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is the most common chronic liver disorder worldwide.[1] It is characterized by hepatic steatosis in the presence of metabolic risk factors, such as obesity, type 2 diabetes mellitus, and dyslipidemia. MASLD not only carries the risk of progression to steatohepatitis, fibrosis, and cirrhosis, but also significantly increases cardiovascular morbidity and mortality,[2] which is the leading cause of death in this population.

Statins are widely prescribed lipid-lowering agents that have been proven to reduce cardiovascular risk in patients with dyslipidemia. Given the high prevalence of dyslipidemia and atherosclerotic cardiovascular disease among patients with MASLD, statins are frequently indicated.[3] However, concerns regarding potential hepatotoxicity and elevated liver transaminase levels often lead to the hesitancy or discontinuation of statins in patients with chronic liver disease.[4] Studies have shown that statins are under-prescribed in patients with MASLD despite the indication for statins in these patients, with Del Ben et al.[5] demonstrating that 50% of their patients with MASLD with indications for statins did not receive any statins. Blais et al.[6] showed that patients whose primary care providers recognized the presence of MASLD were less likely to receive statins than those with undetected MASLD.

However, the hesitation to use statin therapy in patients with MASLD due to potential hepatotoxicity is mostly unwarranted. The current consensus recommends that statins (if required for the treatment of dyslipidemia or CVD risk reduction) should be prescribed for patients with MASLD, even with modestly elevated serum liver enzyme levels (<3× the upper limit of normal).[7]

One study showed that statins are not only safe but may also exert beneficial effects on liver histology and reduce the risk of fibrosis in patients with MASLD.[8] Nonetheless, real-world data examining the longitudinal effects of statins on transaminase trends in patients with MASLD, especially across different statin types and doses, remain limited and inconsistent.

This study aimed to address this gap by retrospectively analyzing the impact of statin therapy on liver transaminase levels over time in patients with MASLD and by exploring whether these effects vary based on the type or dose of statin used. Understanding this relationship is crucial for informing clinical decision-making and optimizing both hepatic and cardiovascular outcomes in this high-risk population.

This study aimed to investigate the effects of statin therapy on liver transaminases and lipid profiles in patients with metabolic dysfunc-

tion–associated steatotic liver disease (MASLD). Specifically, changes in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels over time in patients with MASLD receiving statins were recorded. In addition, this study evaluated whether various statin types and doses had varying impacts on liver transaminase levels and examined the influence of statin type and dose on low-density lipoprotein (LDL) cholesterol reduction.

Materials and Methods

Study Population and Setting

We retrospectively reviewed the records of patients from the medical and gastroenterology outpatient clinics between January 2023 and December 2024. Patients with MASLD and those who had been on statins for ≥12 months were included.

Patients diagnosed with MASLD confirmed by liver ultrasonography and meeting any one of the following cardiometabolic criteria were included:

Cardiometabolic risk factors in adults include overweight or obesity, defined by a BMI >25 kg/m² (or >23 kg/m² in Asian populations), and central obesity, defined by ethnicity-specific waist circumference cutoffs (≥94 cm for European men and ≥80 cm for women; ≥90 cm for South Asian/Chinese men and ≥80 cm for women; ≥85 cm for Japanese men and ≥90 cm for women). Dysglycemia was characterized by prediabetes (HbA1c 5.7–6.4%, fasting plasma glucose 5.6–6.9 mmol/L, or 2-hour OGTT plasma glucose 7.8–11 mmol/L) or type 2 diabetes (HbA1c ≥6.5%, fasting plasma glucose ≥7.0 mmol/L, 2-hour OGTT plasma glucose ≥11.1 mmol/L, or treatment for type 2 diabetes). Dyslipidemia is defined as plasma triglycerides >1.7 mmol/L or HDL-cholesterol <1.0 mmol/L in men and <1.3 mmol/L in women, or on lipid-lowering treatment. Elevated blood pressure was defined as ≥130/85 mmHg or the use of antihypertensive therapy.[9]

Patients who were less than 18 years old, or who had hepatitis B or C, autoimmune hepatitis, Wilson's disease, primary biliary cholangitis, primary sclerosing cholangitis, hemochromatosis, congenital liver diseases, drug-induced hepatitis, and significant alcohol intake were excluded. Patients with no baseline liver transaminases available at the time of statin initiation were excluded. Of the 104 patients recruited, only 21 underwent transient elastography, of which two had advanced chronic liver disease (ACLD).

Study Design

The first time statins were prescribed to the patient was set as the baseline (0 months), and the liver transaminases and baseline lipid profiles were recorded. Liver transaminases and lipid profiles were recorded again at 3, 6, and 12 months. Other data collected included patient demographics, weight, BMI, statin type and dose, HbA1c levels, and ultrasonography findings.

The data were anonymized, and no identifiable information was reported.

Statistical Analysis

Statistical analyses were performed using SPSS version 30 (IBM, Chicago, IL, USA). Basic descriptive statistics, including means and standard deviations, were used to characterize the study patients. In this study, age, BMI, ALT, AST, LDL-C, total cholesterol, and HbA1c were treated as continuous variables for both descriptive and inferential analyses, with the means, standard deviations, and ranges reported. ALT and AST trends over time were analyzed as continuous variables using Friedman's test, given their non-parametric distribution. LDL-C was similarly analyzed as a continuous variable. The Kruskal-Wallis test was performed to determine whether there was any correlation between statin type and dose with ALT/AST trends, and the relationship between statin type and dose with the LDL trend.

For subgroup analyses, statin doses were categorized into standard clinical dose ranges (e.g., simvastatin 20–40 mg, atorvastatin 20–80 mg, and rosuvastatin 10–40 mg) to facilitate comparisons between potency levels. Multivariate analyses were performed with adjustments for potential confounders, including age, BMI, diabetes mellitus, hypertension, and chronic kidney disease, when assessing the effects of statin therapy on ALT and AST levels.

Ethics Approval and Consent

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Patient confidentiality and data privacy were strictly maintained throughout the study.

Ethics approval was obtained from the Ministry of Health Malaysia Medical Research and Ethics Committee. Informed consent was not required for this retrospective study.

Results

Participants' Baseline Characteristics

A total of 104 patients were included in this study. The mean age was 53.97±13.66 years, and the mean BMI was 34.26±12.40 kg/m². Most participants had multiple metabolic comorbidities: 86.0% had diabetes mellitus, 88.5% had hypertension, and 98.1% had dyslipidemia. Additionally, 14.4% had ischemic heart disease, 12.5% had a history of stroke, and 27.9% had chronic kidney disease. In terms of demographics, this study included three main ethnic groups in Malaysia (79 Malay – 76%, 13 Chinese – 12.5%, 12 Indian – 11.5%), and gender was equally distributed (52 male, 52 female).

The statins used were simvastatin (n=23: 20 mg, n=9; 40 mg, n=14), atorvastatin (n=69: 10 mg, n=1; 20 mg, n=15; 40 mg, n=48; 60 mg, n=4; 80 mg, n=1), rosuvastatin (n=11: 10 mg, n = 3; 20 mg, n=7; 40 mg, n=1), pravastatin (n=1: 40 mg, n=1) (Table 1).

Impact of Statin Use on Liver Transaminases

Friedman's test demonstrated no significant change in ALT levels across the study period (baseline, 3, 6, and 12 months): $\chi^2(3)=0.340$, p=0.952. Post-hoc pairwise comparisons with Bonferroni correction revealed no significant differences between any of the time points (all adjusted p>0.60). Similarly, AST levels remained stable over time ($\chi^2(3)=0.342$, p=0.926; all adjusted p>0.50) (Fig. 1, 2).

Effect of Statin Types and Doses on LDL-C

Kruskal-Wallis analysis showed no significant difference in LDL-C levels at 0, 3, 6, and 12 months among the different statin types and doses (H=15.507, df=9, p=0.078). Although there was a trend towards lower LDL-C levels with higher doses and higher-potency statins, this was not statistically significant (Fig. 3).

Table 1. Baseline characteristics of the study participants

Parameter	Mean±SD	Range
Age (years)	53.97±13.66	27–86
Weight (kg)	85.21±25.43	40.0–186.0
BMI (kg/m^2)	34.26±12.40	10.6–72.5
ALT (U/L)	31.49±19.11	6–107
AST (U/L)	29.96 ±14.32	8–83
LDL-C (mmol/L)	2.89±1.14	1.24–6.37
Total cholesterol (mmol/L)	4.97±1.41	2.29–9.55
HDL-C (mmol/L)	1.25±0.28	0.45–1.89
Triglycerides (mmol/L)	1.80±0.94	0.67–5.59
HbA1c (%)	8.79±2.45	5.3–15.6

BMI: Body mass index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; HbA1c: Hemoglobin A1c.

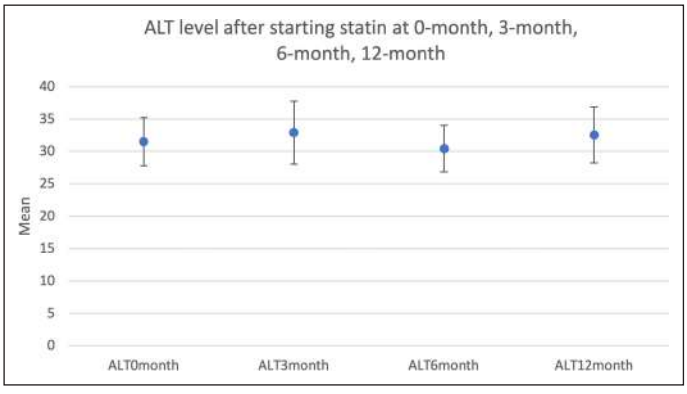

Figure 1. ALT level after starting statin at 0-month, 3-month, 6-month, 12-month.

ALT: Alanine aminotransferase.

Effect of Statin Types and Doses on Liver Transaminases

For liver transaminases, statin types and doses demonstrated no significant effect on ALT and AST level trends in multivariate analysis after adjusting for age, BMI, diabetes mellitus, and chronic kidney disease (p=0.512) (Fig. 4).

Discussion

In this study, we investigated the effects of statin therapy on liver transaminases and lipid profiles in patients with MASLD. Our findings indicate that statin use for >12 months did not lead to significant elevations in ALT or AST levels. Furthermore, we observed no significant differences in ALT or AST trends when comparing different statin types or doses, even after adjusting for potential confounders, including age, BMI, diabetes mellitus, hypertension, and chronic kidney disease.

MASLD is now recognized not only as the most common chronic liver disease worldwide but also as an important cardiovascular risk factor. The cardiovascular burden among patients with MASLD is

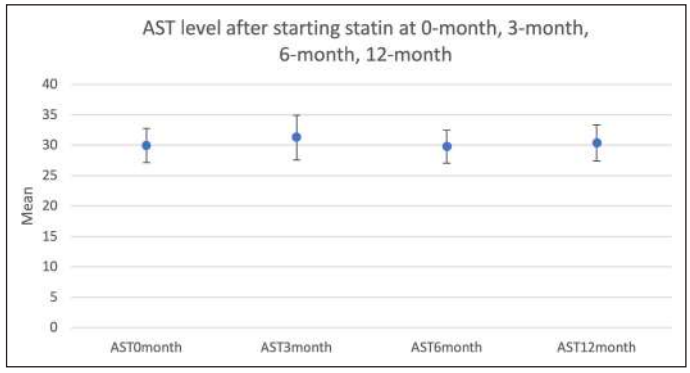

Figure 2. AST level after starting statin at 0-month, 3-month, 6-month, 12-month.

AST: Aspartate aminotransferase.

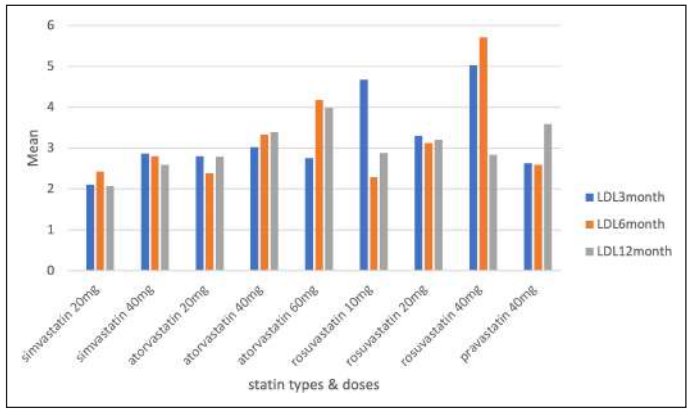

Figure 3. LDL level at 3, 6, 12-month post statin initiation among various statin types and doses.

LDL: Low-density lipoprotein.

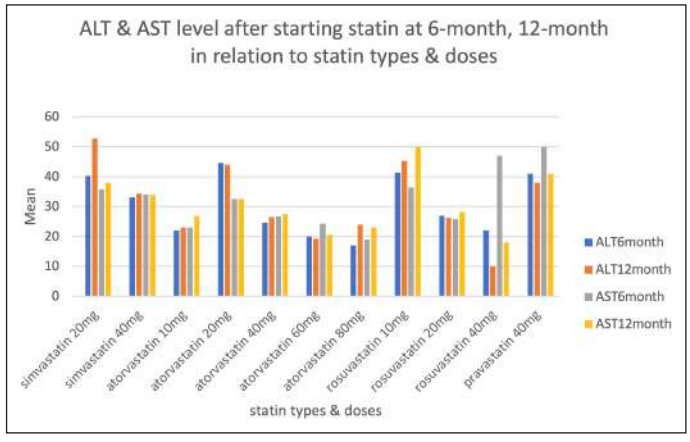

Figure 4. ALT and AST level after starting statin at 6-month, 12-month in relation to statin types and doses.

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

well established. Previous studies have shown that MASLD is independently associated with subclinical atherosclerosis, electrocardiographic abnormalities, and an increased prevalence of ischemic heart disease, cerebrovascular disease, and peripheral vascular disease.[10,11] For example, a large study in Taiwan involving over 2,000 middle-

aged male workers found that individuals with ultrasound-confirmed MASLD were more likely to exhibit ischemic changes on resting ECG, independent of traditional risk factors such as lipid profiles and smoking status.[12] Similarly, Targher et al.[13] demonstrated that patients with type 2 diabetes mellitus and MASLD had a higher prevalence of coronary and cerebrovascular diseases than diabetic patients without MASLD.

Despite the strong association between MASLD and cardiovascular disease, statins, which are widely proven to reduce cardiovascular morbidity and mortality, are often under-prescribed in this population.[6] This is largely due to concerns regarding potential hepatotoxicity.

In a large-scale cohort study, the incidence rate of statin-induced liver injury was rare and was estimated to be 13–15 events per 100,000 person-years.[14] In our study, three patients had transient elevation of liver transaminases, which improved over time; these transient elevations were not statistically significant. We did not observe any significant statin-induced liver injury, which could be partly due to our relatively small sample size. However, it is important to note that our findings contribute to the growing body of evidence indicating that statins do not adversely affect liver transaminases in patients with MASLD, supporting their use in this group of patients.

These results are consistent with emerging evidence suggesting that statins are safe for use in patients with MASLD. Several studies have shown that statins do not increase the risk of hepatotoxicity in this population and may even have potential hepatoprotective effects by improving steatosis and reducing inflammation.[15,16] Our findings reinforce that statins should not be withheld from patients with MASLD when lipid-lowering therapy is indicated, such as in patients at high risk of cardiovascular disease.[17]

However, the effectiveness of statins in treating metabolic dysfunction-associated steatohepatitis (MASH) remains unclear, as no large randomized controlled trials have evaluated their impact on histological outcomes.[9]

Although we noted a trend in which higher doses and higher-potency statins (e.g., atorvastatin 40–80 mg and rosuvastatin 20–40 mg) were associated with lower LDL-C levels, these differences did not achieve statistical significance in our sample. This may be attributed to the limited sample sizes in certain statin subgroups and variability in patient adherence or lifestyle factors, which were not controlled for in this retrospective analysis. Nevertheless, our observations align with other pharmacological data showing a dose-dependent LDL-lowering effect of statins.[18]

Limitations

A major strength of our study is the real-world setting involving patients with multiple comorbidities representative of those observed in clinical practice. The 12-month follow-up and multivariate adjustment for key confounders (age, BMI, diabetes mellitus, hypertension, chronic kidney disease, and baseline liver transaminase levels) enhanced the validity of our findings.

However, our study had some limitations. The relatively small sample size, particularly within certain statin dose groups, reduced the power to detect small differences in outcomes. Liver histology was not available; therefore, we could not assess the impact of statins on fibrosis or steatosis progression. In addition, transient elastography was only performed for a small number of patients in this study, and the degree of fibrosis could not be determined for other patients.

Since this was a retrospective study conducted in the outpatient clinics of a single center, there is a possibility of selection bias. This could lead to the overrepresentation of patients who were more adherent to follow-up or more engaged in care. Unmeasured confounders (e.g., lifestyle factors such as diet, exercise, and alcohol intake below the exclusion threshold) could have influenced liver transaminases or lipid profiles independently of statin use. Medication adherence was not directly measured; therefore, statin exposure may have been overestimated if prescriptions were not consistently taken. We acknowledge this in the study limitations and recommend future prospective studies to assess adherence.

Conclusion

Our study provides further evidence that statin therapy in patients with MASLD is not associated with significant liver transaminase elevation or hepatotoxicity over 12 months of treatment. Statins of varying types and doses did not result in significant differences in ALT or AST levels. Trends in LDL-C reduction with higher-potency statins were observed, but were not statistically significant in this cohort. Statins are safe for use in patients with MASLD who meet the criteria for lipid-lowering therapy. Further studies are warranted to explore the long-term hepatic effects of statins in patients with MASH by measuring histological outcomes.

Ethics Committee Approval: The Ministry of Health Malaysia Medical Research and Ethics Committee granted approval for this study (date: 23.05.2025, number: NMRR ID-25-01114-G1D).

Informed Consent: Informed consent was not required for this retrospective study.

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: No artificial intelligence (AI)– assisted technologies were used during the write up of this manuscript.

Author Contributions: Concept – PJWW, SCN; Design – PJWW, SG; Supervision – RR; Materials – SCN, RR; Data Collection and/or Processing – PJWW, SCN; Analysis and/or Interpretation – PJWW, SG; Literature Search – PJWW, SG; Writing – PJWW; Critical Reviews – RR.

Peer-review: Externally peer-reviewed.

References

1. Fernandez CJ, Nagendra L, Pappachan JM. Metabolic dysfunction-associated fatty liver disease: An urgent call for global action. TouchREV Endocrinol 2024;20(1):5-9. [CrossRef]
2. Chan WK, Chuah KH, Rajaram RB, Lim LL, Ratnasingam J, Vethakkan SR, et al. Metabolic dysfunction-associated steatotic liver disease (MASLD): A state-of-the-art review. J Obes Metab Syndr 2023;32(3):197-213. [CrossRef]
3. Martin A, Lang S, Goeser T, Demir M, Steffen HM, Kasper P, et al. Management of dyslipidemia in patients with non-alcoholic fatty liver disease. Curr Atheroscler Rep 2022;24(7):533-546. [CrossRef]
4. Wright AP, Adusumalli S, Corey KE. Statin therapy in patients with cirrhosis. Frontline Gastroenterol 2015;6(4):255-261. [CrossRef]
5. Del Ben M, Polimeni L, Baratta F, 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]
6. 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]

7. Zhou XD, Targher G, Byrne CD, Somers V, Kim SU, Chahal CAA, et al. An international multidisciplinary consensus statement on MAFLD and the risk of CVD. Hepatol Int 2023;17(4):773-791. [CrossRef]
8. Nascimbeni F, Aron-Wisnewsky J, Pais R, et al. Statins, antidiabetic medications and liver histology in patients with diabetes with non-alcoholic fatty liver disease. BMJ Open Gastroenterol 2016;3(1):e000075. [CrossRef]
9. 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.
10. Byrne CD, Targher G. NAFLD: A multisystem disease. J Hepatol 2015;62(1 Suppl):S47-S64. [CrossRef]
11. Targher G, Day CP, Bonora E. Risk of cardiovascular disease in patients with NAFLD. N Engl J Med 2010;363(14):1341-1350. [CrossRef]
12. Lin YC, Lo HM, Chen JD. Sonographic fatty liver, overweight and ischemic heart disease. World J Gastroenterol 2005;11(31):4838-4842. [CrossRef]
13. Targher G, Arcaro G. Non-alcoholic fatty liver disease and increased risk of cardiovascular disease. Atherosclerosis 2007;191(2):235-240. [CrossRef]
14. Verma SK, Huang J, Hutchinson HG, Estevez I, Kuang K, Reynolds SL, et al. Statin use and severe acute liver injury among patients with elevated alanine aminotransferase. Clin Epidemiol 2022;14:1535-1545. [CrossRef]
15. Athyros VG, Tziomalos K, Gossios TD, Griva T, Anagnostis P, Kargiotis K, et al. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: A post-hoc analysis. Lancet 2010;376:1916-1922. [CrossRef]
16. Boutari C, Pappas PD, Anastasilakis D, Mantzoros CS. Statins' efficacy in non-alcoholic fatty liver disease: A systematic review and meta-analysis. Clin Nutr 2022;41(10):2195-2206. [CrossRef]
17. Ho A, Kiener T, Nguyen QN, Le QA. Effect of statin use on liver enzymes and lipid profile in patients with non-alcoholic fatty liver disease (NAFLD). J Clin Lipidol 2024;18(4):e501-e508. [CrossRef]
18. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/multisociety guideline on the management of blood cholesterol. J Am Coll Cardiol 2019;73(24):e285-e350. [CrossRef]

Research Article

HEPATOLOGY FORUM

HBV prophylaxis with TAF in immunosuppressive therapy

doi: 10.14744/hf.2025.62002

Efficacy and tolerability of tenofovir alafenamide fumarate prophylaxis in HBV-infected individuals receiving chemo/immunosuppressive therapy

Feyza Dilber[1], Serdar Durak[2], Yasemin Unsal[3], Mehmet Demir[4], Abdullah Emre Yildirim[5], Zeynep Melekoglu Ellik[6], Shahin Mehdiyev[1], Haydar Adanir[7], Suna Yapali[8], Coskun Ozer Demirtas[1], Enver Ucbilek[9], Yasemin Balaban[10], Nergis Ekmen[3], Hale Gokcan[6], Elif Sitre Koc[8], Dinc Dincer[7], Orhan Sezgin[9], Halis Simsek[10], Nurdan Tozun[8], Mehmet Arslan[2], Ramazan Idilman[6], Digdem Ozer Etik[11,*], Pinar Gokcen[12,*], Derya Ari[13,*], Kamil Ozdil[12,*], Meral Akdogan[13,*], Sedat Boyacioglu[11*]

*[1]Department of Gastroenterology, Marmara University School of Medicine, Istanbul, Turkiye; [2]Department of Gastroenterology, Karadeniz Technical University School of Medicine, Trabzon, Turkiye; [3]Department of Gastroenterology, Gazi University School of Medicine, Ankara, Turkiye; [4]Department of Gastroenterology, School of Medicine, Mustafa Kemal University, Hatay, Turkiye; [5]Department of Gastroenterology, School of Medicine, Gaziantep University, Gaziantep, Turkiye; [6]Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkiye; [7]Department of Gastroenterology, Akdeniz University School of Medicine, Antalya, Turkiye; [8]Department of Gastroenterology, Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Turkiye; [9]Department of Gastroenterology, Mersin University School of Medicine, Mersin, Turkiye; [10]Department of Gastroenterology, Hacettepe University School of Medicine, Ankara, Turkiye; [11]Department of Gastroenterology, Baskent University School of Medicine, Ankara, Turkiye; [12]Department of Gastroenterology, Health Sciences University, Umraniye Training and Research Hospital, Istanbul, Turkiye; [13]Department of Gastroenterology, Ankara City Hospital, Ankara, Turkiye; *Member of Viral Hepatitis Special Interest Group*

Abstract

Background and Aim: This study aimed to determine the efficacy and safety of tenofovir alafenamide fumarate (TAF) prophylaxis in hepatitis B virus (HBV)-infected or HBV-experienced individuals with benign and malignant diseases receiving chemo/immunosuppressive or biological modifier therapy.

Materials and Methods: This is a multicenter, observational study in which data from 13 centers were reviewed and entered into a standardized electronic case report form.

Results: A total of 158 individuals who received TAF prophylaxis were included in the analysis. Before starting the prophylaxis, 51 individuals were hepatitis B surface antigen positive, while 107 were HBV-experienced. Thirty patients had detectable HBV DNA levels. Twelve of them had abnormal serum alanine aminotransferase levels. Forty patients were switched to TAF. Solid tumors (34%) were the most common primary disease types. The median follow-up period was 17.2 months. From baseline to the end of the follow-up period, none of the patients had clinical, biochemical, or serological evidence of HBV reactivation under TAF prophylaxis. The virological response rate was 87%. HBV suppression was well maintained after switching in the 40 patients who were switched to TAF treatment. All patients maintained their chemo/immunosuppressive therapy without interruption. TAF prophylaxis was well tolerated. No drug discontinuation due to adverse effects was observed. No HBV-related morbidity or mortality was observed during the TAF prophylaxis. No significant differences were found in the glomerular filtration rate change or hypophosphatemia during TAF prophylaxis, but the serum triglyceride levels were significantly increased (p=0.019).

Conclusion: TAF prophylaxis is effective, safe, and tolerable in preventing chemo/immunosuppressive or biological modifier-induced HBV reactivation in HBV-infected or HBV-experienced individuals.

Keywords: Chemotherapy; efficacy; HBV infection; immunosuppressive therapy; prophylaxis; safety; tenofovir alafenamide fumarate.

Introduction

Hepatitis B virus (HBV) infection is a global public health problem affecting approximately 300 million people worldwide, with 1.5 million new infections each year.[1] A significant proportion of these individuals develop chronic hepatitis, cirrhosis, and hepatocellular carcinoma, which are associated with an increased risk of liver-related morbidity and mortality.[2] In 2019, HBV resulted in an estimated 820,000 deaths.[1] Despite a successful HBV vaccination program and efforts to reduce transmission and prevention in Turkiye, HBV infection remains a major public health problem, especially in the adult population. In 2009, an epidemiologic study determined that hepatitis B surface antigen (HBsAg) positivity was around 4% and that hepatitis B core antibody (anti-HBc) positivity was 31% in Turkiye.[3]

How to cite this article: Dilber F, Durak S, Unsal Y, Demir M, Yildirim AE, Melekoglu Ellik Z, et al. Efficacy and tolerability of tenofovir alafenamide fumarate prophylaxis in HBV-infected individuals receiving chemo/immunosuppressive therapy. Hepatology Forum 2026; 7(1):26–31.

Received: August 22, 2025; **Accepted:** September 12, 2025; **Available online:** December 08, 2025

Corresponding author: Ramazan Idilman; Department of Gastroenterology, Ankara University School of Medicine, Ankara, Turkiye
Phone: +90 533 542 93 17; **e-mail:** idilman@medicine.ankara.edu.tr

HBV reactivation (HBVr) is a well-recognized complication of chemo/immunosuppressive and biological modifier therapies in HBV-infected or HBV-experienced individuals.[4] HBVr is characterized by the emergence of HBV particles in patients with previously resolved HBV or an increase in HBV viremia in patients with previously chronic HBV infection.[5] Reactivation can occur spontaneously, but it is generally triggered by immunosuppressive therapy. HBVr is a serious event that can result in hepatic decompensation, acute liver failure, and death.[6] Several risk factors, such as host factors (male gender, older age, severity of liver disease), virological factors (HBV DNA levels), primary disease (lymphoma, stem cell transplantation), and type and degree of an immunosuppressive agent, are associated with HBVr.[6,7] There is a rapid expansion of new immunosuppressive agents, such as monoclonal antibodies, immune checkpoint inhibitors, and tyrosine-kinase inhibitors, which are used in the treatment of various autoimmune, dermatologic, and rheumatologic diseases and many cancers. It has been demonstrated that a risk gradient of immunosuppressive drugs could affect HBVr.[8] Thus, these drugs have been categorized into low-, moderate-, and high-risk groups based on their estimates of HBVr.

HBVr can be prevented when at-risk individuals are identified through screening and started on antiviral prophylaxis if indicated. Antiviral prophylaxis with potent nucleos(t)ide analogs (NUCs) is strongly recommended for HBV-infected patients or HBV-experienced individuals who are considered high risk for HBVr undergoing chemo/immunosuppressive and biological modifier therapies.[8] Previous studies have shown that antiviral prophylaxis is associated with an 87% relative risk reduction of HBVr and an 84% relative risk reduction of HBV-associated hepatitis flares.[9] Lamivudine (LAM), entecavir (ETV), and tenofovir disoproxil fumarate (TDF) may have potential use in the prevention of HBVr in patients undergoing chemo/immunosuppressive therapy. As high long-term antiviral efficacy leading to undetectable HBV DNA levels is necessary, clinical guidelines recommend the use of potent NUCs with high genetic barriers, such as ETV or TDF, over LAM prophylaxis against HBVr in such patients.[9,10] More recent antiviral agents, such as tenofovir alafenamide fumarate (TAF), which is a prodrug proven to be non-inferior to TDF by providing a more stable plasma concentration of tenofovir, have also been proposed to have some beneficial aspects, such as less drug exposure to bone and kidneys.[11] Little data have been gathered on the efficacy and tolerability of TAF prophylaxis in HBV-infected patients undergoing chemo/immunosuppressive and biological modifier therapies. Thus, the aim of the study was to determine the efficacy and tolerability of TAF prophylaxis in HBV-infected or HBV-experienced individuals undergoing chemo/immunosuppressive and biological modifier therapies.

Materials and Methods

Patients

Between January 2019 and June 2021, a total of 326 HBV-infected or HBV-experienced patients who were candidates for chemo/immunosuppressive and/or biological modifier therapies were enrolled in this investigation. TAF was administered at a dose of 25 mg/day at the initiation of chemo/immunosuppressive therapy. A specific electronic case report form (CRF) was designed for data collection and recording. Each center entered the relevant data into the CRF. This study was approved by the Ankara University Ethics Committee of the Ankara Medical School (12.06.2020/09.2020.698), and written informed consent was waived due to the retrospective nature of the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

The laboratory investigations conducted included serum alanine aminotransferase (ALT), aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, bilirubin, creatinine, fasting glucose levels, lipid profile, and prothrombin time. Complete blood cell counts were obtained using the local central laboratory of each unit. HBsAg, anti-HBs antibody, HBeAg, anti-HBe antibody, anti-HBc IgM and IgG antibodies, and anti-delta antibody were performed. HBV DNA levels were measured using the Roche COBAS TaqMan assay (lower limit of quantitation of 20 IU/mL).

Definitions

HBVr was defined as the presence of abnormal serum ALT levels (>1.3-fold increase above the upper limit of normal), detection of HBV DNA in individuals with previously undetectable HBV DNA levels, a ≥2 log increase in HBV DNA level from baseline, or sero-reversion of HBsAg in HBsAg-negative individuals.

Hypophosphatemia was defined as a serum phosphate level of less than 2.5 mg/dL.

The primary endpoint of the study was to determine the incidence of HBVr and hepatitis flare during TAF prophylaxis. The secondary endpoint was to determine the tolerability and adverse effects of TAF in such patients.

Safety

Safety and tolerability analyses were assessed during TAF prophylaxis. Adverse events (AEs), serious AEs, laboratory abnormalities, drug discontinuation due to AEs, and deaths were evaluated. Serum creatinine level and estimated glomerular filtration rates (eGFR) were evaluated. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.

Follow-up

All patients were seen at three- or six-month intervals in the outpatient clinic after antiviral prophylaxis was started. A physical examination was performed, and vital signs and patient compliance were assessed. Blood was drawn to determine metabolic, biochemical, and serological parameters. HBsAg and HBeAg loss and seroconversion were monitored.

Statistical Analysis

Means and standard deviations, medians, ranges and interquartile ranges, and frequencies and percentages were used in descriptive statistics. For categorical variables, differences between groups were assessed using the chi-squared test or Fisher's exact test as appropriate. GLMMs (Generalized Linear Mixed Models) were conducted for comparisons versus baseline values. R vers. 2.15.3 software (R Core Team, 2013) was used for data analyses. P-values of less than 0.05 were considered statistically significant.

Results

A total of 158 HBV-infected or HBV-experienced individuals with benign and malignant diseases who received TAF prophylaxis were included in the analysis. The remaining 168 patients who were lost to follow-up (n=78), followed short term (<6 months) (n=63), or died (n=27) due to primary disease were excluded (Fig. 1). The mean age

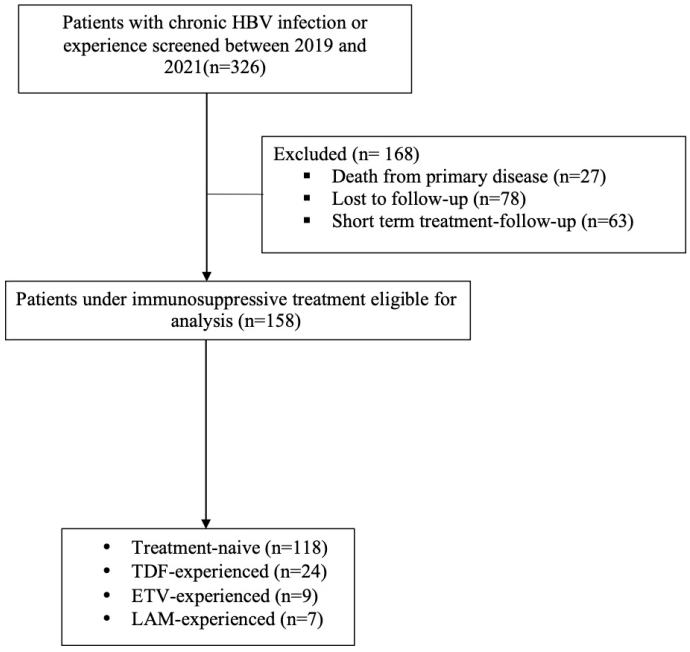

Figure 1. Study flow chart.

ETV: Entecavir; HBV: Hepatitis B virus; LAM: Lamivudine; TDF: Tenofovir disoproxil fumarate.

was 59.5±12.2 years, and the gender distribution was predominantly male (52.5%). Before starting TAF prophylaxis, 51 individuals (32.3%) were HBsAg-positive, while the remaining 107 individuals (67.7%) were HBV-experienced (anti-HBs positivity and anti-HBc IgG positivity). Thirty patients had a detectable HBV DNA level: 27 were HBsAg-positive, and the remaining three were only anti-HBc IgG-positive as occult hepatitis B infection. Twelve of these 30 patients had abnormal serum ALT levels (>40 U/L). Overall, only eight patients (8/158, 5%) were HBeAg-positive. Before TAF prophylaxis, 118 patients were treatment-naive. Forty patients were initially treated with TDF (n=24), ETV (n=9), or LAM (n=7) and were switched to TAF due to older age (>60 years), renal dysfunction, or osteoporosis. The characteristics of the patients are summarized in Table 1.

Solid tumors (33.5%) were the most common primary disease types, followed by rheumatologic/autoimmune diseases (32.9%) and myeloproliferative diseases (32.2%). Overall, 48% of the patients received cytotoxic chemotherapy, 17% received B-cell–depleting therapy, 13% received anti-TNF therapy, 8% received glucocorticoid therapy, and 12% received biological modifier therapies (imatinib, revlimid, ocrelizumab, bevacizumab, or ibrutinib). The characteristics of the primary diseases and chemo/immunosuppressive and/or biological modifier therapies are presented in Table 1. The median follow-up period was 17.2 months (range, 9.4–25 months).

During and after the administration of chemo/immunosuppressive and/or biological modifier therapies, none of the patients had clinical, biochemical, or serological evidence of HBVr during TAF prophylaxis. From baseline to the end of the follow-up period, the virological response rate was 87%. Serum ALT levels were significantly improved in patients with abnormal ALT levels from baseline to the end of the follow-up period (p=0.04). HBV suppression was well maintained after switching in the 40 patients who were switched to TAF treatment.

Table 1. Baseline characteristics of patients who received TAF prophylaxis for HBV reactivation

	Whole cohort (n=158)
Age, years, median (min–max)	59.6 (23–85)
Male sex, n (%)	83 (53)
Hypertension, n (%)	62 (41)
Diabetes mellitus, n (%)	37 (24)
Chronic renal failure, n (%)	28 (19)
Osteoporosis, n (%)	27 (32)
Diagnoses requiring IS therapy, n (%)	
Solid malignancies	53 (34)
Rheumatologic/autoimmune	52 (33)
Myeloproliferative disease	51 (32)
Stem cell transplantation	2 (1)
IS treatment type, n (%)	
Cytotoxic chemotherapy	77 (48)
B cell suppressing therapies	27 (17)
Anti-TNF	21 (13)
Glucocorticoids	13 (8)
Others	20 (12)
Previous nucleoside/nucleotide use (%)	
Treatment naive	118 (75)
Tenofovir disoproxil fumarate	24 (15)
Entecavir	9 (6)
Lamivudine	7 (4)
Initial HBV status, n (%)	
HBs-Ag positive	51 (32)
Anti-HBc positive	107 (68)
HBe-Ag positive	8 (5)
Detectable HBV-DNA	27
Follow-up period, months	17.2±7.8
Exitus from underlying disease, n (%)	27 (17)

IS: Immunosuppressive; TNF: Tumor-necrosis factor; HBV: Hepatitis B virus.

Safety

TAF prophylaxis was well tolerated. Headache, nausea, and fatigue were the most common adverse effects. No drug discontinuation was observed due to adverse effects. No HBV-related morbidity or mortality was observed. All patients maintained their chemo/immunosuppressive therapy without interruption. No significant clinical side effects or serious AEs were reported during TAF prophylaxis

Changes in laboratory values during the follow-up period in treatment-naive and TDF-experienced patients are presented in Table 2 and Table 3. In the treatment-naive group, the mean eGFR change

Table 2. Changes in laboratory values of patients who received TAF prophylaxis **(treatment-naive)**

Treatment-naive (n=118	Baseline (mean±SD)	6-months (mean±SD)	12-months (mean±SD)	18-months (mean±SD)	24-months (mean±SD)	p value (pairwise comparisons vs baseline)			
						6-mon.	12-mon.	18-mon.	24-mon.
Fasting glucose (mg/dL)	110.7±37.1	117.6±37.7	122.9±61.6	112.4±38.1	103.0±22.5	0.095	0.033*	0.147	0.693
Total cholesterol (mg/dL)	200.5±55.1	199.5±50.0	222.3±50.1	236.8±100.0	252.3±92.0	0.322	0.290	0.484	0.187
Triglycerides (mg/dL)	147.5±90.1	179.3±111.7	165.17±106.72	168.9±95.5	168.7±77.7	0.050	0.506	0.083	0.019*
HDL (mg/dL)	46.2±14.5	45.6±11.5	53.1±16.3	54.6±20.9	60.1±21.7	0.755	0.165	0.754	0.244
LDL (mg/dL)	125.8±43.8	119.5±35.3	146.6±39.8	149.3±90.7	140.5±91.3	0.788	0.318	0.502	0.877
eGFR (mL/min)	83.2±26.5	84.2±23.7	82.7±26.1	84.1±27.8	91.5±27.3	0.423	0.906	0.126	0.936
Blood phosphate (mg/dL)	3.5±0.8	3.4±0.7	3.3±0.6	3.4±0.6	3.3±0.6	0.061	0.015*	0.069	0.150

eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SD: Standard deviation; Mon: Months; *: Indicates p-values <0.05.

Table 3. Changes in laboratory values of patients who received TAF prophylaxis **(TDF experienced)**

TDF-experienced (n=24	Baseline (mean±SD)	6-months (mean±SD)	12-months (mean±SD)	18-months (mean±SD)	24-months (mean±SD)	p value (pairwise comparisons vs baseline)			
						6-mon.	12-mon.	18-mon.	24-mon.
Fasting glucose (mg/dL	93.81±13.07	122.89±41.79	105±37.09	107.5±46.48	91.67±17.36	0.039*	0.244	0.263	0.920
Total cholesterol (mg/dL)	203±48.85	199.5±50.2	183.33±29.74	208±0	216.5±12.02	0.998	0.996	0.867	0.652
Triglycerides (mg/dL)	141.44±75.16	142.64±39.55	116.33±30.24	156±0	141.5±20.51	0.976	0.829	0.582	0.999
HDL (mg/dL)	47.63±17.9	46.5±10.33	63.33±22.05	69±0	62.5±9.19	0.758	0.270	0.477	0.377
LDL (mg/dL)	122.67±38.16	124.49±36.84	105±20.66	136±0	139±4.24	0.329	0.998	0.496	0.795
eGFR (mL/min)	82.68±23.68	83.97±23.13	83.89±23.39	78.59±30.48	100.7±12	0.571	0.314	0.361	0.138
Blood phosphate (mg/dL)	3.34±0.77	3.51±0.71	3.02±0.63	3.31±0.97	3.08±0.71	0.436	0.405	0.947	0.636

eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SD: Standard deviation; Mon: Months; *: Indicates p-values <0.05.

from baseline to the end of the follow-up period during TAF prophylaxis was generally stable (82.9 mL/min to 91.5 mL/min). Serum phosphorus levels remained stable in 87% of the patients, temporarily decreased in 8.5%, and decreased in 4.6% during TAF prophylaxis. At baseline, hypophosphatemia (<2.5 mg/dL) was found in seven patients. At the end of the follow-up period, hypophosphatemia improved in six of these seven patients. No differences were found in the eGFR change and hypophosphatemia in the follow-up of patients with TDF experience.

Serum triglyceride (TG) levels were significantly increased from baseline to the end of the follow-up period in antiviral treatment-naive patients (p=0.019). Serum fasting glucose levels increased at 48 weeks (p=0.033) but improved at 96 weeks in these patients. However, serum fasting low-density lipoprotein cholesterol (LDL) levels were slightly increased (mean from 125.8±43.8 mg/dL to 140.5±91.3 mg/dL, p=0.877) (Table 3). Serum fasting glucose levels and lipid profiles did not significantly change in the follow-up of patients with TDF experience.

Overall, 27 patients died because of progression of primary diseases.

Discussion

This is the first multicenter observational study with a large sample to determine the efficacy and tolerability of TAF prophylaxis in HBV-infected or HBV-experienced individuals receiving chemo/immunosuppressive and/or biological modifier therapies. No HBVr or HBV-related morbidity or mortality was observed during TAF prophylaxis. TAF prophylaxis also enabled patients treated with these agents to complete their treatment protocol without interruption because of HBVr. Two single-center studies have recently reported that TAF prophylaxis is effective against HBV infection in HBV-infected patients undergo-

ing chemotherapy.[12,13] This result indicates that TAF prophylaxis in HBV-infected or HBV-experienced individuals receiving chemo/immunosuppressive and/or biological modifier therapies prevents chemo/immunosuppressive therapy–induced HBVr.

Current HBV clinical practice guidelines recommend ETV, TDF, and TAF as the first-line treatment options in patients with chronic hepatitis B (CHB).[14,15] Real-world studies have shown that TAF is effective and tolerable without the emergence of drug resistance in patients with CHB.[16–18] Therefore, TAF should be preferable to TDF or ETV in patients of older age (>60 years), with renal dysfunction, bone disease (osteopenia/osteoporosis), or prior NUC experience.[14,15,19] TAF does not require renal dose adjustment in patients with chronic kidney disease (CKD) and is not affected by food digestion.[20] Taking advantage of these benefits, TAF has been widely used in patients with CHB in clinical practice. However, limited data report the efficacy and tolerability of TAF prophylaxis in HBV-infected or HBV-experienced individuals receiving chemo/immunosuppressive and/or biological modifier therapies in preventing chemo/immunosuppressive therapy–induced HBVr. The present study shows that TAF treatment has a high virological response rate, comparable with a previous study demonstrating a virological response rate of 96% more than one year after starting TAF prophylaxis.[13] Notably, all patients who switched from other NUC treatments to TAF had a comparably high virological response rate after switching.

Minimal renal dysfunction has been reported during long-term NUC therapy, but the nephrotoxic potential is higher with TDF treatment than with ETV or TAF.[14] In addition, fluctuations in renal function tests have been frequently described, and a significant proportion of patients may experience acute kidney injury (AKI) and CKD stage migration during chemo/immunosuppressive therapies.[21,22] AKI is associated with increased morbidity and mortality during this therapy. AKI may also lead to interruption of the treatment protocol. Chemotherapeutic agents such as cisplatin, as well as higher baseline serum creatinine, bilirubin levels, and hypoalbuminemia, are independent risk factors for the development of AKI in such individuals. Lee et al.[13] found no significant difference in the incidence of renal events among the ETV, TDF, and TAF groups receiving chemo/immunosuppressive therapy. In the present study, no significant changes were found in the mean eGFR and serum creatinine levels from baseline to the end of the follow-up period during TAF prophylaxis. No major renal-related adverse effects were observed. Serum phosphate levels were stable in most of the patients. It should be noted that hypophosphatemia improved in six of the seven patients during TAF prophylaxis.

According to previous reports, switching from TDF to TAF seems to be associated with body weight gain, cardiovascular risk scores, and altered lipid profiles with higher LDL and TG levels.[23–32] In the present study, prophylactic TAF treatment was shown to be associated with higher fasting glucose levels at 48 weeks and higher TG levels at 98 weeks. However, the clinical importance of these effects is not yet clearly understood.

Our study has several limitations. As described in the Materials and Methods section, this study aimed to collect data on patients who received prophylactic TAF. Unfortunately, there was no control group to compare the virological response rate and safety potency among the groups. TAF has been demonstrated to have a greater extent of reduction in serum HBsAg levels compared with ETV.[17] Several automated assays have been developed to quantify serum HBsAg levels. The Architect HBsAg QT assay (Abbott Diagnostics, Abbott Park, IL, USA) and the Elecsys HBsAg II assay (Roche Diagnostics, Indianapolis, IN, USA) are the most widely used. Standard HBsAg quantification assays were not routinely used in clinical practice in Turkiye. Bone mineral density at the hip and spine decreases during TDF and TAF treatments. However, this study did not include data regarding body weight or bone mineral density during prophylactic TAF treatment.

Conclusion

TAF prophylaxis prevents chemo/immunosuppressive therapy–induced HBVr in HBV-infected or HBV-experienced individuals receiving chemo/immunosuppressive and/or biological modifier therapies. Prophylactic TAF treatment is safe and tolerable in such individuals.

Ethics Committee Approval: The Ankara University Clinical Research Ethics Committee granted approval for this study (date: 12.06.2020, number: 09.2020.698).

Informed Consent: written informed consent was waived due to the retrospective nature of the study.

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

Financial Disclosure: This is an investigator-sponsored Clinical Trial Study investigating the REAL-Life Efficacy and TolerabilitY of Tenofovir Alafenamide Fumarate (TAF) in special groups of Hepatitis B patients (REALITY) which is conducted on behalf of Turkish Association for The Study of Liver (TASL) by the grant of Gilead Sciences, Inc, Foster City CA. (IN-TR-320-5958).

Use of AI for Writing Assistance: Not declared.

Author Contributions: Author Contributions: Concept – RI; Design – RI, SY, FD,HG; Supervision – RI, SY, FD, HG; Data Collection and/or Processing – SD, YU, MD, AEY, ZME, SP, HA, ES, EU, YB; Analysis and/or Interpretation – DOE, PG, DA, FD, COD; Literature Search – FD, COE; Writing – FD, COD; Critical Reviews – FD, SD, YU, MD, AEY, ZME, SM, HA, SY, COD, EU, YB, NE, HG, ESK, DD, OS, HS, NT, MA, RI, DOE, PG, DA, KO, MA, SB.

Acknowledgments: We appreciate the TASL Viral Hepatitis Special Interest Group for their contribution in the study design, data collection and preparation of the manuscript.

Peer-review: Externally peer-reviewed.

References

1. Organization WH. Hepatitis B: WHO; 2022 [Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b.
2. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology. 2009;49(5 Suppl):S45-55. [CrossRef]
3. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect. 2015;21(11):1020-6. [CrossRef]
4. Aygen B, Demir AM, Gumus M, Karabay O, Kaymakoglu S, Koksal AS, et al. Immunosuppressive therapy and the risk of hepatitis B reactivation: Consensus report. Turk J Gastroenterol. 2018;29(3):259-69. [CrossRef]
5. Myint A, Tong MJ, Beaven SW. Reactivation of Hepatitis B Virus: A Review of Clinical Guidelines. Clin Liver Dis (Hoboken). 2020;15(4):162-7. [CrossRef]
6. Smalls DJ, Kiger RE, Norris LB, Bennett CL, Love BL. Hepatitis B Virus Reactivation: Risk Factors and Current Management Strategies. Pharmacotherapy. 2019;39(12):1190-203. [CrossRef]
7. Loomba R, Liang TJ. Hepatitis B Reactivation Associated With Immune Suppressive and Biological Modifier Therapies: Current Concepts, Management Strategies, and Future Directions. Gastroenterology. 2017;152(6):1297-309. [CrossRef]

8. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015;148(1):221-44 e3. [CrossRef]
9. Reddy KR, Beavers KL, Hammond SP, Lim JK, Falck-Ytter YT, American Gastroenterological Association I. American Gastroenterological Association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015;148(1):215-9; quiz e16-7. [CrossRef]
10. Lau G, Yu ML, Wong G, Thompson A, Ghazinian H, Hou JL, et al. APASL clinical practice guideline on hepatitis B reactivation related to the use of immunosuppressive therapy. Hepatol Int. 2021;15(5):1031-48. [CrossRef]
11. Lee WA, He GX, Eisenberg E, Cihlar T, Swaminathan S, Mulato A, et al. Selective intracellular activation of a novel prodrug of the human immunodeficiency virus reverse transcriptase inhibitor tenofovir leads to preferential distribution and accumulation in lymphatic tissue. Antimicrob Agents Chemother. 2005;49(5):1898-906. [CrossRef]
12. Inada K, Kaneko S, Kurosaki M, Yamashita K, Kirino S, Osawa L, et al. Tenofovir alafenamide for prevention and treatment of hepatitis B virus reactivation and de novo hepatitis. JGH Open. 2021;5(9):1085-91. [CrossRef]
13. Lee IC, Lan KH, Su CW, Li CP, Chao Y, Lin HC, et al. Efficacy and Renal Safety of Prophylactic Tenofovir Alafenamide for HBV-Infected Cancer Patients Undergoing Chemotherapy. Int J Mol Sci. 2022;23(19). [CrossRef]
14. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370-98.
15. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560-99. [CrossRef]
16. Lampertico P, Buti M, Fung S, Ahn SH, Chuang WL, Tak WY, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study. Lancet Gastroenterol Hepatol. 2020;5(5):441-53. [CrossRef]
17. Uchida Y, Nakao M, Yamada S, Tsuji S, Uemura H, Kouyama JI, et al. Superiority of tenofovir alafenamide fumarate over entecavir for serum HBsAg level reduction in patients with chronic HBV infection: A 144-week outcome study after switching of the nucleos(t)ide analog. PLoS One. 2022;17(2):e0262764. [CrossRef]
18. Agarwal K, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, et al. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. J Hepatol. 2018;68(4):672-81. [CrossRef]
19. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10(1):1-98. [CrossRef]
20. Tamaki N, Kurosaki M, Nakanishi H, Itakura J, Inada K, Kirino S, et al. Comparison of medication adherence and satisfaction between entecavir and tenofovir alafenamide therapy in chronic hepatitis B. J Med Virol. 2020;92(8):1355-8. [CrossRef]
21. Perazella MA, Shirali AC. Nephrotoxicity of Cancer Immunotherapies: Past, Present and Future. J Am Soc Nephrol. 2018;29(8):2039-52. [CrossRef]
22. Santos MLC, de Brito BB, da Silva FAF, Botelho A, de Melo FF. Nephrotoxicity in cancer treatment: An overview. World J Clin Oncol. 2020;11(4):190-204. [CrossRef]
23. Gomez M, Seybold U, Roider J, Harter G, Bogner JR. A retrospective analysis of weight changes in HIV-positive patients switching from a tenofovir disoproxil fumarate (TDF)- to a tenofovir alafenamide fumarate (TAF)-containing treatment regimen in one German university hospital in 2015-2017. Infection. 2019;47(1):95-102. [CrossRef]
24. Kuo PH, Sun HY, Chuang YC, Wu PY, Liu WC, Hung CC. Weight gain and dyslipidemia among virally suppressed HIV-positive patients switching to co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide. Int J Infect Dis. 2020;92:71-7. [CrossRef]
25. Taramasso L, Berruti M, Briano F, Di Biagio A. The switch from tenofovir disoproxil fumarate to tenofovir alafenamide determines weight gain in patients on rilpivirine-based regimen. AIDS. 2020;34(6):877-81. [CrossRef]
26. Mallon PW, Brunet L, Hsu RK, Fusco JS, Mounzer KC, Prajapati G, et al. Weight gain before and after switch from TDF to TAF in a U.S. cohort study. J Int AIDS Soc. 2021;24(4):e25702. [CrossRef]
27. Mallon PWG, Brunet L, Fusco JS, Prajapati G, Beyer A, Fusco GP, et al. Lipid Changes After Switch From TDF to TAF in the OPERA Cohort: LDL Cholesterol and Triglycerides. Open Forum Infect Dis. 2022;9(1):ofab621. [CrossRef]
28. Plum PE, Maes N, Sauvage AS, Frippiat F, Meuris C, Uurlings F, et al. Impact of switch from tenofovir disoproxil fumarate-based regimens to tenofovir alafenamide-based regimens on lipid profile, weight gain and cardiovascular risk score in people living with HIV. BMC Infect Dis. 2021;21(1):910. [CrossRef]
29. Brunet L, Mallon P, Fusco JS, Wohlfeiler MB, Prajapati G, Beyer A, et al. Switch from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide in People Living with HIV: Lipid Changes and Statin Underutilization. Clin Drug Investig. 2021;41(11):955-65. [CrossRef]
30. Ikeda M, Wakabayashi Y, Okamoto K, Yanagimoto S, Okugawa S, Moriya K. Changing trends in lipid profile and biomarkers of renal function and bone metabolism before and after switching from tenofovir disoproxil fumarate to tenofovir alafenamide: a prospective observational study. AIDS Res Ther. 2021;18(1):30. [CrossRef]
31. Kauppinen KJ, Aho I, Sutinen J. Switching from tenofovir alafenamide to tenofovir disoproxil fumarate improves lipid profile and protects from weight gain. AIDS. 2022;36(10):1337-44. [CrossRef]
32. Milinkovic A, Berger F, Arenas-Pinto A, Mauss S. Reversible effect on lipids by switching from tenofovir disoproxil fumarate to tenofovir alafenamide and back. AIDS. 2019;33(15):2387-91. [CrossRef]

HEPATOLOGY FORUM

doi: 10.14744/hf.2025.29517

Future burden of MASLD in the United States: A state-level forecasting study, 2022-2050

Thanathip Suenghataiphorn[1], Kanachai Boonpiraks[2], Vitchapong Prasitsumrit[3], Narathorn Kulthamrongsri[4], Pojsakorn Danpanichkul[3]

[1]Department of Internal Medicine, Griffin Hospital, Connecticut, United States; [2]University of Kansas Medical Center, Kansas City, United States; [3]Department of Internal Medicine, Texas Tech University Health Science Center, Texas, United States; [4]University of Hawaii, Honolulu, Hawaii, United States

Abstract

Background and Aim: The rising prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) poses a significant public health challenge, yet the future burden at a subnational level is poorly quantified. State-specific projections are crucial for guiding policy, resource allocation, and targeted public health interventions. We project the future burden of MASLD by state to 2050.

Materials and Methods: We developed a state-level forecasting model using data from the Global Burden of Disease (GBD) 2021 study and state-level population projections from the Weldon Cooper Center. For each state, historical age- and sex-specific MASLD DALY rates (1990–2021) were projected to 2050 using automatic ARIMA/ETS time-series forecasting. Projected rates were then applied to annual state population projections to estimate the absolute DALY burden. Associated direct healthcare costs were calculated using a derived national-average cost per MASLD DALY, discounted at 3% annually. A probabilistic sensitivity analysis (PSA) with 1,000 iterations was performed to quantify uncertainty in baseline DALY rates and costs.

Results: Over the projection period (2022–2050), the total discounted MASLD burden in the U.S. is projected to be 5.5 million DALYs, with associated healthcare costs exceeding $2.3 trillion. The absolute burden is concentrated in the most populous states, with California (Mean DALYs: 444,363; 95% UI: 395,767–494,159), Texas (386,956; 95% UI: 337,640–435,164), and Florida (311,884; 95% UI: 275,974–347,758) projected to have the highest lifetime burdens. However, DALY rates per 100,000 population are projected to be highest in states within the South and Appalachia.

Conclusion: The future burden of MASLD in the United States is projected to be substantial, growing, and geographically unequal, with distinct hotspots of high per-capita burden and divergent future trends. These state-level projections underscore the urgent need for tailored, regional public health strategies and provide essential data to inform state-level policy and resource allocation to address the escalating MASLD epidemic.

Keywords: DALY; economic model; global burden of disease (GBD); MASLD; state-variation.

How to cite this article: Suenghataiphorn T, Boonpiraks K, Prasitsumrit V, Kulthamrongsri N, Danpanichkul P. Future burden of MASLD in the United States: A state-level forecasting study, 2022–2050. Hepatology Forum 2026; 7(1):32–37.

Received: October 11, 2025; **Revised:** November 13, 2025; **Accepted:** November 22, 2025; **Available online:** December 00, 2025

Corresponding author: Thanathip Suenghataiphorn; Department of Internal Medicine, Griffin Hospital, Connecticut, United States
Phone: +1 443 484 84 64; **e-mail:** Thanathip.sue@gmail.com

Hepatology Forum - Available online at www.hepatologyforum.org

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), has emerged as the most common chronic liver condition in the United States[1] and a leading cause of cirrhosis, hepatocellular carcinoma, and liver transplantation.[2] Driven by the parallel epidemics of obesity and type 2 diabetes, the prevalence of MASLD has risen dramatically over the past three decades,[3] imposing a substantial and growing burden on the U.S. healthcare system and society.[4]

While national-level studies have effectively highlighted the scale of the MASLD epidemic,[5] they often mask significant regional heterogeneity. The burden of MASLD and its primary drivers are not uniformly distributed across the country;[6] rather, they exhibit distinct geographic patterns influenced by state-level variations in demographics,[7] socioeconomic factors,[8] lifestyle behaviors,[9] and public health infrastructure.[10] Consequently, effective public health planning, resource allocation, and the implementation of targeted prevention strategies,[11] as seen in other diseases,[12] depend on a clear understanding of the future trajectory of MASLD at a subnational level.

To date, a critical gap exists in the literature: there are no comprehensive, state-level projections of the future health and economic burden of MASLD. Policymakers, healthcare providers, and public health officials in individual states currently lack the forward-looking, data-driven evidence needed to prepare for the coming wave of MASLD-related morbidity and mortality. Quantifying the expected rise in Disability-Adjusted Life Years (DALYs)—a summary measure of population health that combines years of life lost with years lived with disability—and the associated healthcare costs is essential for justifying investments in prevention, optimizing healthcare capacity, and addressing health disparities.

The Global Burden of Disease (GBD) study offers vital estimates, serving as crucial proxies for the burden of conditions now largely under the MASLD umbrella, including severe sequelae like cirrhosis and related HCC. The terminological evolution from NAFLD to MASLD signifies a refined pathophysiological understanding. MASLD diagnosis hinges on hepatic steatosis coupled with metabolic dysfunction. Given MASLD criteria align closely with the NAFLD diagnosis,[13–16] historical NAFLD epidemiological data remain largely applicable. While the GBD 2021 dataset predates this updated nomenclature, the present study prospectively harmonizes these GBD estimates with current MASLD terminology to accurately reflect the contemporary disease burden and its multifaceted impact, as also utilized in other studies.[17,18] Recent epidemiological studies directly comparing the diagnostic

criteria for NAFLD and MASLD have demonstrated a substantial overlap, with the vast majority of individuals with NAFLD also meeting the criteria for MASLD,[19,20] thus supporting the use of historical NAFLD data as a reliable proxy for the MASLD burden in population-level forecasting.

This study aims to address this critical gap by projecting the future burden of MASLD for all 50 U.S. states and the District of Columbia from 2022 to 2050. Using a robust forecasting model based on historical disease trends and state-specific demographic projections, we seek to provide the first comprehensive, state-level estimates of the future health (DALYs) and direct economic burden of MASLD in the United States.

Materials and Methods

We developed a state-level microsimulation model to project the future health and economic burden of MASLD for all 50 U.S. states and the District of Columbia from 2022 to 2050. The model was built and analyzed using R (The R Project for Statistical Computing). This study adheres to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022 reporting guidelines where applicable.

Model Overview

The model synthesizes data on historical disease burden, state-level population projections, and healthcare costs. The core analytical process involved four main stages: (1) processing and harmonizing input data; (2) forecasting future MASLD DALY rates for each state using time-series analysis; (3) calculating the projected annual absolute DALYs and associated costs by applying the forecasted rates to state population projections; and (4) performing probabilistic and deterministic sensitivity analyses to quantify uncertainty and test model assumptions.

Data Sources

All model inputs, including their sources and underlying assumptions, are detailed in Appendix Table 1. Appendix Data 1 shows the CHEERS checklist.

MASLD Burden Data: Historical data on MASLD burden from 1990 to 2021 were extracted from the Global Burden of Disease (GBD) 2021 study.[21] We obtained state-level, age-, and sex-specific DALY rates (per 100,000 population) for the cause "Total burden related to Non-alcoholic fatty liver disease (NAFLD)."

Population Data: State-level historical population data (1990–2021) were sourced from the GBD 2021 study. State-level population projections from 2022 to 2050 by age and sex were obtained from the Weldon Cooper Center for Public Service National Population Projections.[22] As the projection data were provided in decadal intervals (2020, 2030, 2040, 2050), we used linear interpolation to estimate annual population counts for each state-sex-age stratum.

Economic Data: The direct annual healthcare cost per MASLD patient was based on a published estimate of long-term annual cost increasement of $1,491 (2015 USD),[23] which was inflated to 2021 USD using the Consumer Price Index for Medical Care.[24] A national-average cost per MASLD DALY was then derived by combining this per-patient cost with national-level GBD 2021 data on total MASLD prevalence and DALYs for the United States. This national-average cost parameter was applied uniformly across all states.

Data Harmonization

A critical step in the modeling process was to harmonize the age structures of the different data sources. The GBD health data is provided in fine-grained age groups, while the state-level population projection data groups all individuals aged 85 and over into a single "85+" category. To ensure consistency, we consolidated the age structure of all datasets to match this limitation, resulting in a final model structure with 11 age groups, concluding with a single "85+ years" group. The aggregation of GBD DALY rates was performed by converting rates to absolute DALY numbers using historical population data, summing these absolute numbers within the new consolidated age groups, and then recalculating a population-weighted aggregate rate.

Burden Projection (Deterministic Analysis)

For each of the 1,326 unique strata (51 states × 2 sexes × 11 age groups), we projected the MASLD DALY rate from 2022 to 2050. The historical DALY rate for each stratum (1990–2021) was treated as a time series. We used the auto.arima() function from the forecast package in R, which automatically selects the best-fitting Autoregressive Integrated Moving Average (ARIMA)[25] or Exponential Smoothing (ETS) model based on the Akaike Information Criterion (AICc). For strata with insufficient historical data (<5 non-zero data points), the forecast conservatively defaulted to the last observed DALY rate.

The projected annual DALY rate for each stratum was then multiplied by the corresponding projected annual population to calculate the absolute number of undiscounted DALYs for each year. These annual DALYs were subsequently multiplied by the derived national-average cost per DALY to estimate annual direct healthcare costs. Both costs and DALYs were discounted at a rate of 3% per annum to their present value in 2021.

Uncertainty and Sensitivity Analyses

Probabilistic Sensitivity Analysis (PSA): To quantify parameter uncertainty, we conducted a PSA with 1,000 iterations. In each iteration, two key parameters were sampled from probability distributions. First, the baseline (2021) DALY rate for each stratum was sampled from a normal distribution, with the mean and standard deviation derived from the point estimate and uncertainty interval provided by the GBD 2021 study. Second, the national-average cost per DALY was sampled from a triangular distribution. The mean and 95% uncertainty intervals (2.5th and 97.5th percentiles) for total discounted DALYs and costs for each state were calculated from the PSA outputs.

One-Way Sensitivity Analysis (OWSA): We performed a deterministic OWSA to assess the impact of key model parameters on the total lifetime discounted costs for the entire U.S. The parameters varied included the cost per MASLD DALY, the discount rate (varied from 0% to 5%), and the overall MASLD DALY rate trend (varied by ±20%). The results were visualized using a tornado diagram.

Results

Projected National Burden of MASLD

Over the 29-year projection period (2022–2050), the total discounted health and economic burden of MASLD in the United States is projected to be substantial. Across all states, the model projects a total of 5.5 million discounted DALYs and $2.3 trillion in associated discounted direct healthcare costs. The undiscounted annual burden is projected to

Table 1. Projected total undiscounted MASLD burden for the United States by decade

Decade	Total annual DALYs	Total annual costs (USD)
2020s	1,671,449	635,283,721,232
2030s	2,274,726	864,577,029,746
2040s	2,460,477	935,177,385,353
2050s	257,483	97,864,122,993

MASLD: Metabolic dysfunction-associated steatotic liver disease; DALYs: Disability-adjusted life years.

increase over time, rising from approximately 215,000 DALYs in 2022 to over 275,000 DALYs in 2050, driven by both population growth and evolving epidemiological trends. The majority of this burden is projected to occur in the latter decades of the analysis period, with over half of the total lifetime costs accumulating after the year 2040 (Table 1). Appendix Table 2 provides the full 50-state projected MASLD burden by state. Appendix Table 3 shows the alternative discount rates.

State-Level Disparities in Absolute Lifetime Burden

The absolute lifetime burden of MASLD is highly concentrated in a small number of populous states (Table 2). California is projected to have the highest burden, with a mean of 444,363 total discounted DALYs (95% Uncertainty Interval [UI]: 395,767–494,159), followed by Texas (Mean DALYs: 386,956; 95% UI: 337,640–435,164) and Florida (Mean DALYs: 311,884; 95% UI: 275,974–347,758). These three states alone are projected to account for approximately 21% of the total national DALY burden. Conversely, states with smaller populations, such as Vermont, the District of Columbia, and Wyoming, are projected to have the lowest absolute burdens, each with fewer than 10,000 total discounted DALYs over the lifetime of the model. The top ten states by absolute DALYs are visualized in Figure 1.

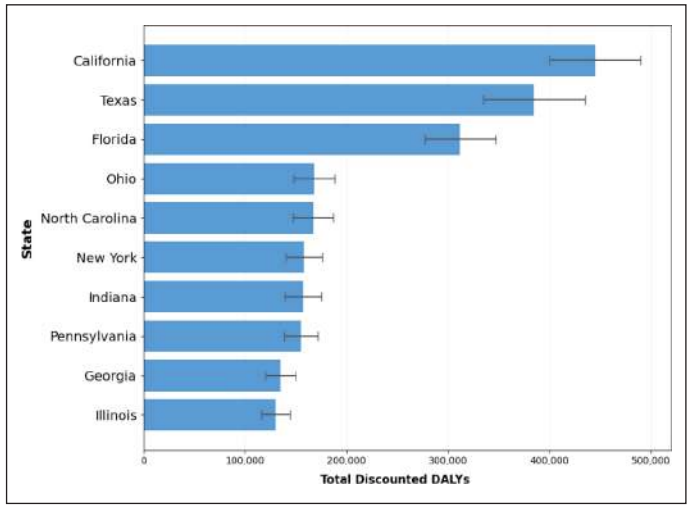

Figure 1. Top 10 states by projected lifetime absolute MASLD DALY burden (2022–2050) with 95% uncertainty intervals.

Geographic Distribution and Future Trends of MASLD DALY Rates

When burden is measured as a population-adjusted rate, a different geographic pattern emerges. The deterministic DALY rate per 100,000 population in 2050 is projected to be highest in states concentrated in the South and Appalachia, including New Mexico, West Virginia, and Kentucky (Appendix Fig. 1). The state-level choropleth map for 2050 visually demonstrates these geographic hotspots of high per-capita burden (Fig. 2).

Furthermore, the future trajectory of the MASLD DALY rate is projected to be highly variable across states (Fig. 3). While the rates in several high-burden states like California and Florida are projected to rise slowly, other states such as Ohio and Wyoming are projected to experience a more pronounced increase. In contrast, the DALY rate in New York is projected to stabilize and slightly decline, suggesting a divergence in future epidemiological trends across the country.

Table 2. Projected lifetime discounted MASLD burden for states with the highest and lowest absolute burden (2022–2050)

State	Total discounted DALYs			Mean costs (USD $)
	Mean DALYs	Lower 95% UI	Upper 95% UI	
California	444,363	395,767	494,159	188.1 B
Texas	386,956	337,640	435,164	163.7 B
Florida	311,884	275,974	347,758	131.9 B
Ohio	168,835	149,648	188,663	71.4 B
North Carolina	167,765	147,313	187,524	71.0 B
Alaska	10,603	9,403	11,946	4.48 B
North Dakota	9,146	8,109	10,228	3.86 B
Wyoming	8,695	7,667	9,750	3.67 B
District of Columbia	7,368	6,440	8,317	3.11 B
Vermont	7,024	6,320	7,797	2,970 M

MASLD: Metabolic dysfunction-associated steatotic liver disease; DALYs: Disability-adjusted life years; UI: Urinary incontinence; B: Billions.

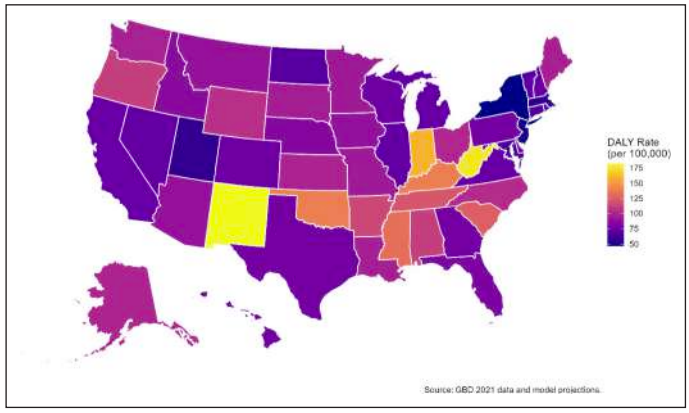

Figure 2. Projected MASLD DALY rate per 100,000 population by state in 2050.

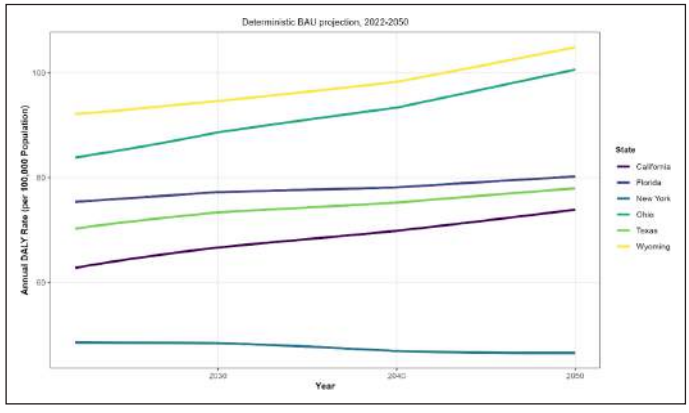

Figure 3. Projected trend in annual MASLD DALY rate for selected states (2022–2050).

Sensitivity Analyses

The one-way sensitivity analysis confirmed that the model's projections of total lifetime costs were most sensitive to the underlying economic assumptions. The cost per MASLD DALY was the single most influential parameter, followed by the discount rate. The underlying epidemiological trend of the MASLD DALY rate was also found to have a substantial impact on the final results (Appendix Fig. 2).

Discussion

In this analytical modeling study, we provide the first comprehensive state-level projections of the health and economic burden of MASLD in the United States through 2050. Our analysis revealed three principal findings: first, the future national burden of MASLD is substantial, projected to exceed 5.5 million DALYs and $2.3 trillion in discounted healthcare costs; second, while the absolute burden is concentrated in populous states like California, Texas, and Florida, the per-capita DALY rates are highest in a different set of states, primarily in the South and Appalachia; and third, the future trajectories of MASLD burden are not uniform, with states exhibiting divergent trends in their projected DALY rates over the coming decades.

Our national-level findings are consistent with previous research indicating a large and growing MASLD burden in the U.S.,[4] with current NHANES database analysis of prevalence of 32%.[20] However, by disaggregating the burden to the state level, our study provides novel and actionable insights. The geographic hotspots of high DALY rates identified by our model closely align with known regional patterns of obesity and type 2 diabetes,[26] the primary drivers of MASLD.[27] For example, the largest increases of obesity occurred in a similar geographic belt stretching from Texas to West Virginia.[28] This geographic pattern is also consistent with well-documented regional disparities in socioeconomic status and healthcare access,[29] which are known determinants of metabolic health outcomes and could exacerbate the burden of MASLD in these 'hotspot' states. This finding reinforces the understanding that MASLD is a key manifestation of the broader metabolic syndrome epidemic[30] and suggests that states with a high prevalence of these risk factors will face the most acute per-capita health challenges from MASLD, as well as long-term challenges from associated liver cancer.[31] The divergent future trends further underscore the importance of subnational analysis, as a single national projection might fail to capture the varying demographic and epidemiological dynamics shaping the future of the disease across the country.

These findings have critical implications for both federal and state-level health policy. For federal agencies and national payers, the immense absolute burden projected for states like California and Texas highlights the need for long-term strategic planning[32] and resource allocation to support the healthcare infrastructure that will be required to manage advanced liver disease in these regions. States with high projected DALY rates, such as New Mexico and West Virginia, have a clear, data-driven mandate to prioritize and intensify primary prevention strategies[33] aimed at reducing obesity and improving metabolic health, as well as utilizing artificial intelligence as seen in other fields.[34] The divergent future trends mean that states cannot rely on national data alone and must invest in their own surveillance and planning to address their unique projected trajectories.

The strengths of this study include the use of comprehensive, longitudinal data from the GBD 2021 study, the application of robust time-series forecasting methods for each of the 1,326 individual strata, and the quantification of uncertainty using a full probabilistic sensitivity analysis. All model parameters, assumptions, and data sources are documented in the supplement. However, this study also has important limitations. First, and most significantly, our economic analysis applied a uniform, national-average cost per DALY across all states due to the absence of state-specific cost data for MASLD. This approach does not capture the substantial regional variations in healthcare prices and utilization and likely over- or underestimates the true economic burden in certain states. Future research would be greatly enhanced by incorporating state-specific medical expenditure indices to provide more granular cost projections. Second, our forecasts are based on historical trends and cannot account for future paradigm shifts, such as the widespread adoption of novel pharmacotherapies for MASLD or major changes in public health policy. Third, our forecasting model relies on time-series analysis of historical trends, which, while robust for short-term projections, carries inherent uncertainty over a long-term (28-year) horizon. These projections are subject to potential model drift and assume that past trends are indicative of the future, which may not capture the full impact of unforeseen shifts in public health, policy, or clinical practice. Fourth, our model relies on the demographic assumptions embedded within the Weldon Cooper Center's state-level population projections. While these projections account for expected trends in fertility, mortality, and state-to-state migration, they may not capture sudden or non-linear demographic shifts that could alter state-specific risk profiles. Fifth, the study did not include a formal statistical correlation between pro-

jected DALY rates and risk factor prevalence and will benefit from further analysis. Finally, the model's age structure was harmonized to the "85+ years" group, the coarsest level of detail available in the state population projection data.

Conclusion

In conclusion, our findings suggest that the health and economic burden of MASLD in the United States will continue to grow substantially through 2050, with significant and enduring disparities between states. This study provides the essential state-level, data-driven evidence needed to inform targeted public health action. These projections underscore the urgent need for state-specific policies and interventions focused on preventing metabolic disease to mitigate the escalating MASLD epidemic and its profound long-term consequences for population health and healthcare expenditures.

Online Appendix Link:
https://hepatologyforum.org/storage/upload/files/1767188973-appendix-en.pdf

Ethics Committee Approval: As this is an epidemiological study, the requirement for formal ethical committee approval was waived for this study because it did not meet the criteria for human subjects research.

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

Financial Disclosure: No funding was sought for this study.

Use of AI for Writing Assistance: The authors acknowledge using Gemini 2.5 Pro (Google) for text editing to improve the fluency of the English language in the preparation of this manuscript. The following prompts were used "Please correct the grammar and fluency of the manuscript below". The authors affirm that the original intent and meaning of the content remain unaltered during editing and that Gemini had no involvement in shaping the intellectual content of this work. The authors assume full responsibility for upholding the integrity of the content presented in this manuscript.

Author Contributions: Concept – TS, VP; Design – TS, NK; Supervision – TS; Data Collection and/or Processing – TS, PD; Analysis and/or Interpretation – TS, PD, NK; Literature Search – TS, PD, KB; Writing – TS, NK; Critical Reviews – TS, KB.

Peer-review: Externally peer-reviewed.

References

1. Lekakis V, Papatheodoridis GV. Natural history of metabolic dysfunction-associated steatotic liver disease. Eur J Intern Med 2024;122:3-10. [CrossRef]
2. Sato-Espinoza K, Chotiprasidhi P, Liza E, Placido-Damian Z, Diaz-Ferrer J. Evolution of liver transplantation in the metabolic dysfunction-associated steatotic liver disease era: Tracking impact through time. World J Transplant 2024;14(4):98718. [CrossRef]
3. Younossi ZM, Kalligeros M, Henry L. Epidemiology of metabolic dysfunction-associated steatotic liver disease. Clin Mol Hepatol 2025;31(Suppl):S32-S50. [CrossRef]
4. Le P, Tatar M, Dasarathy S, Alkhouri N, Herman WH, Taksler GB, et al. Estimated burden of metabolic dysfunction-associated steatotic liver disease in US adults, 2020 to 2050. JAMA Netw Open 2025;8(1):e2454707. [CrossRef]
5. Huang M, Chen H, Wang H, Zhang Y, Li L, Lan Y, et al. Global burden and risk factors of MASLD: trends from 1990 to 2021 and predictions to 2030. Intern Emerg Med 2025;20(4):1013-1024. [CrossRef]
6. Bae JH. Racial and ethnic disparities in metabolic dysfunction-associated steatotic liver disease outcomes: A call for culturally sensitive interventions: Editorial on "Differences in liver and mortality outcomes of non-alcoholic fatty liver disease by race and ethnicity: A longitudinal real-world study". Clin Mol Hepatol 2024;30(4):665-668. [CrossRef]
7. Nguyen VH, Le I, Ha A, Le RH, Rouillard NA, Fong A, et al. Differences in liver and mortality outcomes of non-alcoholic fatty liver disease by race and ethnicity: A longitudinal real-world study. Clin Mol Hepatol 2023;29(4):1002-10128. [CrossRef]
8. Agbim U, Carr RM, Pickett-Blakely O, Dagogo-Jack S. Ethnic disparities in adiposity: Focus on non-alcoholic fatty liver disease, visceral, and generalized obesity. Curr Obes Rep 2019;8(3):243-254. [CrossRef]
9. Leslie T, Pawloski L, Kallman-Price J, Escheik C, Hossain N, Fang Y, et al. Survey of health status, nutrition and geography of food selection of chronic liver disease patients. Ann Hepatol 2014;13(5):533-540. [CrossRef]
10. Yang TC, South SJ. Neighborhood effects on body mass: Temporal and spatial dimensions. Soc Sci Med 2018;217:45-54. [CrossRef]
11. Cole MB, Wilson IB, Trivedi AN. State variation in quality outcomes and disparities in outcomes in community health centers. Med Care 2017;55(12):1001-1007. [CrossRef]
12. Chin HB, Howards PP, Kramer MR, Johnson CY. Understanding the roles of state demographics and state policies in epidemiologic studies of maternal-child health disparities. Am J Epidemiol 2024;193(6):819-826. [CrossRef]
13. Thrift AP, Nguyen TH, Pham C, Balakrishnan M, Kanwal F, Loomba R, et al. The prevalence and determinants of NAFLD and MAFLD and their severity in the VA primary care setting. Clin Gastroenterol Hepatol 2023;21(5):1252-1260.e5. [CrossRef]
14. Song R, Li Z, Zhang Y, Tan J, Chen Z. Comparison of NAFLD, MAFLD and MASLD characteristics and mortality outcomes in United States adults. Liver Int 2024;44(4):1051-1060. [CrossRef]
15. Peng HY, Lu CL, Zhao M, Huang XQ, Huang SX, Zhuo ZW, et al. Clinical characteristics of MASLD/MetALD/MAFLD/NAFLD and the relative risk analysis on metabolic disorders. BMC Gastroenterol 2025;25(1):372. [CrossRef]
16. Elsabaawy M, Naguib M, Abuamer A, Shaban A. Comparative application of MAFLD and MASLD diagnostic criteria on NAFLD patients: insights from a single-center cohort. Clin Exp Med 2025;25(1):36. [CrossRef]
17. 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]
18. Ruan S, Huang L, Song J, Yi Z, Sun W, Zhou F, et al. Global burden trends and forecasts for MAFLD in adolescents and young adults from 1990 to 2021. Sci Rep 2025;15(1):13534. [CrossRef]
19. Huang X, Yu R, Tan X, Guo M, Xia Y, Zou H, et al. Comparison of NAFLD, MAFLD, and MASLD Prevalence and Clinical Characteristics in Asia Adults. J Clin Exp Hepatol 2025;15(1):102420. [CrossRef]
20. Kalligeros M, Vassilopoulos A, Vassilopoulos S, Victor DW, Mylonakis E, Noureddin M. Prevalence of steatotic liver disease (MASLD, MetALD, and ALD) in the United States: NHANES 2017-2020. Clin Gastroenterol Hepatol 2024;22(6):1330-1332.e4. [CrossRef]
21. GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet 2024;403(10440):2100-2132. [CrossRef]
22. Lombard H, Sen S, Cai Q. National population projections. Weldon Cooper Center. University of Virginia. 2024. Available at: https://www.coopercenter.org/national-population-projections Accessed on Dec 29, 2025.
23. Allen AM, Van Houten HK, Sangaralingham LR, Talwalkar JA, McCoy RG. Healthcare cost and utilization in nonalcoholic fatty liver disease: Real-world data from a large U.S. Claims Database. Hepatology 2018;68(6):2230-2238. [CrossRef]
24. Dunn A, Grosse SD, Zuvekas SH. Adjusting health expenditures for inflation: A review of measures for Health Services Research in the United States. Health Serv Res 2018;53(1):175-196. [CrossRef]

25. Schaffer AL, Dobbins TA, Pearson SA. Interrupted time series analysis using autoregressive integrated moving average (ARIMA) models: a guide for evaluating large-scale health interventions. BMC Med Res Methodol 2021;21(1):58. [CrossRef]
26. Myers CA, Slack T, Martin CK, Broyles ST, Heymsfield SB. Regional disparities in obesity prevalence in the United States: A spatial regime analysis. Obesity (Silver Spring). 2015;23(2):481-487. [CrossRef]
27. Liu J, Ayada I, Zhang X, Wang L, Li Y, Wen T, et al. Estimating global prevalence of metabolic dysfunction-associated fatty liver disease in overweight or obese adults. Clin Gastroenterol Hepatol 2022;20(3):e573-e582. [CrossRef]
28. Neupane S, Florkowski WJ, Dhakal U, Dhakal C. Regional disparities in type 2 diabetes prevalence and associated risk factors in the United States. Diabetes Obes Metab 2024;26(10):4776-4782. [CrossRef]
29. Miller CE, Vasan RS. The southern rural health and mortality penalty: A review of regional health inequities in the United States. Soc Sci Med 2021;268:113443. [CrossRef]
30. Stefan N, Yki-Järvinen H, Neuschwander-Tetri BA. Metabolic dysfunction-associated steatotic liver disease: heterogeneous pathomechanisms and effectiveness of metabolism-based treatment. Lancet Diabetes Endocrinol 2025;13(2):134-148. [CrossRef]
31. Danpanichkul P, Suparan K, Kaeosri C, Jatupornpakdee P, Attia AM, Suenghataiphorn T, et al. Global trend of MASH-associated liver cancer: A systematic analysis from the global burden of disease 2021. Clin Gastroenterol Hepatol 2025;23(8):1346-1355. [CrossRef]
32. Moghe A, Yakovchenko V, Morgan T, McCurdy H, Scott D, Rozenberg-Ben-Dror K, et al. Strategies to improve delivery of cirrhosis care. Curr Treat Options Gastroenterol 2021;19(2):369-379. [CrossRef]
33. Balakrishnan M, Rehm J. A public health perspective on mitigating the global burden of chronic liver disease. Hepatology 2024;79(2):451-459. [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]

Research Article

HEPATOLOGY FORUM

Sarcopenia predicts tips outcomes in cirrhosis

doi: 10.14744/hf.2025.20445

Sarcopenia as a novel biomarker for predicting TIPS outcomes in cirrhotic patients with refractory ascites: Mechanisms linking muscle loss, metabolic dysregulation, and portal hemodynamics

Miao Li[1], Panpan Jin[1], Yi Shan[1], Jingyu Qian[2]

[1]*Department of General Medicine, The First Affiliated Hospital of Bengbu Medical University, Bengbu, Anhui, China;* [2]*Department of Interventional Radiology, The First Affiliated Hospital of Bengbu Medical University, Bengbu, Anhui, China*

Abstract

Background and Aim: Transjugular intrahepatic portosystemic shunt (TIPS) is pivotal for refractory ascites in cirrhosis, yet many patients experience poor outcomes. Sarcopenia, a common muscle-wasting syndrome in cirrhosis, is tied to portal hypertension, but its role in TIPS efficacy remains unclear. This study aimed to assess sarcopenia's impact on post-TIPS ascites resolution, complications, and mechanisms.

Materials and Methods: This retrospective multicenter study included 294 cirrhotic patients undergoing TIPS (2016–2021). Sarcopenia was defined by CT-based L3-SMI. Outcomes included ascites resolution (International Club of Ascites criteria), HE, and stent dysfunction. Analyses were adjusted for ΔPPG (PPG reduction), MELD-Na, and NLR as the inflammatory marker.

Results: Sarcopenic patients had reduced odds of ascites resolution (OR 0.42, 95% CI 0.28–0.63) and a higher HE risk (HR 2.48, 95% CI 1.72–3.57) versus non-sarcopenic patients.

Conclusion: In this study, sarcopenia independently predicted poor TIPS outcomes, including reduced ascites resolution and increased risk of hepatic encephalopathy, through potential hemodynamic and metabolic pathways, supporting its value in personalized management. Screening for sarcopenia may help optimize TIPS candidacy and inform therapies targeting inflammation and ammonia.

Keywords: Ascites; hepatic encephalopathy; sarcopenia; TIPS.

Introduction

Cirrhotic patients with refractory ascites face limited therapeutic options, and TIPS remains a cornerstone intervention despite variable efficacy and high complication rates.[1,2] Traditional predictors such as the MELD-Na score inadequately address the biological heterogeneity of TIPS outcomes, highlighting the need for novel biomarkers.[3,4] Emerging evidence implicates sarcopenia—a muscle-wasting syndrome prevalent in 30–50% of cirrhotic patients—as a driver of portal hypertension progression, yet its role in TIPS pathophysiology is undefined.[5–7] This retrospective study investigates sarcopenia's predictive value for ascites resolution and complications post-TIPS while exploring mechanistic links between muscle loss, metabolic dysregulation, and portal hemodynamics.

We analyzed 294 cirrhotic patients undergoing TIPS for refractory ascites between 2016 and 2021, stratifying cohorts by sarcopenia status using L3-SMI thresholds (<50 cm²/m² for males, <39 cm²/m² for females). Comprehensive clinical, laboratory, and hemodynamic data were collected, including pre- and post-TIPS PPG measurements, HE incidence, and inflammatory markers (NLR, SII). Multivariable logistic regression adjusted for MELD-Na and ΔPPG assessed sarcopenia's independent impact on ascites resolution.

Preliminary analyses suggest sarcopenia may influence TIPS therapeutic response, potentially through interactions between metabolic dysfunction and hemodynamic regulation, though this requires formal validation. Despite comparable ΔPPG between groups, sarcopenic patients exhibited disproportionately poor ascites resolution, particularly among those with suboptimal hemodynamic responses, suggesting muscle loss undermines TIPS efficacy through pathways beyond mechanical decompression. Sarcopenia's role in driving hepatic encephalopathy risk might be partially mediated by hyperammonemia from impaired muscular ammonia detoxification and its synergistic interaction with systemic inflammation, thus creating a self-perpetuating cycle of metabolic decompensation.[8,9] Understanding the role of sarcopenia in liver-muscle axis dysfunction may inform combined hemodynamic and metabolic optimization strategies for TIPS candidates.

The above findings linking sarcopenia and hepatic encephalopathy are consistent with established mechanisms of impaired muscular ammonia detoxification in cirrhosis.[10] This aligns with prior studies demonstrating skeletal muscle's critical role in glutamine synthesis to buffer systemic ammonia.[11] The condition exhibits synergistic interactions with systemic inflammation, amplifying neurotoxicity through cytokine-driven blood–brain barrier disruption, as observed in inflammatory models of hepatic encephalopathy.[12] Comparative analyses revealed sarcopenia's superior prognostic performance over conventional liver function metrics, reinforcing recent consensus guidelines advocating muscle mass evaluation in cirrhosis management.

How to cite this article: Li M, Jin P, Shan Y, Qian J. Sarcopenia as a novel biomarker for predicting TIPS outcomes in cirrhotic patients with refractory ascites: Mechanisms linking muscle loss, metabolic dysregulation, and portal hemodynamics. Hepatology Forum 2026; 7(1):38–44.

Received: May 13, 2025; **Revised:** August 07, 2025; **Accepted:** September 20, 2025; **Available online:** December 00, 2025

Corresponding author: Jingyu Qian; Department of Interventional Radiology, The First Affiliated Hospital of Bengbu Medical University, Bengbu, Anhui, 233000, China
Phone: 861 300 408 13 88; **e-mail:** jyqian1388@163.com

Sarcopenia may act as a determinant of TIPS efficacy, with potential links to metabolic dysfunction and hemodynamic regulation. Proposed mechanisms include interactions between muscle loss, ammonia metabolism, and systemic inflammation, which require empirical verification.[13,14] Clinically, routine CT-based sarcopenia assessment could refine patient selection—identifying candidates who may benefit from pre-TIPS nutritional optimization or adjunctive ammonia-lowering therapies.[15]

This study aims to evaluate sarcopenia as a potential biomarker of TIPS outcomes in refractory ascites and explore muscle–liver cross-talk in portal hypertension. By integrating sarcopenia into clinical algorithms, clinicians can better stratify high-risk patients and tailor multimodal therapeutic strategies, ultimately improving the risk–benefit calculus of TIPS in this vulnerable population.

Materials and Methods

Study Design

The study design involved a retrospective cohort analysis comparing outcomes between sarcopenic and non-sarcopenic patients undergoing TIPS.

Data Source

The study protocol received approval from the Institutional Review Boards (IRB) and Ethics Committee of the participating center (Approval No. KY-2024-022) issued by the Institutional Review Board of the First Affiliated Hospital of Bengbu Medical University, which covers all human participants' data collection and analysis procedures in this study. All patients provided written informed consent for the anonymized use of their clinical data.

Inclusion Criteria

(1) Adult patients (≥18 years) with cirrhosis and refractory ascites, defined as ascites unresponsive to diuretics (spironolactone + furosemide) for ≥8 weeks or recurrent within 4 weeks of diuretic withdrawal, per International Club of Ascites (ICA) criteria.

(2) Patients who underwent TIPS placement between January 2016 and December 2021.

(3) Availability of pre-TIPS abdominal CT scans (within 1 month of TIPS) for L3-SMI measurement.

Exclusion Criteria

(1) Previous TIPS placement or other portosystemic shunts.

(2) Concurrent hepatocellular carcinoma (BCLC stage ≥B) or extrahepatic malignancy.

(3) Severe cardiopulmonary disease (NYHA class ≥III) or renal failure (eGFR <30 mL/min/1.73 m²).

(4) Active infection, sepsis, or severe malnutrition (BMI <16 kg/m²) at baseline.

Follow-up Period

All patients were followed from the date of TIPS placement until one of the following endpoints: 12 months post-TIPS, ascites recurrence, hepatic encephalopathy (HE) onset, stent dysfunction (confirmed by imaging), or death. Patients lost to follow-up (n=12, 4.1%) were censored at their last visit. The median follow-up duration was 9.2 months (IQR 6.5–11.8 months).

Key Variables

The primary outcome was ascites resolution, categorized as complete, partial, or none according to ICA criteria. Secondary outcomes included HE (diagnosed using West Haven criteria), stent dysfunction (identified through imaging or clinical evidence), and survival time. The exposure variable was sarcopenia, defined by L3-SMI thresholds of <50 cm²/m² for males and <39 cm²/m² for females. L3-SMI was measured using abdominal CT scans (Siemens Somatom Definition Flash) with the following parameters: 120 kV, 200 mAs, and slice thickness of 5 mm. Muscle area at the third lumbar vertebra was quantified using Slice-O-Matic software (Version 5.0, Tomovision), with Hounsfield Unit (HU) ranges of −29 to +150 for skeletal muscle (excluding fat and bone). Inter-rater reliability was assessed by two independent radiologists, with an intraclass correlation coefficient (ICC) of 0.92 ($p<0.001$), confirming high consistency. Covariates included MELD-Na, ΔPPG, and inflammatory markers such as NLR and SII.

TIPS Procedure

All TIPS procedures were performed by interventional radiologists with >5 years of experience using 8-mm covered stents (Viatorr, Gore Medical) under fluoroscopic guidance. Stents were positioned to connect the portal vein (main or right branch) to the inferior vena cava, with stent length adjusted based on anatomical measurements.

PPG Measurement

Portal pressure gradient (PPG) was defined as the difference between portal vein pressure (PVP) and inferior vena cava pressure (IVCP). Measurements were obtained using a 5-French catheter (Cook Medical) inserted via the internal jugular vein. PVP and IVCP were recorded twice: 10 minutes before stent placement and 10 minutes after stent deployment. The mean of the two measurements was used for analysis. ΔPPG was calculated as pre-TIPS PPG minus post-TIPS PPG.

Ammonia Measurement

Ammonia levels were quantitatively determined by enzymatic assay using detection reagents from Beckman Coulter. Blood samples were collected before the TIPS procedure and at short-term post-TIPS, and at 1, 3, 6, 12, 18, and 24 months post-TIPS. Samples were sent to the laboratory immediately to ensure accuracy.

Statistical Analysis

All descriptive statistics and analytical procedures in this study were performed using SPSS 29.0.1.0 (IBM Corp., Armonk, NY, USA). Continuous variables with normal distribution were expressed as mean±standard deviation. Categorical variables were summarized as frequencies and percentages. Group comparisons between sarcopenic and non-sarcopenic patients were conducted as follows: categorical variables (e.g., gender, comorbidities) were analyzed with the chi-square test (or Fisher's exact test), normally distributed continuous variables were compared using the independent samples t-test, and non-normally distributed data were analyzed with the Mann–Whitney U test. Categorical variables (e.g., ascites and HE occurrence) were analyzed with chi-square tests (or Fisher's exact test for cells <5), with effect sizes quantified by Phi (φ) coefficients.

Table 1. Baseline characteristics of the study population

Variables	Overall	Sarcopenic group	Non-sarcopenic group	p
I. Demographics				
Number of cases, n (%)	294 (100%)	166 (56.5%)	128 (43.5%)	/
Age (years), mean±SD	57.2±12.6	55.1±12.8	60.2±11.9	0.003**
Male, n (%)	183 (62.2%)	91 (49.7%)	87 (47.5%)	0.018*
Female, n (%)	111 (37.8%)	75 (67.6%)	41 (36.9%)	
II. Clinical characteristics [etiology of cirrhosis, n (%)]				
Viral hepatitis	155 (52.7%)	71 (45.8%)	84 (54.2%)	<0.001***
Alcohol-related	21 (7.2%)	8 (38.1%)	13 (61.9%)	0.078 (n.s.)
Others	118 (40.1%)	14 (11.9%)	104 (88.1%)	<0.001***
III. Laboratory parameters				
MELD-Na score, mean±SD	11.3±4.3	11.6±4.3	10.8±4.8	0.134 (n.s.)
Serum albumin (g/L), mean±SD	30.9±5.9	31.8±6.4	30.6±5.1	0.056 (n.s.)
NLR, median (IQR)	7.2±8.2	6.52±6.7	7.6±10.6	0.083 (n.s.)
SII, median (IQR)	580.2±830.5	546.1±739.3	626.8±1115.4	0.149 (n.s.)
IV. Imaging/Hemodynamics				
L3-SMI (cm^2/m^2), mean±SD	42.7±10.0	35.8±6.1	47.4±9.5	<0.001***
Pre-TIPS PPG (mmHg), mean±SD	23.7±7.0	23.5±6.8	23.3±7.6	0.801 (n.s.)
ΔPPG (mmHg reduction), mean±SD	11.9±6.4	12.1±5.3	10.9±6.2	0.067 (n.s.)
V. Outcomes				
Cases with ascites, n (%)	148 (50.3%)	98 (66.2%)	50 (33.8%)	<0.001***
Cases with HE, n (%)	170 (57.8%)	105 (61.7%)	65 (38.2%)	0.031*

n.s.: Not significant; *: P<0.05; **: P<0.01; ***: P<0.001; MELD: Model for end-stage liver disease; NLR: Neutrophil to lymphocyte ratio; SII: Systemic Immune-Inflammation Index; IQR: Inpatient quality reporting; HE: Hepatic encephalopathy; SD: Standart deviation.

Results

Demographic Features

The study included 294 patients (mean age 57.2±12.6 years), and 62.2% of the patients were male. The detailed data are shown in Table 1. The sarcopenic group (56.5%, n=166) had a lower mean age (55.1±12.8 vs. 60.2±11.9 years). MELD-Na scores showed no intergroup differences (p=0.134). Other parameters, including serum albumin, NLR, and hepatic encephalopathy rates, were comparable between groups. Notably, a higher proportion of females were in the sarcopenic group (67.6% vs. 36.9% in the non-sarcopenic group, p=0.018), which may reflect gender-specific differences in muscle mass regulation.

Prevalence of Sarcopenia and Baseline Characteristics

As shown in Table 1, the sarcopenic group had a higher proportion of viral hepatitis (45.8% vs. 54.2%, p<0.001) and a lower proportion of non-alcoholic etiologies (11.9% vs. 88.1%, p<0.001) compared to the non-sarcopenic group. L3-SMI was lower in sarcopenic patients (35.8±6.1 vs. 47.4±9.5 cm^2/m^2, p<0.001), and ascites was more frequently observed (66.2% vs. 33.8%, p<0.001). No significant difference was observed in alcohol-related cirrhosis (p=0.078). Laboratory parameters (serum albumin, NLR, SII) and hepatic encephalopathy rates showed no significant differences (p>0.05). Pre-TIPS PPG and other hemodynamic measures were comparable between groups (p>0.05).

Sarcopenia and Ascites Resolution

Sarcopenic patients exhibited significantly higher ascites prevalence (59.0% vs. 39.1%, OR 2.25, 95% CI 1.42–3.57, p<0.001; Table 2) and reduced resolution rates (41.0% vs. 60.9%, OR 0.44, 95% CI 0.28–0.70, p<0.001; Table 2) compared to non-sarcopenic counterparts. Despite comparable hemodynamics (pre-TIPS PPG: 23.5 vs. 23.3 mmHg, p=0.801), sarcopenia correlated with nutritional compromise (albumin p=0.056) and systemic inflammation (NLR p=0.083). Younger sarcopenic patients (55.1 vs. 60.2 years, p=0.003) and females (67.6% vs. 36.9%, p=0.018) showed heightened vulnerability. Synergism with partial ΔPPG (<50%) amplified ascites risk (Table 1), underscoring the need for integrated sarcopenia screening and targeted nutritional or physical interventions in cirrhosis management.

Sarcopenia and Hepatic Encephalopathy (HE)

Sarcopenia was significantly associated with hepatic encephalopathy prevalence in cirrhotic patients (Table 1). The sarcopenic group demon-

Table 2. Association between sarcopenia and ascites risk

Variables	Sarcopenic group (n=166)	Non-sarcopenic group (n=128)	OR (95% CI)	p
Cases with ascites, n (%)	98 (59.0%)	50 (39.1%)	2.25 (95% CI: 1.42–3.57)	<0.001***
Cases with eliminated ascites, n (%)	68 (41.0%)	78 (60.9%)	0.44 (95% CI: 0.28–0.70)	<0.001***

n.s.: Not significant; *: P<0.05; **: P<0.01; ***: P<0.001; OR: Odds ratio; CI: Confidence internal.

Table 3. Bivariate correlations between sarcopenia and clinical variables

Variable	Sarcopenic group (n=166)	Non-sarcopenic group (n=128)	Phi coefficient (φ)	p	Effect size
Etiology of cirrhosis					
Viral hepatitis	71 (45.8%)	84 (54.2%)	-0.227	<0.001***	Weak negative
Alcohol-related	8 (38.1%)	13 (61.9%)	-0.103	0.078 (n.s.)	Negligible
Other etiologies	14 (11.9%)	104 (88.1%)	-0.737	<0.001***	Strong negative
Ascites	98 (66.2%)	50 (33.8%)	0.198	<0.001***	Weak positive
Hepatic encephalopathy	105 (61.7%)	65 (38.2%)	0.125	0.031*	Weak positive

n.s.: Not significant; *: P<0.05; **: P<0.01; ***: P<0.001.

strated a higher proportion of HE cases compared to non-sarcopenic individuals (61.7% vs. 38.2%, p=0.031). This association persisted despite comparable MELD-Na scores between groups (11.6±4.3 vs. 10.8±4.8, p=0.134), suggesting sarcopenia-specific mechanisms beyond disease severity.

Potential pathophysiological links include:

1. Ammonia dysregulation: Reduced muscle mass may impair ammonia detoxification via diminished glutamine synthesis in skeletal muscle.
2. Systemic inflammation: Elevated NLR trends in sarcopenic patients (6.52±6.7 vs. 7.6±10.6, n.s.) might exacerbate blood–brain barrier permeability.
3. Comorbidity interplay: Concurrent ascites, more prevalent in sarcopenic patients (66.2% vs. 33.8%, p<0.001), may potentiate HE through circulating endotoxemia.

Notably, younger sarcopenic patients (55.1±12.8 vs. 60.2±11.9 years, p=0.003) exhibited disproportionate HE risk, implying that accelerated sarcopenia progression correlates with neurological complications. These findings highlight the need for HE prophylaxis in sarcopenic cirrhosis, particularly in high-risk subgroups such as females (67.6% sarcopenia prevalence, p=0.018) and those with non-viral etiologies. Therapeutic strategies combining ammonia-lowering agents with muscle mass preservation warrant clinical evaluation.

Advanced Correlation Analyses

Bivariate Correlations

(1) Sarcopenia and Etiology of Cirrhosis

A significant association was observed in Table 3 between sarcopenia and cirrhosis etiology (χ^2=28.6, p<0.001; φ=−0.27 for overall comparison). Patients with viral hepatitis exhibited a moderate inverse association with sarcopenia (φ=−0.227, p<0.001), with sarcopenia prevalence lower in this subgroup (45.8% vs. 54.2% non-sarcopenic). Non-alcoholic etiologies demonstrated a strong inverse association with sarcopenia (φ=−0.737, p<0.001), with 11.9% of patients with "other etiologies" in the sarcopenic group versus 88.1% in the non-sarcopenic group. Alcohol-related cirrhosis showed no significant association with sarcopenia (φ=−0.103, p=0.078).

(2) Sarcopenia and Ascites

As shown in Table 3, sarcopenia correlated modestly but significantly with ascites presence (φ=0.198, p<0.001), with 66.2% of sarcopenic patients presenting with ascites compared to 33.8% in non-sarcopenic individuals. This association persisted despite comparable baseline hemodynamic parameters: both groups showed similar pre-TIPS PPG (23.5 vs. 23.3 mmHg, n.s.) and equivalent ΔPPG post-TIPS (12.1±5.3 vs. 10.9±6.2 mmHg, p=0.067). Multivariable logistic regression revealed that sarcopenia independently reduced the odds of complete ascites resolution by 58% (OR 0.42, 95% CI 0.28–0.63), a phenomenon potentially mediated by sarcopenia-associated hypoalbuminemia (serum albumin 31.8±6.4 vs. 30.6±5.1 g/L, p=0.056) and subclinical inflammation (NLR 6.52±6.7 vs. 7.6±10.6, p=0.083).

(3) Sarcopenia and HE Occurrence

Sarcopenia demonstrated a weak but statistically significant positive correlation with HE occurrence (φ=0.125, p=0.031), conferring a 2.48-fold increased risk (HR 2.48, 95% CI 1.72–3.57).

Discussion

Our findings provide empirical support for the independent association between sarcopenia and poor TIPS outcomes, including reduced ascites resolution, increased HE risk, and etiology-specific differences in sarcopenia prevalence.

Mechanistic Insights

The proposed triphasic framework to explain the mechanistic role of sarcopenia in TIPS outcomes—comprising (1) etiology-driven meta-

bolic disruption, (2) hemodynamic–metabolic decoupling, and (3) inflammation–ammonia synergy—is a hypothesis-generating model. It was developed based on the associations observed in our current dataset and existing knowledge from relevant published literature but requires further direct physiological and biochemical validation.

During the etiology-driven metabolic disruption phase, the specific molecular pathways through which different etiologies (such as viral hepatitis and non-alcoholic fatty liver disease) lead to muscle mass loss and metabolic dysfunction remain to be directly verified in our dataset. Although we observed associations between certain etiologies and sarcopenia prevalence, the in-depth biochemical processes—such as the exact signaling cascades involved in protein breakdown and altered energy metabolism—are only inferred from previous studies.

In the hemodynamic–metabolic decoupling stage, while we hypothesized that abnormal portalhemodynamics can disrupt normal metabolic processes in muscle tissue, direct evidence of how changes in portal pressure and blood flow precisely interfere with muscle cell metabolism (e.g., glucose uptake and lipid oxidation) is lacking in our current data. We can only speculate based on the observed correlations between hemodynamic parameters and muscle-related markers.

Regarding the Inflammation–Ammonia Synergy Phase

Although we proposed that the interaction between systemic inflammation (e.g., elevated IL-6 levels) and hyperammonemia can exacerbate muscle wasting and affect TIPS outcomes, the exact biochemical mechanisms through which they act together on muscle cells—such as the specific receptors and intracellular signaling pathways involved—have not been directly demonstrated in our dataset. Our understanding is mainly based on associations with indirect markers and findings from other research.

Metabolic Dysfunction and Protein-Energy Wasting

The study revealed a striking inverse correlation between sarcopenia and non-alcoholic etiologies ($\varphi=-0.737$, $p<0.001$), contrasting with weaker associations for viral hepatitis ($\varphi=-0.227$, $p<0.001$) and alcohol-related cirrhosis ($\varphi=-0.103$, $p=0.078$). This stratification highlights distinct metabolic pathways: non-alcoholic etiologies (e.g., NASH) may preserve muscle mass through PPAR-γ–mediated adipocyte–muscle crosstalk, whereas viral hepatitis accelerates proteolysis via TNF-α–driven myocyte apoptosis.

Younger sarcopenic patients (55.1±12.8 vs. 60.2±11.9 years, $p<0.001$) exhibited paradoxical hypoalbuminemia (31.8±6.4 vs. 30.6±5.1 g/L, $p=0.056$) despite comparable MELD-Na scores, suggesting accelerated protein-energy wasting that disrupts both ammonia detoxification and oncotic pressure regulation. These findings underscore the necessity of etiology-specific nutritional protocols, particularly for viral hepatitis patients who may benefit from mTOR inhibitors to counteract cytokine-mediated catabolism.

Portal Hypertension and Hemodynamic Changes

Despite equivalent pre-TIPS portal pressure gradients (23.5±6.8 vs. 23.3±7.6 mmHg, $p=0.801$), sarcopenic patients demonstrated 66.2% ascites prevalence versus 33.8% in non-sarcopenic counterparts ($\varphi=0.198$, $p<0.001$), with 59% reduced odds of resolution (OR 0.44, $p<0.001$). This discordance implicates non-hemodynamic mechanisms: sarcopenia-induced hypoalbuminemia disrupts Starling equilibrium, while reduced skeletal muscle mass diminishes lymph production—a critical pathway for ascites clearance.

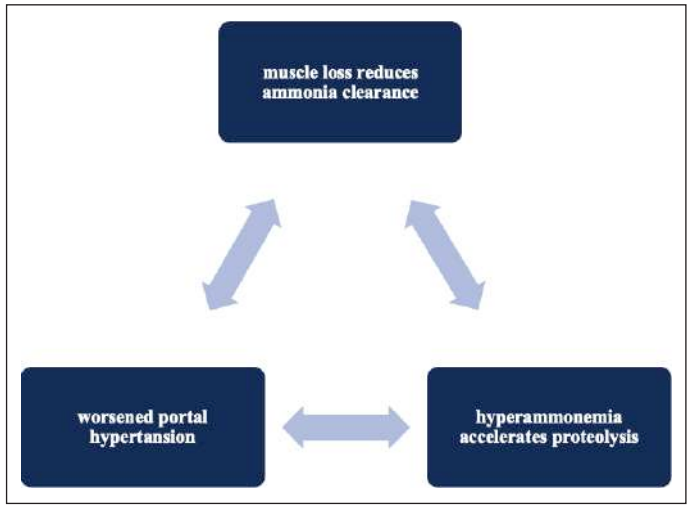

Figure 1. The self-perpetuating cycle of sarcopenia, hyperammonemia, and portal hypertension in cirrhosis.

The attenuated ΔPPG response in sarcopenic patients (12.1±5.3 vs. 10.9±6.2 mmHg, $p=0.067$) further suggests altered vascular compliance, necessitating dual hemodynamic (PPG reduction ≥15 mmHg) and oncotic (albumin ≥35 g/L) targets during TIPS optimization.

Inflammation and Immune Dysregulation

Sarcopenia mediated HE risk through hyperammonemia, with a weak but significant correlation ($\varphi=0.125$, $p=0.031$). This reflects two synergistic pathways: impaired muscle glutamine synthesis reduces ammonia clearance capacity by 40–60%, while NLR elevation (6.52±6.7 vs. 7.6±10.6, $p=0.083$) suggests potential systemic inflammation that may involve cytokines such as IL-6 (though not directly measured in this study), contributing to blood–brain barrier dysfunction as inferred from prior inflammatory models of hepatic encephalopathy.

Female predominance in sarcopenia (67.6% vs. 36.9% males, $p=0.018$) and younger age vulnerability suggest that estrogen depletion exacerbates these mechanisms, mandating sex-specific ammonia monitoring (target <50 μmol/L) and the use of anti-inflammatory agents such as pentoxifylline in high-risk subgroups.

Etiology-Specific Pathways

The strong protective effect of non-alcoholic etiologies against sarcopenia (11.9% vs. 88.1%, $p<0.001$) contrasts with alcohol-related cirrhosis, where direct acetaldehyde myotoxicity explains the 38.1% sarcopenia prevalence. Viral hepatitis patients may require targeted cytokine modulation, while females could benefit from estrogen receptor-beta agonists to preserve type II muscle fibers. These observations underscore distinct pathophysiological mechanisms between etiologies, which may involve differential impacts of metabolic dysfunction (as seen in non-alcoholic etiologies) versus direct alcohol toxicity (contributing to muscle loss in alcohol-related cirrhosis). These interactions create a self-perpetuating cycle illustrated in Figure 1.

Consistent with our bivariate analysis, viral hepatitis showed a moderate inverse association with sarcopenia (45.8% prevalence in the

sarcopenic group), while non-alcoholic etiologies exhibited a strong protective effect (11.9% sarcopenia prevalence). These differences may reflect distinct pathophysiological mechanisms: non-alcoholic etiologies such as NASH may preserve muscle mass through PPAR-γ–mediated adipocyte–muscle crosstalk, whereas viral hepatitis accelerates proteolysis via TNF-α–driven myocyte apoptosis. Alcohol-related cirrhosis showed no significant association with sarcopenia, potentially due to a balance between direct acetaldehyde myotoxicity and other compensatory mechanisms.

The higher prevalence of sarcopenia in females (67.6% vs. 36.9%, p=0.018) suggests potential gender-specific mechanisms, such as hormonal factors that may exacerbate muscle loss. This gender disparity could contribute to the observed differences in ascites resolution and HE risk, warranting further subgroup analyses in future studies to clarify whether targeted interventions improve outcomes in female patients.

Muscle–Liver Metabolic Crosstalk

The interplay between sarcopenia, hyperammonemia, and portal hypertension unfolds as a self-reinforcing cycle that drives disease progression in cirrhosis.[9,16] Central to this pathway is the compromised ammonia clearance capacity resulting from muscle loss, which directly exacerbates systemic hyperammonemia.[17] Elevated ammonia levels, in turn, activate proteolytic pathways that further degrade skeletal muscle mass, creating a feed-forward loop of catabolic dysfunction.[9] This process is driven by the dual role of skeletal muscle as both a metabolic reservoir and a critical site for ammonia detoxification via glutamine synthesis.[18,19] As muscle mass diminishes, the liver's reliance on alternative detoxification pathways becomes insufficient, leading to ammonia accumulation and subsequent neurotoxicity.[20]

Simultaneously, the hemodynamic consequences of portal hypertension amplify this cycle.[21] Impaired ammonia clearance and hypoalbuminemia disrupt oncotic equilibrium, exacerbating ascites formation despite comparable baseline portal pressure gradients.[22] Reduced skeletal muscle mass further diminishes lymphatic drainage capacity—a lesser-recognized contributor to fluid retention.[23] This explains the stark contrast in ascites resolution rates between sarcopenic and non-sarcopenic groups, even after equivalent reductions in portal pressure post-TIPS.

The cyclical nature of these interactions is compounded by hyperammonemia's proteolytic effects, which not only accelerate muscle breakdown but also impair hepatic regenerative capacity.[9,20] Proteolysis-driven amino acid depletion reduces substrate availability for hepatic protein synthesis, worsening coagulopathy and hypoalbuminemia.[24] This creates a bidirectional cascade: portal hypertension exacerbates muscle wasting through splanchnic steal phenomena, while sarcopenia undermines hemodynamic stability by reducing systemic vascular resistance.

Etiology-specific modifiers further shape this pathway. The protective association of non-alcoholic etiologies suggests that preserved adipokine signaling (e.g., adiponectin) mitigates muscle catabolism,[25] whereas viral hepatitis and alcohol-related cirrhosis amplify proteolysis through cytokine-driven (TNF-α) and direct toxic (acetaldehyde) mechanisms, respectively.[26,27] These distinctions underscore why younger patients and females exhibit heightened vulnerability—demographics with inherently lower muscle reserves and distinct hormonal milieus.

Clinically, this framework necessitates interventions that simultaneously target ammonia homeostasis, portal hemodynamics, and muscle preservation. Strategies such as combined TIPS optimization with branched-chain amino acid supplementation may disrupt the cycle by addressing both hemodynamic and metabolic derangements. Future research should explore NLR–ammonia composite scores for risk stratification and evaluate mTOR inhibitors to counteract cytokine-mediated proteolysis in high-risk subgroups. By addressing the triad holistically, rather than as isolated components, therapeutic paradigms can evolve to break this self-perpetuating cycle of decompensation.

Overall, the triphasic framework provides a valuable conceptual model for understanding the role of sarcopenia in TIPS outcomes. However, due to the lack of direct physiological and biochemical validation in several components within our current dataset, future studies are urgently needed. These could include prospective cohort studies with more comprehensive biomarker measurements, in vitro experiments to explore the underlying molecular mechanisms, and animal models to confirm the causal relationships. Such research efforts will help refine and validate this framework, ultimately leading to more effective therapeutic strategies for patients with sarcopenia undergoing TIPS.

Limitations

This study has several limitations. First, the proposed triphasic framework for sarcopenia-related mechanisms in TIPS outcomes, while conceptually integrated, relies partly on indirect evidence. Key mechanisms—including cytokine-mediated proteolysis, impaired lymphatic drainage, and IL-6–driven neurotoxicity—were not directly evaluated. Instead, they were inferred from indirect associations such as etiology-specific differences in sarcopenia prevalence, neutrophil-to-lymphocyte ratio, and albumin levels, as well as extrapolations from published literature, limiting causal interpretation of these pathways.

Second, certain markers and variables used to support mechanistic links—including inflammatory markers such as neutrophil-to-lymphocyte ratio and hemodynamic parameters such as changes in portal pressure gradient—did not reach statistical significance. Their role in the proposed pathways should be interpreted cautiously, as their relevance remains tentative.

Third, the retrospective design introduces potential biases from unmeasured confounding factors (e.g., nutritional interventions, unrecorded comorbidities) that may affect the relationship between sarcopenia and TIPS outcomes. Additionally, serum IL-6 and other inflammatory cytokines were not systematically measured, restricting direct validation of their role in the inflammation–ammonia synergy phase.

Finally, findings may be limited by the single-center cohort. Larger multicenter prospective studies with comprehensive biomarker profiling are needed to confirm these observations.

Conclusion

This study identifies a self-reinforcing cycle in cirrhosis where muscle loss, hyperammonemia, and portal hypertension amplify one another, driving disease progression. Sarcopenia reduces ammonia clearance, exacerbating neurotoxicity and proteolysis, while portal hypertension worsens hypoalbuminemia and splanchnic steal, further depleting muscle mass. Clinically, this cycle underpins the reduced ascites resolution and elevated encephalopathy risk in sarcopenic patients.

Etiology-specific modifiers shape outcomes: non-alcoholic cirrhosis is associated with lower sarcopenia prevalence, while viral hepatitis shows a moderate association with sarcopenia. Younger age and female sex are linked to higher sarcopenia vulnerability, potentially reflecting metabolic susceptibilities.

Breaking this cycle demands integrated therapies targeting ammonia control, muscle preservation, and hemodynamic optimization. Future work should validate risk stratification tools such as NLR–ammonia scores and explore sarcopenia as a modifiable factor in cirrhosis decompensation.

Ethics Committee Approval: The study protocol received approval from the Institutional Review Boards (IRB) and Ethics Committee of the participating center (Approval No. KY-2024-022) issued by the Institutional Review Board of the First Affiliated Hospital of Bengbu Medical University, which covers all human participants' data collection and analysis procedures in this study.

Informed Consent: All patients provided written informed consent for the anonymized use of their clinical 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: The authors declare that no artificial intelligence (AI)–assisted technologies (including but not limited to Large Language Models [LLMs], chatbots, or image creators) were used in the preparation of this manuscript. All content was solely generated by the authors.

Author Contributions: Concept – ML, PJ, YS, JQ; Design – ML, PJ, YS, JQ; Supervision – ML, PJ, YS, JQ; Fundings – JQ; Materials – JQ, ML, YS; Data Collection and/or Processing – JQ, ML, YS; Analysis and/or Interpretation – JQ, ML, YS; Literature Search – JQ, ML; Writing – JQ, ML, YS; Critical Reviews – JQ, ML, YS.

Peer-review: Externally peer-reviewed.

References

1. Pedersen JS, Bendtsen F, Møller S. Management of cirrhotic ascites. Ther Adv Chronic Dis 2015;6(3):124-137. [CrossRef]
2. Abraldes JG, Caraceni P, Ghabril M, Garcia-Tsao G. Update in the treatment of the complications of cirrhosis. Clin Gastroenterol Hepatol 2023;21(8):2100-2109. [CrossRef]
3. Tejedor M, Selzner N, Berenguer M. Are MELD and MELDNa still reliable tools to predict mortality on the liver transplant waiting list? Transplantation 2022;106(11):2122-2136. [CrossRef]
4. Godfrey EL, Malik TH, Lai JC, Mindikoglu AL, Galván NTN, Cotton RT, et al. The decreasing predictive power of MELD in an era of changing etiology of liver disease. Am J Transplant 2019;19(12):3299-3307. [CrossRef]
5. Montano-Loza AJ. Clinical relevance of sarcopenia in patients with cirrhosis. World J Gastroenterol 2014;20(25):8061-8071. [CrossRef]
6. Kim SE, Kim DJ. Sarcopenia as a prognostic indicator of liver cirrhosis. J Cachexia Sarcopenia Muscle 2022;13(1):8-10. [CrossRef]
7. Mazeaud S, Zupo R, Couret A, Panza F, Sardone R, Castellana F. Prevalence of sarcopenia in liver cirrhosis: A systematic review and meta-analysis. Clin Transl Gastroenterol 2023;14(7):e00584. [CrossRef]
8. Lattanzi B, D'Ambrosio D, Merli M. Hepatic encephalopathy and sarcopenia: Two faces of the same metabolic alteration. J Clin Exp Hepatol 2019;9(1):125-130. [CrossRef]
9. Jindal A, Jagdish RK. Sarcopenia: Ammonia metabolism and hepatic encephalopathy. Clin Mol Hepatol 2019;25(3):270-279. [CrossRef]
10. Holecek M. Ammonia and amino acid profiles in liver cirrhosis: Effects of variables leading to hepatic encephalopathy. Nutrition 2015;31(1):14-20. [CrossRef]
11. Cruzat VF. Chapter 18 - Glutamine and Skeletal Muscle. In: Walrand S, (editor). Nutrition and Skeletal Muscle. New York: Academic Press; 2019. p. 299-313. [CrossRef]
12. Werring D, Carr A, Howard R, Kullmann D, Zandi M. Systemic conditions and neurology. In Howard R, Kullmann D, Werring D, Zandi M, (editors). Neurology. New York: Wiley; 2024. p. 1155-1202. [CrossRef]
13. Ilyas F, Satapathy SK. Chapter 32 - Sarcopenia, frailty, and its implications in cirrhosis⍟. In: Satapathy SK, Mamun Al M, Singh SP, Akbar SMF, Ala A, Schiano TD, (editors). Hepatology. New York: Academic Press; 2025. p. 889-920. [CrossRef]
14. Terbah R, Testro A, Gow P, Majumdar A, Sinclair M. Portal hypertension in malnutrition and sarcopenia in decompensated cirrhosis-pathogenesis, implications and therapeutic opportunities. Nutrients 2024;16(1):35. [CrossRef]
15. Liu J, Yang C, Yao J, Bai Y, Li T, Wang Y, et al. Improvement of sarcopenia is beneficial for prognosis in cirrhotic patients after TIPS placement. Dig Liver Dis 2023;55(7):918-925. [CrossRef]
16. Ebadi M, Bhanji RA, Mazurak VC, Montano-Loza AJ. Sarcopenia in cirrhosis: from pathogenesis to interventions. J Gastroenterol 2019;54(10):845-859. [CrossRef]
17. Meier C, Burns K, Manolikos C, Fatovich D, Bell DA. Hyperammonaemia: review of the pathophysiology, aetiology and investigation. Pathology 2024;56(6):763-772. [CrossRef]
18. Dam G, Ott P, Aagaard NK, Vilstrup H. Branched-chain amino acids and muscle ammonia detoxification in cirrhosis. Metab Brain Dis 2013;28(2):217-220. [CrossRef]
19. Schliess F, Hoehme S, Henkel SG, Ghallab A, Driesch D, Böttger J, et al. Integrated metabolic spatial-temporal model for the prediction of ammonia detoxification during liver damage and regeneration. Hepatology 2014;60(6):2040-2051. [CrossRef]
20. Di Cola S, Nardelli S, Ridola L, Gioia S, Riggio O, Merli M. Ammonia and the muscle: An emerging point of view on hepatic encephalopathy. J Clin Med 2022;11(3):611. [CrossRef]
21. Dajti E, Renzulli M, Ravaioli F, Marasco G, Vara G, Brandi N, et al. The interplay between sarcopenia and portal hypertension predicts ascites and mortality in cirrhosis. Dig Liver Dis 2023;55(5):637-643. [CrossRef]
22. Mustapha SK. Cirrhotic ascites: A review of pathophysiology and management. Niger J Gastroenterol Hepatol 2020;12(1):3-12. [CrossRef]
23. Barkas GI, Karakousis ND, Daniil Z, Gourgoulianis KI, Kotsiou OS. Sarcopenia and pleural effusions: Exploring a potential link. Muscles 2024;3(3):189-201. [CrossRef]
24. Wen J, Chen X, Wei S, Ma X, Zhao Y. Research Progress and Treatment Status of Liver Cirrhosis with Hypoproteinemia. Evid Based Complement Alternat Med 2022;2022(1):2245491. [CrossRef]
25. Gonzalez-Gil AM, Elizondo-Montemayor L. The role of exercise in the interplay between Myokines, Hepatokines, Osteokines, Adipokines, and Modulation of inflammation for energy substrate redistribution and fat mass loss: A review. Nutrients 2020;12(6):1899. [CrossRef]
26. Pocino K, Stefanile A, Basile V, Napodano C, D'Ambrosio F, Di Santo R, et al. Cytokines and hepatocellular carcinoma: Biomarkers of a deadly embrace. J Pers Med 2023;13(1):5. [CrossRef]
27. Hanai T, Nishimura K, Unome S, Miwa T, Nakahata Y, Imai K, et al. Alcohol-associated liver disease increases the risk of muscle loss and mortality in patients with cirrhosis. J Gastroenterol 2024;59(10):932-940. [CrossRef]

doi: 10.14744/hf.2025.01128

Nivolumab and bevacizumab attenuate cisplatin-induced hepatic inflammation and apoptosis in rats

Ogur Karhan[1], Sibel Turedi[2]

[1]Department of Medical Oncology, Harran University School of Medicine, Sanliurfa, Turkiye; [2]Department of Histology and Embryology, Harran University School of Medicine, Sanliurfa, Turkiye

Abstract

Background and Aim: Hepatotoxicity represents a significant adverse effect associated with cancer treatment. The present study was designed to evaluate the possible hepatoprotective effects of bevacizumab and nivolumab when administered concomitantly with cisplatin.

Materials and Methods: A total of forty-two male Wistar Albino rats were randomly allocated into six groups: control, bevacizumab (10 mg/kg), nivolumab (3 mg/kg), cisplatin (12 mg/kg), cisplatin plus bevacizumab, and cisplatin plus nivolumab. Histological assessment of liver tissues was performed using hematoxylin and eosin (H&E) and Masson's trichrome staining. Immunohistochemical evaluation was conducted for inflammatory markers (TNF-α, IL-6), the angiogenic factor VEGF, and apoptotic markers (Bax, Bcl-2, Caspase-3).

Results: Administration of cisplatin resulted in hepatotoxic changes, including disruption of normal hepatic cord architecture, cytoplasmic vacuolization, hemorrhage, mononuclear cell infiltration, and enhanced collagen accumulation. Co-treatment with bevacizumab or nivolumab significantly alleviated these histopathological changes ($p<0.001$). In addition, levels of inflammatory and pro-apoptotic markers (TNF-α, Bax, Caspase-3) were markedly reduced, whereas expression of the anti-apoptotic protein Bcl-2 was increased in the combination treatment groups compared with the cisplatin-only group. In the cisplatin + nivolumab group, the TNF-α level was 1.0 (0.8–1.2), whereas in the cisplatin-only group it was 2.0 (1.8–2.0) ($p=0.03$). The Bcl-2 level in the cisplatin + nivolumab group was 1.0 (0.8–1.2), while it was 0.2 (0–0.6) in the cisplatin group ($p=0.04$).

Conclusion: Bevacizumab and nivolumab exhibited hepatoprotective properties when combined with cisplatin, as demonstrated by histological improvement and regulation of inflammatory and apoptotic signaling pathways.

Keywords: Bevacizumab; liver Injury; nivolumab.

How to cite this article: Karhan O, Turedi S. Nivolumab and bevacizumab attenuate cisplatin-induced hepatic inflammation and apoptosis in rats. Hepatology Forum 2026; 7(1):45–50.

Received: December 18, 2025; **Revised:** December 24, 2025; **Accepted:** January 02, 2026; **Available online:** January 00, 2026

Corresponding author: Ogur Karhan; Harran Universitesi Tip Fakultesi, Tibbi Onkoloji Anabilim Dali, Sanliurfa, Turkiye
Phone: +90 535 606 92 69; **e-mail:** dr_karhan@yahoo.com

Hepatology Forum - Available online at www.hepatologyforum.org

Introduction

Recent advances in cancer therapy, particularly immune checkpoint inhibitors (ICIs) and targeted agents, have improved clinical outcomes across multiple malignancies.[1,2] Nivolumab, a programmed death-1 (PD-1) monoclonal antibody, and bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, are widely used alone or in combination with chemotherapy for several cancers, including hepatocellular carcinoma (HCC).[3]

Chemotherapy may enhance the efficacy of immune checkpoint inhibitors by increasing tumor antigen exposure after cancer cell death and by depleting immunosuppressive cells in the tumor microenvironment.[4] Likewise, bevacizumab inhibits angiogenesis and promotes vascular normalization, improving intratumoral chemotherapy delivery.[5]

The liver is an essential organ indispensable for sustaining life, and hepatic metastasis is associated with poor prognosis regardless of the primary tumor site.[6] Moreover, liver metastases are known to induce an immunosuppressive tumor microenvironment.[7] Chemotherapeutic agents can induce various hepatic injuries, including acute hepatitis, hepatic necrosis, portal vein thrombosis, sinusoidal obstruction syndrome, and hepatic steatosis.[8]

Cisplatin, one of the most widely used cytotoxic agents, can induce hepatotoxicity primarily through oxidative stress and mitochondrial dysfunction.[9] Nivolumab may induce hepatotoxicity through T-lymphocyte activation and loss of peripheral tolerance.[10] Conversely, bevacizumab is generally not associated with hepatotoxicity and is even speculated to exert a hepatoprotective effect.

This study sought to characterize the hepatic effects of cisplatin, nivolumab, and bevacizumab individually and in combination, with particular focus on the hepatic impact of cisplatin–nivolumab and cisplatin–bevacizumab regimens.

Materials and Methods

Ethical Procedures and Animals

In this study, a total of forty-two healthy male Wistar Albino rats (8–10 weeks old, weighing 200–270 g) were obtained from the Harran University (HRÜ) Experimental Animal Application and Research Center, Şanlıurfa, Turkey. All animals were housed under controlled environmental conditions (temperature: 22±2°C; relative humidity: 50% ± 10%; light/dark cycle: 12/12 hours). Rats were provided with standard laboratory chow with free access to water. Throughout the experimental period, animal care and handling were performed in accordance with the "Guide for the Care and Use of Laboratory Animals" published by the National Institutes of Health (NIH, USA).

Experimental Design

In this study, forty-two male Wistar Albino rats (8–10 weeks old, weighing 200–270 g) were randomly assigned into six experimental groups as follows:

Control group (n=6): Received a single intraperitoneal (i.p.) injection of normal saline and were sacrificed on day 14.

Bevacizumab (B) group (n=6): Received 10 mg/kg i.p. bevacizumab on days 1 and 7 and were sacrificed on day 14.[11]

Nivolumab (N) group (n=6): Received 3 mg/kg i.p. nivolumab on days 1 and 7 and were sacrificed on day 14.[12]

Cisplatin (C) group (n=8): Received a single i.p. dose of 12 mg/kg cisplatin on day 1 and were sacrificed on day 14.[13]

Cisplatin + Bevacizumab (CB) group (n = 8): Received 12 mg/kg i.p. cisplatin on day 1, followed by bevacizumab 10 mg/kg i.p. on days 1 and 7, and were sacrificed on day 14.

Cisplatin + Nivolumab (CN) group (n = 8): Received 12 mg/kg i.p. cisplatin on day 1, followed by nivolumab 3 mg/kg i.p. on days 1 and 7, and were sacrificed on day 14.

At the end of the experimental period, all animals were sacrificed under deep anesthesia via exsanguination. Liver tissues were collected for histopathological examination under light microscopy.

Histopathological Evaluation

At the end of the experimental period, liver tissue samples from all groups were fixed in 10% neutral buffered formalin for histopathological examination. Following fixation, tissues were dehydrated through a graded series of ethanol, cleared in xylene, and embedded in paraffin to obtain tissue blocks. Sections of 5 µm thickness were cut using a semi-automated microtome (Thermo Shandon Finesse ME+, Runcorn, UK). The obtained sections were stained with hematoxylin and eosin (H&E) for general histological assessment and with Masson's Trichrome (Trichrome Masson Stain Kit, Sigma-Aldrich, Code: HT15-1KT, St. Louis, MO, USA) for evaluation of collagen deposition and fibrosis.

Histopathological evaluations were performed under a light microscope by an experienced and blinded histologist using a Zeiss Axioskop II microscope (Carl Zeiss Microscopy GmbH, Göttingen, Germany). Images were captured using a Zeiss Axiocam MRc camera system (Carl Zeiss MicroImaging GmbH, Göttingen, Germany) and digitally archived.

Each microscopic sample was semi-quantitatively scored for hepatic degeneration/regeneration according to the following criteria: hepatocellular degeneration, sinusoidal dilatation, inflammatory cell infiltration, hemorrhage, and degree of fibrovascular area formation.[14,15] The severity of lesions was graded on a four-point scale as follows: normal=0, mild=1, moderate=2, and severe=3.

Immunohistochemistry (IHC) Staining

Immunohistochemical analyses were performed on liver tissue sections to evaluate inflammation, apoptosis, and vascular structural alterations. The localization and expression of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), vascular endothelial growth factor (VEGF), B-cell lymphoma 2 (Bcl-2), Bcl-2-associated X protein (Bax), and caspase-3 (Cas-3) were examined.

Paraffin-embedded liver tissue blocks obtained from each experimental group were sectioned at 5 µm thickness and deparaffinized. Following deparaffinization, the sections were rinsed and washed in phosphate-buffered saline (PBS) for 5 minutes. Antigen retrieval was performed by boiling the sections in citrate buffer (pH 6.0). After cooling and washing in PBS, endogenous peroxidase activity was blocked using 3% hydrogen peroxide (H_2O_2) for 10 minutes.

Primary antibodies—TNF-α (Santa Cruz Biotechnology, Inc., Cat. No. sc-52746), IL-6 (Cat. No. sc-28343), VEGF (Cat. No. sc-7269), Bax (Cat. No. sc-7480), Bcl-2 (Cat. No. sc-7382), and Caspase-3 (Cat. No. sc-56053)—were diluted 1:100 and applied to the sections, which were then incubated at +4 °C overnight. After washing, the sections were incubated with a biotinylated secondary antibody using a commercial detection kit (Thermo Scientific, MA, USA; Cat. No. TP-060-HL), according to the manufacturer's protocol.

3,3′-Diaminobenzidine (DAB) substrate kit (Sigma-Aldrich, St. Louis, MO, USA; Cat. No. D3939) was used as the chromogen. Counterstaining was performed with Mayer's hematoxylin, and the slides were mounted with Entellan. All sections were examined under a light microscope, and representative images were captured.

For immunohistochemical evaluation, five randomly selected microscopic fields per section were analyzed. Positive immunoreactivity for TNF-α, IL-6, VEGF, Bax, Bcl-2, and Cas-3 was identified as brown cytoplasmic or nuclear staining. Immunohistochemical labeling was evaluated semiquantitatively based on both the intensity and distribution of specific staining. The staining intensity was assessed using the H-score method, where 0 indicated negative staining, 1+ weak, 2+ moderate, and 3+ strong staining. The H-score was calculated according to the following formula:

H-score = (percentage of cells stained at 1+) × 1 + (percentage of cells stained at 2+) × 2 + (percentage of cells stained at 3+) × 3.

This scoring system yields a total value ranging from 0 to 300, with 300 representing 100% of cells showing strong positive staining.[16,17]

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro–Wilk test. Since most variables did not follow a normal distribution, comparisons among groups were conducted using the Kruskal–Wallis test. When statistically significant differences were identified, post hoc pairwise comparisons were performed using the Sidak correction method via JASP software (Version 0.17; University of Amsterdam, The Netherlands). Results are presented as median values and minimum–maximum. A p-value of less than 0.05 was considered statistically significant.

Results

A comparison of body-weight trajectories showed a significant decrease in the cisplatin (C) group relative to controls (244 g vs. 302 g, p=0.001). No other treatment groups exhibited statistically significant differences in body weight (Appendix Table 1).

Histopathologic Examination

Histopathological Findings

Light microscopic examination showed no histological changes in the control, bevacizumab, or nivolumab groups, where hepatocytes were regularly arranged around the central vein and normal lobular and sinusoidal architecture was maintained (Fig. 1a–c).

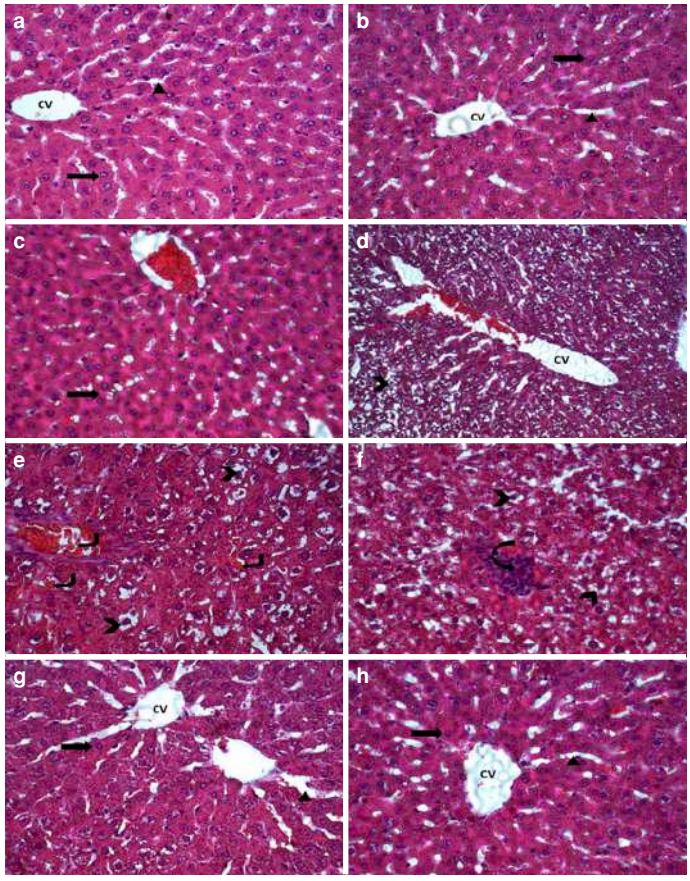

Figure 1. Light microscopic micrographs of liver tissue from experimental groups. Control group **(a)**; Bevacizumab group **(b)**; Nivolumab group **(c)**; Cisplatin group **(d–f)**; Cisplatin + Bevacizumab group **(g)**; Cisplatin + Nivolumab group **(h)**. CV: central vein; sinusoid (arrowhead); hepatocyte (arrow); inflammatory cell infiltration (curved arrow); hemorrhage and sinusoidal dilatation (wavy arrow); hepatocellular degeneration (double bracket). (H&E staining; A–C and E–H: x40, D: x20).

In contrast, cisplatin caused clear hepatic injury, including central vein congestion and dilatation, disruption of hepatic cords (Fig. 1d), hepatocellular degeneration with cytoplasmic vacuolation, hemorrhage, and mononuclear cell infiltration (Fig. 1e, f).

Co-administration of bevacizumab or nivolumab with cisplatin (Fig. 1g, h) markedly reduced these effects, with less hepatocellular vacuolation and mononuclear infiltration, and largely preserved central vein and sinusoidal structure.

Body-weight comparison showed a significant reduction in the cisplatin group compared with controls (302 g vs. 244 g, p=0.001), while no significant differences were observed in the other groups (Appendix Table 1).

Masson's Trichrome Staining Findings

Masson's Trichrome staining was used to assess connective tissue and collagen deposition in the periportal area. Bevacizumab and nivolumab did not produce any noticeable changes in connective tissue or collagen levels compared with the control group (Appendix Fig.1a–c). In contrast, cisplatin caused a marked increase in collagen deposition and connective tissue, along with distortion of the normal hepatosinusoidal architecture (Appendix Fig. 1d).

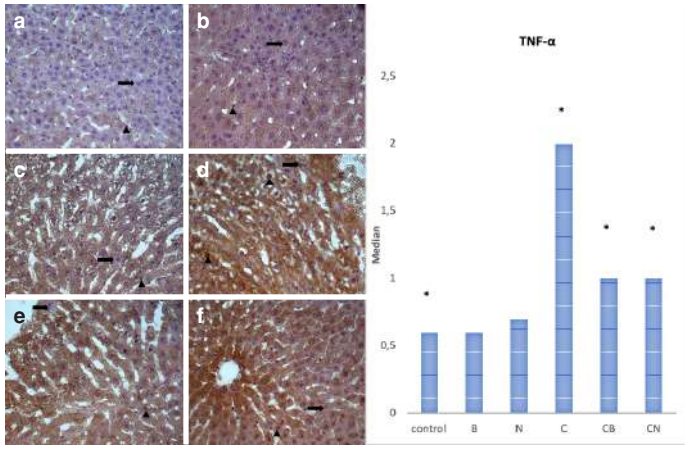

Figure 2. Immunohistochemical micrographs of liver sections stained for TNF-α in the experimental groups. Control group **(a)**; Bevacizumab group **(b)**; Nivolumab group **(c)**; Cisplatin group **(d)**; Cisplatin + Bevacizumab group **(e)**; Cisplatin + Nivolumab group **(f)**. TNF-α positive staining (arrowhead); negative staining (arrow). Magnification: x40. Median value was presented for all groups. *Showed statistically difference between cisplatin and other groups. Bevacizumab (B), Nivolumab (N), Cisplatin (C), Cisplatin+Bevacizumab (CB), Cisplatin+Nivolumab (CN).

Co-administration of bevacizumab or nivolumab with cisplatin reduced these fibrotic changes, showing decreased collagen accumulation and less architectural distortion, with liver morphology appearing similar to the control group (Appendix Fig. 1e, f). Histopathological and morphometric findings are summarized in Table 1.

Immunohistochemical Expression of Inflammatory Markers (TNF-α, IL-6)

To assess hepatic inflammation after treatment with bevacizumab (B), nivolumab (N), cisplatin (C), and their combinations (BC and NC), immunohistochemical staining for TNF-α and IL-6 was performed, and H-scores were calculated for each group.

There was a significant difference in TNF-α expression among the groups (p<0.001). Post hoc analysis showed this difference was mainly due to increased TNF-α in the cisplatin group compared with controls [2.0 (1.8–2.0) vs. 0.6 (0.4–0.8); p=0.02]. TNF-α levels were significantly lower in the cisplatin + bevacizumab [1.0 (0.8–1.2); p=0.03] and cisplatin + nivolumab [1.0 (0.8–1.2); p=0.03] groups than in the cisplatin-only group (Fig. 2).

IL-6 expression also differed significantly (p<0.001), with the greatest increase in the cisplatin group compared with controls [0.4 (0.2–0.8) vs. 1.8 (1.0–2.0); p=0.04]. However, no significant differences were found between cisplatin and the cisplatin + bevacizumab [1.8 (1.0–2.0) vs. 1.1 (0.8–1.2); p=0.05] or cisplatin + nivolumab [1.8 (1.0–2.0) vs. 1.0 (0.6–1.2); p=0.09] groups (Appendix Fig. 2).

Immunohistochemical Expression of VEGF and Apoptosis Markers (Bax, Bcl-2, Caspase-3)

There was a significant difference in VEGF expression among the groups (p<0.001). Subgroup analysis showed that VEGF levels were significantly higher in the cisplatin + bevacizumab group compared with the control group [1.5 (1.2–1.6) vs. 0.7 (0.2–1.0); p=0.04]. VEGF expression was also significantly elevated in the cisplatin + beva-

Table 1. Histopathological and morphometric parameters in experimental groups

Groups	Body weight (g)	VC (μm)	Hepatocyte degeneration	Hemorrhage	Sinusoidal dilatation	Inflammatory cell infiltration	FBD
Control	302 (271–317)[b]	8.8 (6.7–12.9)[b]	0.2 (0–0.4)[b]	0.3 (0.2–0.6)[b]	0.3 (0–0.6)[b]	0.4 (0.2–0.6)[b]	0.2 (0.2–0.4)[b]
Bevacizumab	278 (246–316)	13.5 (10.2–16.5)[b]	0.4 (0.2–0.8)[b]	0.4 (0.4–0.8)[b]	0.4 (0.2–0.8)[b]	0.6 (0.4–0.6)[b]	0.4 (0.2–0.6)[b]
Nivolumab	270 (265–298)[b]	13.2 (12–18.5)[b]	0.5 (0.2–1)[b]	0.6 (0.4–0.8)[b]	0.6 (0.4–0.8)[b]	0.6 (0.4–0.8)[b]	0.4 (0.2–0.6)[b]
Cisplatin	244 (235–264)[a]	86 (60–103)[a]	2.1 (1.8–2.6)[a]	1.4 (1–1.8)[a]	1.4 (1.2–1.6)[a]	1.5 (1.2–1.6)[a]	1.4 (1.2–1.8)[a]
Cisplatin+ Bevacizumab	260 (240–276)	33 (28–39)[a,b]	1 (0.8–1.2)[a,b]	1 (0.8–1)[a]	0.9 (0.8–1)[a,b]	0.7 (0.6–1)[b]	0.7 (0.4–0.8)[b]
Cisplatin+ Nivolumab	247 (240–276)	29 (20–33)[a,b]	0.8 (0.6–1)[a,b]	1 (0.8–1.2)[a]	0.8 (0.6–1)[b]	0.6 (0.4–1)[b]	0.5 (0.2–0.8)[b]

VC: Vascular congestion; FBD: Fibrovascular density. Data are expressed as median (minimum–maximum). a; P<0.05 compared to the control group; b; P<0.05 compared to the cisplatin group.

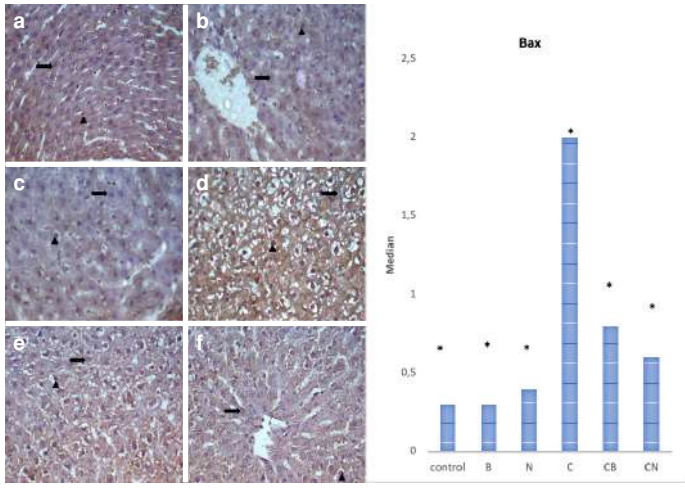

Figure 3. Immunohistochemical micrographs of liver sections stained for Bax in the experimental groups. Control group **(a)**; Bevacizumab group **(b)**; Nivolumab group **(c)**; Cisplatin group **(d)**; Cisplatin + Bevacizumab group **(e)**; Cisplatin + Nivolumab group **(f)**. Bax positive staining (arrowhead); negative staining (arrow). Magnification: x40. *Showed statistically difference between cisplatin and other groups. Bevacizumab (B), Nivolumab (N), Cisplatin (C), Cisplatin+Bevacizumab (CB), Cisplatin+Nivolumab (CN).

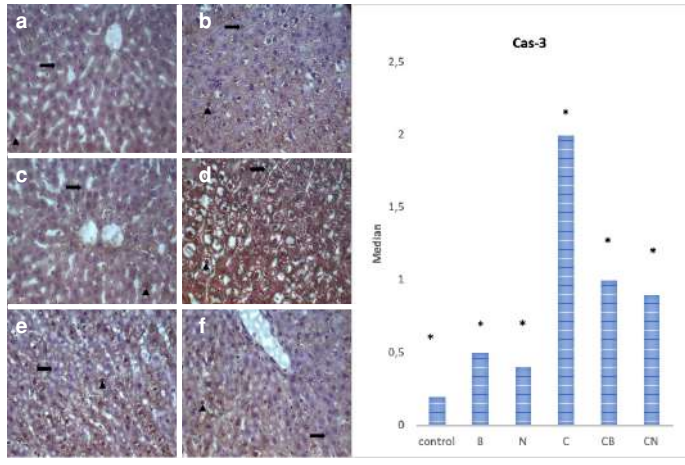

Figure 4. Immunohistochemical micrographs of liver sections stained for Caspase-3 in the experimental groups. Control group **(a)**; Bevacizumab group **(b)**; Nivolumab group **(c)**; Cisplatin group **(d)**; Cisplatin + Bevacizumab group **(e)**; Cisplatin + Nivolumab group **(f)**. Caspase-3 positive staining (arrowhead); negative staining (arrow). Magnification: x40. *Showed statistically difference between cisplatin and other groups. Bevacizumab (B), Nivolumab (N), Cisplatin (C), Cisplatin+Bevacizumab (CB), Cisplatin+Nivolumab (CN).

cizumab group compared with the cisplatin group [1.5 (1.2–1.6) vs. 0.8 (0.6–1.0); p=0.03] and the bevacizumab group [1.5 (1.2–1.6) vs. 0.7 (0.6–0.8); p=0.03] (Appendix Fig. 3).

Apoptotic activity was assessed by Bax, Bcl-2, and Caspase-3 expression. Bax levels were significantly higher in the cisplatin group compared with controls [2.0 (1.8–2.4) vs. 0.3 (0.2–0.6); p=0.04]. Bax expression was markedly reduced in the cisplatin + bevacizumab [0.8 (0.6–1.0); p=0.04] and cisplatin + nivolumab [0.6 (0.2–0.8); p=0.04] groups compared with cisplatin alone (Fig. 3).

Bcl-2 expression showed the opposite pattern. The cisplatin + bevacizumab group had significantly higher Bcl-2 levels than the cisplatin group [1.1 (0.6–1.4) vs. 0.2 (0–0.6); p=0.04], and the cisplatin + nivolumab group showed a similar increase [1.0 (0.8–1.2) vs. 0.2 (0–0.6); p=0.04] (Fig. 4).

Caspase-3 expression also differed significantly. Cisplatin treatment markedly increased Cas-3 compared with controls [2.0 (1.6–2.4) vs. 0.2 (0–0.6); p=0.004]. Both the cisplatin + bevacizumab [1.0 (0.8–1.0); p=0.03] and cisplatin + nivolumab [0.9 (0.4–1.2); p=0.04] groups showed significantly lower Cas-3 levels than the cisplatin group, indicating a protective effect against cisplatin-induced apoptosis (Appendix Fig. 4).

Immunohistochemical expression levels of inflammatory, angiogenic, and apoptotic markers are summarized in Table 2.

Discussion

Cisplatin remains a cornerstone chemotherapeutic agent across multiple malignancies, yet its clinical utility is frequently restricted by dose-dependent adverse events, among which hepatotoxicity represents a notable limitation. In our study, nivolumab and bevacizumab alone did not cause any histopathological liver changes. Anti–PD-1 agents are known to induce hepatotoxicity in about 2–5% of patients, and nivolumab-related hepatotoxicity has been reported in roughly 1% of melanoma cases.[18,19] This adverse effect, however, usually appears after the fifth

Table 2. Immunohistochemical expression levels of ınflammatory, angiogenic, and apoptotic markers

Groups	TNF-α	IL-6	VEGF	Bax	Bcl-2	Caspase-3
Control	0.6 (0.4–0.8)[b]	0.4 (0.2–0.8)[b]	0.7 (0.2–1)	0.3 (0.2–0.6)[b]	0.5 (0.4–0.6)	0.2 (0–0.6)[b]
Bevacizumab	0.6 (0.4–1)[b]	0.5 (0.4–0.6)[b]	0.7 (0.6–0.8)	0.3 (0.2–0.4)[b]	0.6 (0.4–0.8)	0.5 (0.2–0.6)[b]
Nivolumab	0.7 (0.2–0.8)[b]	0.5 (0.2–0.8)[b]	0.8 (0.6–0.8)	0.4 (0.2–0.6)[b]	0.7 (0.4–1))	0.4 (0.2–0.8)[b]
Cisplatin	2 (1.8–2)[a]	1.8 (1–2)[a]	0.8 (0.6–1)	2 (1.8–2.4)[a]	0.2 (0–0.6)	2 (1.6–2.4)[a]
Cisplatin+ Bevacizumab	1 (0.8–1.2)[a,b]	1.1 (0.8–1.2)	1.5 (1.2–1.6)[a,b]	0.8 (0.6–1)[b]	1.1 (0.6–1.4)[b]	1 (0.8–1)[a,b]
Cisplatin+ Nivolumab	1 (0.8–1.2)[b]	1 (0.6–1.2)	1.1 (0.8–1.4)	0.6 (0.2–0.8)[b]	1 (0.8–1.2)[a,b]	0.9 (0.4–1.2)[b]

Data are expressed as median (minimum–maximum). a; p<0.05 compared to the control group. b; p<0.05 compared to the cisplatin group.

week of treatment.[20] Because the animals in our study were sacrificed on day 14, nivolumab-related hepatotoxicity was not detected.

Bevacizumab has been reported to have a protective effect when combined with chemotherapy in patients with colorectal cancer and liver metastases.[21] Animal studies have also shown that presurgical bevacizumab promotes liver regeneration after hepatectomy in rats,[22] and it can reduce hepatic fibrosis and exhibit hepatoprotective activity in experimental fibrosis models.[23]

In our study, bevacizumab administration in healthy rats caused no histopathological changes under light microscopy. Additionally, no significant differences were found in inflammatory, apoptotic, or anti-apoptotic marker expression compared with the control group. These results align with previous findings, indicating that bevacizumab does not produce adverse effects on normal liver histology in healthy rats.

Cisplatin is known for its dose-limiting toxicities, including nephrotoxicity, neurotoxicity, and hepatotoxicity. In this study, cisplatin caused clear hepatic injury—central vein dilatation and congestion, cytoplasmic vacuolation, mononuclear infiltration, and increased collagen deposition. These findings are consistent with previous reports confirming cisplatin-induced hepatotoxicity.[24]

Cisplatin hepatotoxicity is mainly driven by oxidative stress, inflammation, and apoptosis. Earlier studies in rats have shown that cisplatin increased ROS production and elevated TNF-α, while reducing IL-10 and upregulating pro-apoptotic proteins including caspase-3, together with decreased Bcl-2.[13] Similar increases in oxidative markers, caspase-3, and VEGF have also been documented.[25]

Consistent with these reports, our findings showed that cisplatin significantly increased inflammatory cytokines TNF-α and IL-6. Apoptotic evaluation revealed decreased anti-apoptotic Bcl-2 and increased pro-apoptotic Bax, caspase-3, and VEGF expression. Although oxidative markers were not measured, our results support the conclusion that cisplatin induces hepatotoxicity through inflammatory activation and enhanced apoptotic signaling.

The relationship between cisplatin and VEGF expression remains controversial. In our study, cisplatin did not significantly change VEGF levels compared with the control, bevacizumab, or nivolumab groups. One experimental study reported increased VEGF after cisplatin, but they measured the mean staining area and used a lower dose (7.5 mg/kg), which may explain the difference.[25] Another study using a human ovarian cancer xenograft model found decreased VEGF expression after cisplatin, likely due to differences between tumor-bearing animals and the healthy rats used in our study.[26]

Co-administration of bevacizumab with cisplatin reduced cisplatin-induced hepatic damage. The cisplatin + bevacizumab group showed improved hepatic architecture, better regeneration, and restoration of normal sinusoidal and portal structures. Inflammatory and pro-apoptotic markers (TNF-α, Bax, Caspase-3) were decreased, while VEGF and the anti-apoptotic protein Bcl-2 were increased compared with cisplatin alone.

These findings agree with a meta-analysis showing that bevacizumab enhances chemotherapy efficacy while reducing oxaliplatin-induced sinusoidal injury.[27] To our knowledge, this is the first experimental study demonstrating that bevacizumab co-administration mitigates cisplatin-induced hepatotoxicity.

Co-administration of nivolumab with cisplatin led to clear histological improvement of cisplatin-induced hepatotoxicity, including hepatocyte regeneration, reduced cytoplasmic vacuolization, and restoration of normal hepatic cord and portal structures compared with cisplatin alone. Immunohistochemically, the cisplatin + nivolumab group showed lower TNF-α expression, reduced inflammatory infiltration, and decreased Bax and Caspase-3 levels, along with increased Bcl-2 expression.

Previous studies have shown that different agents can reduce cisplatin-induced hepatotoxicity by limiting oxidative damage, apoptosis, and inflammation. For example, the SGLT2 inhibitor dapagliflozin provided hepatoprotection when given with cisplatin through its antioxidant effects.[28] Ganoderma lucidum mushroom extract similarly reduced cisplatin-induced liver injury by decreasing oxidative stress and related apoptosis.[13] Licorice has also been reported to protect against cisplatin-induced hepatic injury by suppressing reactive oxygen species (ROS) generation.[29]

To the best of our knowledge, this is the first study showing that nivolumab co-administration reduces cisplatin-induced hepatotoxicity. Nivolumab decreased TNF-α levels and reduced inflammatory cell infiltration, suggesting a possible anti-inflammatory effect. In addition, the increase in the anti-apoptotic protein Bcl-2 and the decrease in pro-apoptotic Bax and Caspase-3 indicate an anti-apoptotic influence likely linked to its anti-inflammatory activity. Since many agents that improve cisplatin-induced hepatotoxicity act by reducing oxidative stress and enhancing antioxidant defenses, it may be speculated that nivolumab could also exert indirect antioxidant effects contributing to hepatoprotection.

Our study has some limitations. First, the experiments were performed in healthy rats, and the presence of cancer or liver metastases could influence hepatic responses and lead to different outcomes. Second, as this is an experimental animal study, the results cannot be directly extrapolated to humans without additional clinical validation.

Conclusion

In conclusion, cisplatin administration caused clear hepatotoxicity, as shown by histopathological and immunohistochemical findings. Co-administration of bevacizumab or nivolumab significantly reduced these hepatotoxic effects. These results suggest that both agents may offer hepatoprotective benefits when combined with cisplatin, possibly through anti-inflammatory and anti-apoptotic mechanisms. Further studies in tumor-bearing models and clinical settings are needed to confirm these findings.

Online Appendix Link:
https://hepatologyforum.org/storage/upload/files/1767602975-appendix-en.pdf

Ethics Committee Approval: The Harran University Clinical Research Ethics Committee granted approval for this study (date: 07.11.2024, number: 2024/006/01-16).

Informed Consent: Written informed consent was obtained from participants.

Conflict of Interest: The authors has 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: Not declared.

Author Contributions: Concept – OK, ST; Design – OK, ST; Supervision – OK, ST; Findings – OK, ST; Materials – ST; Data Collection and/or Processing – OK, ST; Analysis and/or Interpretation – OK; Literature Search – OK, ST; Writing Manuscript – OK, ST; Critical Review – OK, ST.

Peer-review: Externally peer-reviewed.

References

1. Zamani MR, Šácha P. Immune checkpoint inhibitors in cancer therapy: what lies beyond monoclonal antibodies? Med Oncol 2025;42(7):273. [CrossRef]
2. Garcia J, Hurwitz HI, Sandler AB, Miles D, Coleman RL, Deurloo R, et al. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook. Cancer Treat Rev 2020;86:102017. [CrossRef]
3. Yau T, Galle PR, Decaens T, Sangro B, Qin S, da Fonseca LG, et al. Nivolumab plus ipilimumab versus lenvatinib or sorafenib as first-line treatment for unresectable hepatocellular carcinoma (CheckMate 9DW): an open-label, randomised, phase 3 trial. Lancet 2025;405(10492):1851-1864. [CrossRef]
4. Sordo-Bahamonde C, Lorenzo-Herrero S, Gonzalez-Rodriguez AP, Martínez-Pérez A, Rodrigo JP, García-Pedrero JM, et al. Chemo-Immunotherapy: A New Trend in Cancer Treatment. Cancers (Basel) 2023;15(11):2912. [CrossRef]
5. Cesca M, Morosi L, Berndt A, Fuso Nerini I, Frapolli R, Richter P, et al. Bevacizumab-induced inhibition of angiogenesis promotes a more homogeneous intratumoral distribution of paclitaxel, improving the antitumor response. Mol Cancer Ther 2016;15(1):125-135. [CrossRef]
6. Waninger JJ, Ma VT, Chopra Z, Pearson AN, Green MD. Evaluation of the prognostic role of liver metastases on patient outcomes: Systematic review and meta-analysis. Cancer J 2023;29(5):279-284. [CrossRef]
7. Xu W, Wang Y, Wang N, Liu J, Zhou L, Guo J. Spatial immune remodeling of the liver metastases: discovering the path to antimetastatic therapy. J Immunother Cancer 2025;13(3):e011002. [CrossRef]
8. Sharma A, Houshyar R, Bhosale P, Choi JI, Gulati R, Lall C. Chemotherapy induced liver abnormalities: an imaging perspective. Clin Mol Hepatol 2014;20(3):317-326. [CrossRef]
9. Katanić Stanković JS, Selaković D, Rosić G. Oxidative damage as a fundament of systemic toxicities induced by cisplatin-the crucial limitation or potential therapeutic target? Int J Mol Sci 2023;24(19):14574. [CrossRef]
10. Savino A, Rossi A, Fagiuoli S, Invernizzi P, Gerussi A, Viganò M. Hepatotoxicity in cancer immunotherapy: Diagnosis, management, and future perspectives. Cancers (Basel) 2024;17(1):76. [CrossRef]
11. Semyachkina-Glushkovskaya O, Diduk S, Anna E, Elina D, Artem K, Khorovodov A, et al. Music improves the therapeutic effects of bevacizumab in rats with glioblastoma: Modulation of drug distribution to the brain. Front Oncol 2022;12:1010188. [CrossRef]
12. Güler İ, Kuzucu İ, Baklacı D, Kum RO, Özhamam Uçaryılmaz E, Özcan M. Evaluation of nivolumab for ototoxic effects: An animal study in rats. J Int Adv Otol 2020;16(2):218-221. [CrossRef]
13. Hassan HM, Al-Wahaibi LH, Elmorsy MA, Mahran YF. Suppression of cisplatin-induced hepatic injury in rats through alarmin high-mobility group box-1 pathway by ganoderma lucidum: Theoretical and experimental study. Drug Des Devel Ther 2020;14:2335-2353. [CrossRef]
14. Fouad AA, Qutub HO, Al-Melhim WN. Punicalagin alleviates hepatotoxicity in rats challenged with cyclophosphamide. Environ Toxicol Pharmacol. 2016;45:158-162. [CrossRef]
15. Turedi S. Protective/preventive effects of quercetin against cyclophosphamide-induced hepatic inflammation, apoptosis and fibrosis in rats. Hepatol Forum 2023;4(3):135-141. [CrossRef]
16. Abueid L, Uslu Ü, Cumbul A, Velioğlu Öğünç A, Ercan F, Alican İ. Inhibition of 5-lipoxygenase by zileuton in a rat model of myocardial infarction. Anatol J Cardiol 2017;17(4):269-275. [CrossRef]
17. Türedi S, Çelik H, Dağlı Ş N, Taşkın S, Şeker U, Deniz M. An examination of the effects of propolis and quercetin in a rat model of streptozotocin-induced diabetic peripheral neuropathy. Curr Issues Mol Biol 2024;46(3):1955-1974. [CrossRef]
18. Schneider BJ, Naidoo J, Santomasso BD, Lacchetti C, Adkins S, Anadkat M, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO Guideline update. J Clin Oncol 2021;39(36):4073-4126. [CrossRef]
19. Robert C, Long GV, Brady B, Dutriaux C, Maio M, Mortier L, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372(4):320-330. [CrossRef]
20. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, et al. Safety Profile of nivolumab monotherapy: A pooled analysis of patients with advanced melanoma. J Clin Oncol 2017;35(7):785-792. [CrossRef]
21. Ribero D, Wang H, Donadon M, Zorzi D, Thomas MB, Eng C, et al. Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastases. Cancer 2007;110(12):2761-2767. [CrossRef]
22. Mori H, Saito YU, Iwahashi S, Ikemoto T, Imura S, Morine Y, et al. Impact of Bevacizumab on Liver Damage After Massive Hepatectomy in Rats. In Vivo 2019;33(5):1469-1476. [CrossRef]
23. Huang Y, Feng H, Kan T, Huang B, Zhang M, Li Y, et al. Bevacizumab attenuates hepatic fibrosis in rats by inhibiting activation of hepatic stellate cells. PLoS One 2013;8(8):e73492. [CrossRef]
24. Fathy M, Darwish MA, Abdelhamid AM, Alrashedy GM, Othman OA, Naseem M, et al. Kinetin ameliorates cisplatin-induced hepatotoxicity and lymphotoxicity via attenuating oxidative damage, cell apoptosis and inflammation in rats. Biomedicines 2022;10(7):1620. [CrossRef]
25. El-Sharouny SH, Rizk A, Rashed LA, Sayed WM, Elmoneam M. Analysis of the therapeutic role of platelet-rich plasma against cisplatin-induced hepatotoxicity in rats: controversy between oxidative and apoptotic markers. Eur J Anat 2019;23(3):201-213.
26. Li W, Wan L, Zhai LY, Wang J. Effects of SC-560 in combination with cisplatin or taxol on angiogenesis in human ovarian cancer xenografts. Int J Mol Sci 2014;15(10):19265-19280. [CrossRef]
27. Jácome AA, Oliveira FA, Lino F, Lima J. Effect of adding bevacizumab to chemotherapy on pathologic response to preoperative systemic therapy for resectable colorectal liver metastases: A systematic review and meta-analysis. Clin Colorectal Cancer 2021;20(3):265-272. [CrossRef]
28. Satyam SM, Bairy LK, Rehman A, Farook M, Khan S, Nair AA, et al. Dapagliflozin: A Promising Strategy to Combat Cisplatin-Induced Hepatotoxicity in Wistar Rats. Biology (Basel) 2024;13(9):672. [CrossRef]
29. Li J, Yang X, Lian X, Li B, Ma Q, Yang L, et al. Licorice attenuates cisplatin-induced hepatotoxicity by alleviating endoplasmic reticulum stress and apoptosis. Front Pharmacol 2025;16:1557125. [CrossRef]

Review

EUS, liver transplantation

HEPATOLOGY FORUM

doi: 10.14744/hf.2025.24960

The role of EUS in liver transplantation

Can Cindoruk[1], Ali Emre Bardak[2], Eda Yildiz[1], Merve Gurakar[1], A. Eylul Donmez[3], Malak Elsawy[1], N. Begum Ozturk[4], Merih Deniz Toruner[5], Cem Simsek[1], Mehmet Cindoruk[6], Ahmet Gurakar[1]

[1]Department of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, Maryland, USA; [2]Department of Medicine, Boston Medical Center - Brighton, Massachusetts, USA; [3]Department of Radiology, Boston Children's Hospital, Harvard Medical School, Massachusetts, USA; [4]Department of Gastroenterology and Hepatology, School of Medicine, Saint Louis University, Missouri, USA; [5]Brown University Warren Alpert School of Medicine, Providence, Rhode Island, USA; [6]Department of Gastroenterology, Gazi University School of Medicine, Ankara, Turkiye

Abstract

Endoscopic ultrasound (EUS) is being increasingly used for both diagnostic and therapeutic purposes in various settings in gastroenterology and hepatology. Similarly, it has also been adopted in liver transplantation (LT), and its utilization is steadily increasing. EUS strengthens LT care in both the pre-transplant and post-transplant periods. Specifically, EUS is valuable in the evaluation of liver parenchyma, portal hypertension assessment and variceal management, tissue sampling when percutaneous or transjugular approaches are contraindicated or impractical, detection and characterization of hepatic and nodal metastases—thereby refining staging and sometimes even eligibility for LT—management of postoperative collections, and enabling biliary and pancreatic interventions in altered anatomy by creating access routes. In this review, we discuss these applications of EUS, along with its current limitations and its evolving role in the setting of LT.

Keywords: Endohepatology; endoscopic ultrasound; EUS; liver diseases; liver transplantation.

Introduction

Liver transplantation (LT) is the only curative therapy for end-stage liver disease.[1] Endoscopy is an essential tool in peritransplant care. In this setting, endoscopic ultrasound (EUS) has become an increasingly important tool, providing high-quality imaging, diagnostic sampling, and minimally invasive therapeutic approaches. Compared with percutaneous or transjugular approaches, EUS offers advantages in patients with challenging anatomy, ascites, coagulopathy, or inconclusive imaging findings.[2,3]

EUS supports diagnosis and risk stratification through the evaluation of portal hypertension, varices, cirrhosis, and focal liver lesions, while also guiding therapeutic procedures such as drainage of hepatic collections and treatment of variceal bleeding. Evidence consistently demonstrates its diagnostic accuracy, safety, and ability to integrate multiple steps into a single procedure.[2–4] The role of EUS in LT continues to expand steadily, and this review aims to provide a comprehensive overview of the diagnostic and therapeutic applications of EUS in LT candidates and recipients[4]

Pre-Transplant Role of EUS

Candidate Assessment for Liver Transplantation

LT assessment should be pursued for patients with decompensated liver cirrhosis who fail to respond to medical therapies.[5] The model for end-stage liver disease (MELD) score is the primary tool for prioritizing patients for LT; a score of ≥15 generally indicates a survival benefit from LT. In patients with hepatocellular carcinoma (HCC), LT eligibility is determined according to the Milan criteria.[6]

For patients with suspected cirrhosis or chronic liver disease, pre-transplant evaluation may integrate endoscopic variceal screening, EUS elastography, EUS-guided portal pressure gradient (EUS-PPG) measurement, and EUS-guided liver biopsy (EUS-LB), often within a single session when clinically indicated.[7]

Portal Hypertension: Definitions, Noninvasive Pathways, and Where EUS Fits

Portal hypertension (PH) results from architectural distortion due to fibrosis/cirrhosis and drives decompensation (varices, ascites, bleeding). The hepatic venous pressure gradient (HVPG) remains the gold standard for assessing PH; it is typically ≤5 mm Hg in healthy individuals, >5 mm Hg in cirrhosis, and ≥10 mm Hg in clinically significant PH (CSPH), at which point varices and decompensation become likely, especially after 12 mm Hg.[8]

Upper endoscopy is the gold standard for diagnosing gastroesophageal varices, which may serve as a surrogate for PH.[9] To reduce unnecessary procedures in compensated advanced chronic liver disease (cACLD), the Baveno VI consensus proposed a noninvasive approach using transient elastography (TE) for liver stiffness measurement (LSM) and platelet count to assess CSPH.[10] Baveno VII advanced this approach with LSM/platelet criteria to rule out (LSM <15 kPa and platelets >150×10³/μL) and to rule in CSPH (LSM ≥25 kPa) in alcohol-, viral-, or non-obese NASH-related cACLD.[11,12] Additionally, the presence of portosystemic collaterals on imaging studies also implies CSPH in cACLD, supporting their use as a component of noninvasive assessment.[13]

How to cite this article: Cindoruk C, Bardak AE, Yildiz E, Gurakar M, Donmez AE, Elsawy M, et al. The role of EUS in liver transplantation. Hepatology Forum 2026; 7(1):51–58.

Received: May 12, 2025; **Revised:** September 18, 2025; **Accepted:** September 30, 2025; **Available online:** November 14, 2025

Corresponding author: Ahmet Gurakar; Department of Gastroenterology and Hepatology, Johns Hopkins University School of Medicine, Maryland, USA
Phone: 410 614 2989; **e-mail:** aguraka1@jhmi.edu

Hepatology Forum - Available online at www.hepatologyforum.org

Despite these advances, HVPG remains the only valid tool for directly assessing PH severity and hemodynamic response to treatment beyond the presence or absence of CSPH in cACLD.[13]

EUS has recently emerged as an adjunct in this setting, offering advantages over conventional upper endoscopy and imaging.[14] EUS demonstrates substantially higher sensitivity for detecting gastric and deep varices than routine endoscopy. It also helps characterize collateral pathways such as periesophageal, paraesophageal, and perforating veins and provides more accurate measurements of variceal size and wall thickness, which are important for bleeding risk assessment.[15–17]

Doppler capability further allows assessment of hemodynamic changes in the left gastric, portal, and azygos venous systems.[16] In addition, EUS-PPG correlates closely with HVPG, providing a minimally invasive alternative when transjugular access is not feasible, and can be performed in the same session as liver biopsy when indicated.[18] These features position EUS as a complementary modality that enhances risk stratification and therapeutic planning in patients with PH, particularly in LT candidates and recipients.

A clinical study in 33 LT candidates further emphasized this role. EUS detected large deep esophageal varices in 36% of patients, 42% of which had not been identified as large on routine endoscopy. Similarly, EUS revealed large deep gastric varices in 36% of patients, 33% of which were not identified at all on routine endoscopy, while 25% had been classified as small varices.[19] These findings indicate that EUS can reveal clinically important varices missed by routine endoscopy, allowing for more accurate bleeding risk assessment and better guidance of preventive strategies in LT candidates.

Therapeutic EUS for Varices

Endoscopic injection of cyanoacrylate (CYA) remains the guideline-recommended conventional approach for cardiofundal varices, but limitations include imprecise targeting, risk of embolization, and the need for repeat sessions.[20,21]

EUS-guided therapy addresses these challenges by enabling direct visualization of the varices and feeding perforators, Doppler confirmation of obliteration, and more controlled delivery of CYA. This precision offered by EUS becomes particularly important in the setting of complex vascular anatomy and active bleeding, where visualization is often poor.[22,23]

Notably, combination therapy with coil plus CYA has demonstrated superior efficacy and durability compared with either modality alone, with higher rates of variceal obliteration and lower rebleeding rates than standard endoscopic CYA injection.[20]

Focal Liver Lesions and Tissue Acquisition

EUS improves the detection of small hepatic lesions, particularly those <10 mm, which can be missed on conventional imaging.[24,25] This was demonstrated in a large prospective study of 730 patients undergoing cancer staging. EUS detected focal liver lesions in 20.5% and metastases in 16.2% of patients, compared with 13.6% and 11.2% by CT or MRI, respectively. Importantly, EUS identified 42 cases of metastases that were missed by CT/MRI, while its miss rate was less than 1%.[24]

EUS real-time elastography (RTE) further refines the distinction and characterization between benign and malignant hepatic focal lesions.[2,26] EUS-LB is useful for sampling lesions with difficult access, such as those in the caudate or left lobe, where percutaneous access is limited.[24]

In HCC, cholangiocarcinoma (CCA), or metastatic liver disease, the advantages of EUS in lesion detection and characterization contribute to more accurate staging and improved selection of candidates for LT or surgical resection, which may potentially influence clinical decision-making and improve outcomes in patients being evaluated for transplantation.[27]

EUS also contributes to extrahepatic nodal staging relevant to LT candidacy. In a prospective cohort of 50 LT candidates with HCC and lymphadenopathy, EUS-FNA provided adequate samples in 92% and identified nodal metastases in 30%, thereby precluding LT for this group of patients. Additionally, granulomatous lymphadenopathy was diagnosed in 8%, requiring appropriate treatment before LT.[28]

Within the scope of a nationwide screening protocol for potential LT in unresectable perihilar CCA in the Netherlands, EUS-guided sampling of 84 nonregional nodes in 75 patients identified malignancy in 4% of patients. This is a small but clinically important proportion, given that positive findings precluded LT, suggesting that EUS assessment may change management in a clinically significant proportion of LT candidates.[29]

It should be noted that in unresectable perihilar CCA under evaluation for LT, EUS-guided fine-needle aspiration (EUS-FNA) or EUS-guided fine-needle biopsy (EUS-FNB) should be strictly avoided due to the risk of peritoneal tumor seeding, which can preclude transplant eligibility.[29,30] Therefore, EUS is primarily utilized to assess and sample nonregional or indeterminate lymph nodes and extra-hilar targets in LT candidates with perihilar CCA.

As for HCC, biopsy—including EUS-FNA/FNB—still carries a low risk for seeding, reported in less than 3% of cases across studies.[6,31] Importantly, current evidence shows that this seeding risk is not clearly associated with worse post-transplant outcomes. Accordingly, guidelines do not strictly prohibit biopsy in LT candidates with HCC but recommend reserving it for indeterminate cases on imaging.[6,31,32]

Portal vein thrombosis (PVT) is common in cirrhosis and in patients with suspected or known HCC.[33] The key question is whether the thrombus is bland or tumoral, as this distinction drives staging, transplant eligibility, and choice of locoregional or systemic therapy. EUS guidance provides a transgastric/duodenal route for real-time Doppler-assisted sampling of the portal thrombus, avoiding a transhepatic tract and potentially lowering bleeding risk in coagulopathic patients.

Small series and case reports show high feasibility and meaningful management impact: in a Spanish cohort of chronic liver disease with PVT, EUS-FNA was attempted in eight candidates, technically successful in seven, malignant in six, and it upstaged or altered treatment in six of seven patients, with no reported immediate adverse events.[34] Earlier reports similarly confirmed malignant thrombus when cross-sectional imaging was inconclusive.[35]

Technical reviews support the safety and practicality of EUS-guided portal venous access in experienced hands, while society guidance still prioritizes conventional imaging techniques such as Doppler/CT/MRI for initial PVT characterization and reserves biopsy for indeterminate cases where results would change management. In the LT pathway, EUS-FNA of PVT is therefore best used as a targeted test to confirm malignancy, clarifying candidacy and directing therapy.[20,36–38]

Beyond diagnosis, EUS is increasingly explored as a therapeutic tool. EUS-guided tumor ablation enables precise targeting with minimal collateral damage, offering a minimally invasive alternative for poorly accessible or high-risk lesions by conventional percutaneous or surgical approaches.[11,39–41]

In a prospective study of 20 patients with 25 caudate lobe tumors, EUS-guided laser ablation achieved 100% complete ablation after one or two sessions, with no procedure-related adverse events. During a median follow-up of 27 months, local tumor progression occurred in 16% and intrahepatic distant recurrence in 75% of patients, with tumor size >2 cm identified as a predictor of local progression.[27] Figure 1 illustrates different EUS techniques mentioned above with target examples.

Post-Transplant Role of EUS

Diagnostic Roles

In the post-LT period, patients may develop graft dysfunction, acute or chronic rejection, surgical complications (e.g., hemorrhage), vascular events, biliary complications, post-transplant lymphoproliferative disorders, *de novo* solid-organ cancers, infections, and other systemic problems.[42]

In this setting, EUS is used primarily to evaluate biliary and parenchymal complications. When combined with fine-needle aspiration/biopsy (FNA/FNB), EUS provides histological diagnosis of parenchymal disease or malignancy.[4] In addition, EUS-PPG measurement is an emerging tool that is highly consistent with HVPG and may streamline assessment in post-LT patients with suspected portal hypertension or fibrosis.[18,43,44]

As for suspected biliary disease, a cohort of 32 patients with post-LT biliary complications was assessed with both EUS and endoscopic retrograde cholangiopancreatography (ERCP).[45] EUS achieved 94.6% sensitivity and accuracy overall, outperforming ERCP in identifying biliary casts and ischemic cholangiopathy, with potential impacts on management. In contrast, EUS was found to be inferior in identifying anastomotic strictures.

Considering these findings, EUS can serve as a first-look triage tool in post-LT cholestasis unless an anastomotic stricture is more likely. A same-session strategy combining EUS-LB with ERCP is also feasible when both ductal and histological assessments are needed.[43,46,47]

EUS is also being explored in intestinal allograft surveillance, especially for chronic rejection. Assessing graft wall morphology and Doppler resistive indices shows early promise; however, further research is needed.

Therapeutic and Access-Creation Roles

Interventional EUS after LT is used selectively, and the evidence base remains limited to small series and case reports.[4] For post-LT intra-abdominal abscesses, percutaneous or surgical drainage is standard, but EUS-guided drainage offers a minimally invasive alternative when conventional approaches fail or are unsuitable.[48]

Beyond abscesses, EUS-guided aspiration/lavage with sclerosants has been successfully applied to symptomatic hepatic cysts.[49–51]

EUS-guided drainage—including those with lumen-apposing metal stents (LAMS)—demonstrates high efficacy for postoperative fluid collections, including those after LT, with technical and clinical success rates exceeding 90%, while adverse events remain infrequent (<10%) and rarely necessitate surgery. Importantly, outcomes are consistent across timing, size, and access route, with most collections resolving without recurrence.[52–54]

EUS also enables creation of access routes for biliary or pancreatic duct interventions in altered anatomy, achieving >90% technical success, with outcomes at least comparable to percutaneous or surgical options and fewer complications with shorter hospital stays. This is especially valuable in post-transplant patients with Roux-en-Y hepaticojejunostomy and in those after pancreaticoduodenectomy, when ERCP is not feasible.[30,55–57] Figure 2 schematizes and provides an overview of EUS usage in the pre-transplant and post-transplant setting.

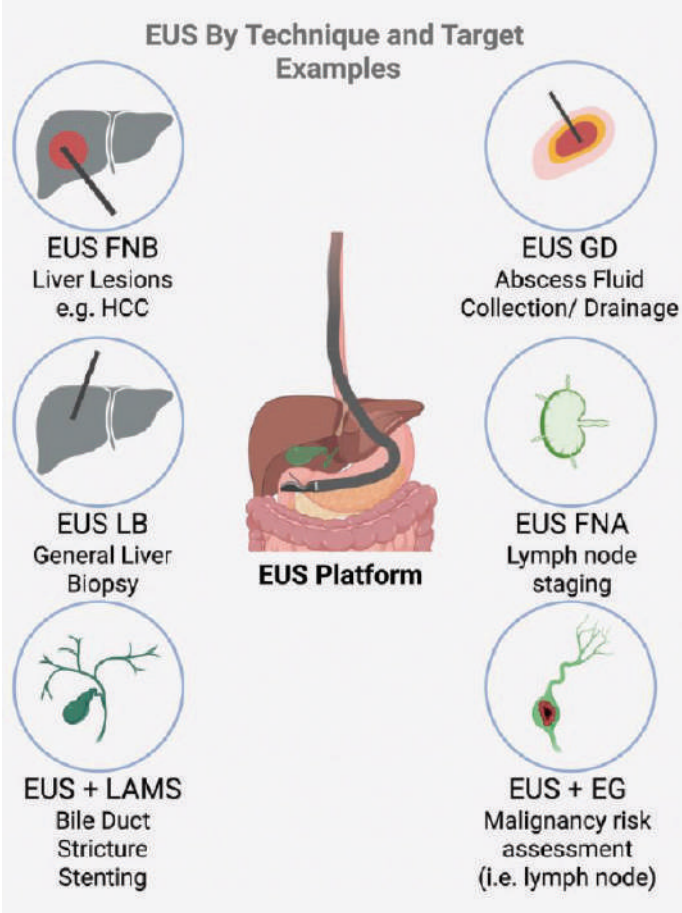

Figure 1. EUS By technique and target examples. EUS is used in different techniques for various purposes. This figure exemplifies diagnostic and therapeutic opportunities given by EUS.

EUS: Endosonographic ultrasonography; EUS-FNB: EUS-fine-needle biopsy; EUS-LB: EUS-guided liver biopsy; EUS-LAMS: EUS-lumen-apposing metal stent; EUS-GD: EUS-guided drainage; EUS-FNA: EUS-fine-needle aspiration; EUS-EG: EUS-guided elastography. Created with BioRender.com

Comparison of EUS-Guided Liver Biopsy Versus Percutaneous Liver Biopsy

Percutaneous liver biopsy (PC-LB) remains the conventional approach for hepatic histology, but pain, bleeding risk, sampling error, and post-procedure monitoring are well-recognized drawbacks.[58] EUS-LB offers an endoscopic, Doppler-guided route under the same sedation used for GI evaluation, with easy access despite ascites or large body habitus, and the option to combine multiple tests in one session.[59,60] In terms of post-procedure logistics, PC-LB typically requires 2–4 hours of right decubitus positioning for tamponade of the puncture site, whereas EUS-LB usually involves about 1 hour of routine recovery without positional restrictions.[621]

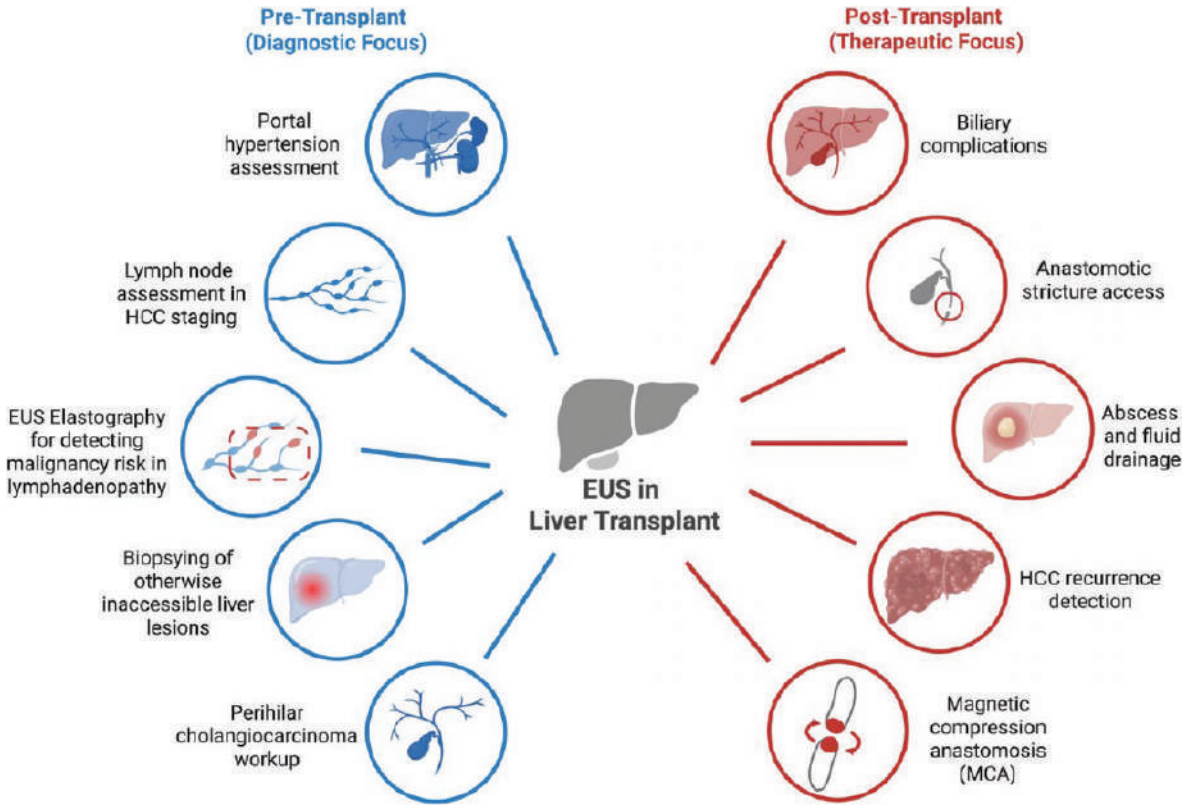

Figure 2. EUS in liver transplant. This figure illustrates EUS use in LT recipients in pre- and post-transplant settings. EUS can be used prior to LT for diagnostic purposes and after LT for therapeutic purposes. For example, pre-transplant EUS is mainly utilized for evaluation of varices and masses, whereas post-transplant EUS is primarily used for biliary complications, and abscess and fluid drainage.

LT: Liver transplantation; EUS: Endosonographic ultrasonography. Created with BioRender.com

Across randomized and observational comparisons, both techniques achieve high diagnostic yield, with largely comparable performance. Randomized controlled trials (RCTs) consistently report less pain, shorter observation time, and better tolerability with EUS-LB. One RCT favored PC-LB for median complete portal tract (CPT) yield (17 vs. 13; p=0.031),[62] whereas another favored EUS-LB for total specimen length (TSL) (2.35 vs. 1.75 cm; p=0.01) and adequacy (TSL ≥2 cm and presence of ≥11 CPT) (70.4% vs. 32.6%; p<0.001), with similar CPTs but more fragmentation after EUS-LB.[63] A meta-analysis of four RCTs showed no difference between EUS-LB and PC-LB for diagnostic adequacy, CPTs, longest or total specimen length, or overall adverse events, while post-procedure pain was lower with EUS-LB.[64,65]

In an observational study, diagnostic adequacy, accuracy, and CPT counts were high and comparable between groups; however, PC-LB had longer TSL (2.74 vs. 1.85 cm; p=0.02) and a shorter procedure time.[66] Yet, in another observational study, EUS-LB was shown to achieve similar or better samples with fewer needle passes and faster overall recovery than PC-LB or transjugular biopsy.[27,67]

EUS-LB was also compared with interventional radiology-guided biopsy (IR-LB) (percutaneous or transjugular), and it was reported that IR-LB yielded more CPTs (13.6 vs. 10.8; p≤0.01), whereas EUS-LB achieved longer total core length (4.6 cm vs. 3.6 cm; p≤0.01), had more fragmented cores, and was associated with fewer complications.[68]

As for LT recipient-specific evidence, a retrospective single-center study suggests that EUS-LB can offer practical advantages without sacrificing tissue quality.[69] The study included 77 LT recipients—31 in the EUS-LB group and 46 in the PC-LB group. The two groups were similar in age, sex, and reason for transplantation. All EUS-LB cases sampled the left hepatic lobe via a transgastric approach, whereas PC-LB targeted only the right lobe. The interval between LT and biopsy was longer in the EUS-LB group (44.1 vs. 24.4 months, p=0.029). EUS-LB yielded longer median aggregate specimen length (7.2 vs. 2.0 cm; p<0.001), longer longest core (1.85 vs. 1.24 cm; p<0.001), and more CPTs (12.0 vs. 7.2; p<0.001), with higher adequacy (61.3% vs. 10.9%; p<0.001).

Regarding symptom burden, the EUS-LB group had less abdominal pain (6.5% vs. 52.2%; p<0.001) and a higher rate of no post-procedural adverse effects (83.9% vs. 47.8%; p=0.001), while no severe events occurred in either group.

Finally, despite rapid growth in EUS expertise in recent years, PC-LB remains more widely accessible compared to EUS-LB.[59,70] Overall, current evidence supports EUS-LB as a safe, diagnostically reliable alternative to PC-LB, and its wider adoption into clinical practice can be expected in the future if further studies continue to confirm its safety and efficacy.

Conclusion

This review synthesizes how EUS complements and, in selected scenarios, improves upon conventional approaches, with an emphasis on its use in the LT setting. Table 1 summarizes the information in this article about the opportunities, successful areas, and limitations of EUS.

Table 1. Advantages and disadvantages of EUS

Advantages (opportunities and successful areas)	Disadvantages (limitations)
Reaching risky areas easily	Large device size
Taking adequate, high quality and great proportion material	Less effective on diagnosing anastomotic structures
Detecting metastatic lymph nodes with high specificity	Longer procedure performing period than PC-LB
Staging HCC	Limited usage on right lobe liver analysis
Detecting varices which cannot be identified by other methods	Less complete portal triad obtaining (Compared with PC-LB)
Gastroesophageal lumen and organ observing	Some studies stated lower effectiveness on drainage usage (considered in different ways)
Positioning nearby liver	Possibility of perforation
Analyzing vascular changes outstanding	–
High specificity measurement of PH	–
No special position required after process	–
Short recovery time	–
Upper anatomy management	–
Bypass removal (when cannot be done by ERCP)	–
Efficient drainage usage (considered in different ways)	–
Capable when other techniques are unavailable	–
Opportunity of usage with different methods at the same time	–
Less complication	–

EUS: Endoscopic ultrasonography; HCC: Hepatocellular carcinoma; PH: Portal hypertension; ERCP: Endoscopic retrograde cholangiopancreatography; PC-LB: Percutaneous liver biopsy.

For LT candidates with portal hypertension, EUS detects deep varices and identifies collateral pathways that routine endoscopy may miss. Doppler assessment and EUS-PPG add hemodynamic context that closely approximates the gold standard HVPG, which is especially valuable when the transjugular approach is impractical.

In the post-transplant setting, EUS serves as a practical tool for evaluating cholestasis—outperforming ERCP for biliary casts and ischemic cholangiopathy but being less sensitive for anastomotic strictures. EUS also supports post-LT portal hypertension assessment with EUS-PPG, as in the pre-transplant period.

In LT candidates with oncological conditions, EUS improves detection of subcentimeter or difficult-to-access hepatic lesions and enables extrahepatic nodal sampling, refining staging and, at times, transplant candidacy by identifying otherwise occult hepatic or nodal metastases.

Additionally, in cirrhotic patients with PVT and suspected or known HCC, thrombus sampling with EUS-FNA may distinguish benign from malignant thrombi when imaging is equivocal, thereby directly impacting management—including transplant eligibility and therapy selection.

Studies comparing biopsy approaches show broadly similar diagnostic performance between EUS-LB and percutaneous or transjugular techniques. Current evidence favors EUS-LB for lower post-procedure pain and faster recovery, whereas some studies report more CPTs or longer cores with PC-LB. In practice, the choice of approach can be individualized according to the clinical question, target lobe, required concomitant procedures, and local expertise.

Within the therapeutic landscape, EUS-guided therapies offer minimally invasive options when surgery or percutaneous techniques are not feasible or have failed. Targeted therapy of varices with coil and CYA improves obliteration and durability. Postoperative collections can be drained with high technical and clinical success and infrequent adverse events. EUS-created access can enable biliary or pancreatic interventions in altered anatomy. EUS-guided tumor ablation has emerged as a promising option, particularly for lesions in difficult-to-access locations such as the caudate lobe. It enables precise targeting with a low rate of immediate adverse events, although outcomes appear size-dependent, and long-term durability requires further validation. Importantly, many diagnostic and therapeutic capabilities can be integrated into a single session, potentially reducing reinterventions and hospital utilization in carefully selected patients.

Besides its advantages, there are also several limitations regarding its use: EUS access to the right hepatic lobe can be constrained; core fragmentation may be greater in EUS-LB compared to other techniques; and procedure duration may be longer, even if recovery is typically shorter. For biliary evaluation, EUS is also less informative than ERCP when an anastomotic stricture is suspected. Complications are uncommon but are considerably influenced by patient factors and operator experience, highlighting the need for structured training, protocolized patient selection, and multidisciplinary planning.

For instance, cervical esophageal perforation—though rare—illustrates these concerns: a national survey linked risk to older age, operators with <1 year of experience, difficult prior intubations, and prominent

cervical osteophytes.[71] Even so, multicenter studies and broader reviews indicate that diagnostic and interventional EUS are safe when performed with appropriate selection and technique.[72,73]

In LT candidates and recipients, who often have altered anatomy and coagulopathy, risk reduction should include competency-based training; explicit pre-procedure review of prior imaging/endoscopy and the potential therapeutic implications of EUS/EUS-FNB findings; careful appraisal of clinical status with clear indications and contraindications; an individualized, team-based procedural plan; and optimization of prerequisites such as anesthesia support, coagulation management, and equipment readiness.[73–75]

In summary, EUS has developed into a versatile tool, providing safe and minimally invasive options for both diagnosis and treatment. Its role is steadily expanding and is increasingly being integrated into routine care within the peritransplant period, complementing and occasionally exceeding conventional methods. Going forward, more research, wider training, and better access will likely make EUS even more central and help improve outcomes for transplant patients.

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 study did not use AI-enabled technology.

Author Contributions: Concept – AG, MC, MG, CS; Design – AG, MC; Supervision – AG, NBO; Data Collection and/or Processing – CC, EY, AEB, AED; Analysis and/or Interpretation – AG, MC, MG, CS; Literature Search – ME, MDT, CC, EY; Writing – CC, EY, AEB, NBO; Critical Review – AG, MC, MG, CS.

Peer-review: Externally peer-reviewed.

References

1. Kwong AJ, Kim WR, Lake JR, Schladt DP, Handarova D, Howell J, et al. OPTN/SRTR 2023 Annual Data Report: Liver. Am J Transplant 2025;25(2):S193-S287. [CrossRef]
2. Alqahtani SA, Ausloos F, Park JS, Jang S. The Role of Endoscopic Ultrasound in Hepatology. Gut Liver 2023;17(2):204-216. [CrossRef]
3. Fung BM, Abadir AP, Eskandari A, Levy MJ, Tabibian JH. Endoscopic ultrasound in chronic liver disease. World J Hepatol 2020;12(6):262-276. [CrossRef]
4. Gadour E, Miutescu B, Okasha HH. Insights and perspectives: EUS in post-liver transplantation care. Endosc Ultrasound 2024;13(5):283-286. [CrossRef]
5. Graziadei I, Zoller H, Fickert P, Schneeberger S, Finkenstedt A, Peck-Radosavljevic M, et al. Indications for liver transplantation in adults: Recommendations of the Austrian Society for Gastroenterology and Hepatology (ÖGGH) in cooperation with the Austrian Society for Transplantation, Transfusion and Genetics (ATX). Wien Klin Wochenschr 2016;128(19-20):679-690. [CrossRef]
6. Singal AG, Llovet JM, Yarchoan M, Mehta N, Heimbach JK, Dawson LA, et al. AASLD Practice Guidance on prevention, diagnosis, and treatment of hepatocellular carcinoma. Hepatology 2023;78(6):1922-1965. [CrossRef]
7. Mahfouz M, Amin S, Carrion AF. The Evolving Role of Advanced Endoscopic Techniques in Hepatology. Gastroenterol Hepatol (N Y) 2021;17(2):67-72.
8. Suk KT. Staging of liver fibrosis or cirrhosis: The role of hepatic venous pressure gradient measurement. World J Hepatol 2015;7(3):607. [CrossRef]
9. Shrestha R, Thapa J, Yadav B, Thapa B, Paudel MS. Endoscopic detection and management of esophagogastric varices. Cureus 2021;13(8):e16825. [CrossRef]
10. De Franchis R. Expanding consensus in portal hypertension. J Hepatol 2015;63(3):743-752. [CrossRef]
11. Laleman W, Vanderschueren E, Mehdi ZS, Wiest R, Cardenas A, Trebicka J. Endoscopic procedures in hepatology: Current trends and new developments. J Hepatol 2024;80(1):124-139. [CrossRef]
12. De Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al. Baveno VII - Renewing consensus in portal hypertension. J Hepatol 2022;76(4):959-974. [CrossRef]
13. Berzigotti A, Tsochatzis E, Boursier J, Castera L, Cazzagon N, Friedrich-Rust M, et al. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol 2021;75(3):659-689. [CrossRef]
14. Termite F, Borrelli De Andreis F, Liguori A, Gasbarrini A, Attili F, Spada C, et al. The Role of Endoscopic Ultrasound in Assessing Portal Hypertension: A State-of-the-Art Literature Review and Evolving Perspectives. Liver Int 2025;45(4):e16176. [CrossRef]
15. Saraireh HA, Bilal M, Singh S. Role of endoscopic ultrasound in liver disease: Where do we stand in 2017? World J Hepatol 2017;9(24):1013. [CrossRef]
16. Campos S, Poley J-W, van Driel L, Bruno MJ. The role of EUS in diagnosis and treatment of liver disorders. Endosc Int Open 2019;7(10):E1262-E1275. [CrossRef]
17. Bai Y, Wang Z, Shi C, Chen L, Mei X, Kong D. Diagnosis and treatment options for cirrhosis with unexplained upper gastrointestinal bleeding: An observational study based on endoscopic ultrasonography. Surg Laparosc Endosc Percutan Tech 2025;35(2):e1355. [CrossRef]
18. Huang JY, Samarasena JB, Tsujino T, Lee J, Hu K-Q, McLaren CE, et al. EUS-guided portal pressure gradient measurement with a simple novel device: a human pilot study. Gastrointest Endosc 2017;85(5):996-1001. [CrossRef]
19. Wiechowska-Kozlowska A, Raszeja-Wyszomirska J, Wasilewicz MP, Bialek A, Wunsch E, Wójcicki M, et al. Upper gastrointestinal endosonography in patients evaluated for liver transplantation. Transplant Proc 2009;41(8):3082-3084. [CrossRef]
20. Ryou M, DeWitt JM, Das KK, Shami VM. AGA Clinical Practice Update on Interventional EUS for Vascular Investigation and Therapy: Commentary. Clin Gastroenterol Hepatol 2023;21(7):1699-1705.e2. [CrossRef]
21. Ryou M, McCarty T, Bazarbashi A, Hathorn K, Thompson C. Combination therapy versus monotherapy for EUS-guided management of gastric varices: A systematic review and meta-analysis. Endosc Ultrasound 2020;9(1):6-15. [CrossRef]
22. Henry Z, Patel K, Patton H, Saad W. AGA clinical practice update on management of bleeding gastric varices: expert review. Clin Gastroenterol Hepatol 2021;19(6):1098-1107.e1. [CrossRef]
23. Florencio De Mesquita C, Antunes VLJ, Milioli NJ, Fernandes MV, Correa TL, Martins OC, et al. EUS-guided coiling plus glue injection compared with endoscopic glue injection alone in endoscopic treatment for gastric varices: a systematic review and meta-analysis. Gastrointest Endosc 2025;101(2):331-340.e8. [CrossRef]
24. Okasha H, Wifi M-N, Awad A, Abdelfatah Y, Abdelfatah D, El-Sawy S, et al. Role of EUS in detection of liver metastasis not seen by computed tomography or magnetic resonance imaging during staging of pancreatic, gastrointestinal, and thoracic malignancies. Endosc Ultrasound 2021;10(5):344. [CrossRef]
25. Gadour E, Awad A, Hassan Z, Shrwani KJ, Miutescu B, Okasha HH. Diagnostic and therapeutic role of endoscopic ultrasound in liver diseases: A systematic review and meta-analysis. World J Gastroenterol 2024;30(7):742-758. [CrossRef]
26. Lisotti A, Serrani M, Caletti G, Fusaroli P. EUS liver assessment using contrast agents and elastography. Endosc Ultrasound 2018;7(4):252. [CrossRef]
27. Ramai D, Pannu V, Facciorusso A, Dhindsa B, Heaton J, Ofosu A, et al. Advances in endoscopic ultrasound (EUS)-guided liver biopsy. Diagnostics (Basel) 2023;13(4):784. [CrossRef]

28. Choudhary NS, Puri R, Saigal S, Bhangui P, Saraf N, Shah V, et al. Impact of endoscopic ultrasound-guided fine-needle aspiration in prospective liver transplant recipients with hepatocellular carcinoma and lymphadenopathy. Indian J Gastroenterol 2016;35(6):465-468. [CrossRef]
29. De Jong DM, Den Hoed CM, Willemssen FEJA, Thomeer MGJ, Bruno MJ, Koerkamp BG, et al. Impact of EUS in liver transplantation workup for patients with unresectable perihilar cholangiocarcinoma. Gastrointest Endosc 2024;99(4):548-556. [CrossRef]
30. Elmunzer BJ, Maranki JL, Gómez V, Tavakkoli A, Sauer BG, Limketkai BN, et al. ACG clinical guideline: Diagnosis and Management of biliary strictures. Am J Gastroenterol 2023;118(3):405-426. [CrossRef]
31. Nie C, Vaska M, Wong JK, Bathe OF, Przybojewski S, Burak KW, et al. Tumor Seeding With Needle Biopsy of Hepatocellular Carcinoma: A Systematic Review. Am J Gastroenterol 2025;120(5):1144-1151. [CrossRef]
32. Tapper EB, Lok AS-F. Use of Liver Imaging and Biopsy in Clinical Practice. N Engl J Med 2017;377(8):756-768. [CrossRef]
33. Khoury T, Massarwa M, Hazou W, Daher S, Hakimian D, Benson AA, et al. Acute Portal Vein Thrombosis Predicts Concomitant Diagnosis of Hepatocellular Carcinoma in Cirrhotic Patients. J Gastrointest Cancer 2019;50(4):759-762. [CrossRef]
34. Gimeno Garcia AZ, Aparicio JR, Barturen A, Moreno M, Nicolas-Perez D, Quintero E. Endoscopic ultrasound-guided fine-needle aspiration of portal vein thrombosis in patients with chronic liver disease and suspicion of hepatocellular carcinoma. Eur J Gastroenterol Hepatol 2018;30(4):418-423. [CrossRef]
35. Kayar Y, Turkdogan KA, Baysal B, Unver N, Danalioglu A, Senturk H. EUS-guided FNA of a portal vein thrombus in hepatocellular carcinoma. Pan Afr Med J 2015;21:86. [CrossRef]
36. Chapman C, Waxman I. EUS-guided portal vein sampling. Endosc Ultrasound 2018;7(4):240. [CrossRef]
37. Davis JPE, Lim JK, Francis FF, Ahn J. AGA Clinical practice update on management of portal vein thrombosis in patients with cirrhosis: Expert review. Gastroenterology 2025;168(2):396-404.e1. [CrossRef]
38. Simonetto DA, Singal AK, Garcia-Tsao G, Caldwell SH, Ahn J, Kamath PS. ACG Clinical Guideline: Disorders of the Hepatic and Mesenteric Circulation. Am J Gastroenterol 2020;115(1):18-40. [CrossRef]
39. Chua T, Faigel DO. Endoscopic Ultrasound-Guided Ablation of Liver Tumors. Gastrointest Endosc Clin N Am 2019;29(2):369-379. [CrossRef]
40. Jiang T, Tian G, Bao H, Chen F, Deng Z, Li J, et al. EUS dating with laser ablation against the caudate lobe or left liver tumors: a win-win proposition? Cancer Biol Ther 2018;19(3):145-152. [CrossRef]
41. Xu M, Xu D, Deng Z, Tian G, Jiang T. Long-term outcomes of endoscopic ultrasound-guided laser ablation for liver tumors in the caudate lobe: 5 years of experience. Scand J Gastroenterol 2023;58(5):558-564. [CrossRef]
42. Agostini C, Buccianti S, Risaliti M, Fortuna L, Tirloni L, Tucci R, et al. Complications in post-liver transplant patients. J Clin Med 2023;12(19):6173. [CrossRef]
43. Han S, Jalil S, Groce JR, Krishna SG, Lara L, Lee PJ, et al. Feasibility of single-session endoscopic ultrasound-guided liver biopsy and endoscopic retrograde cholangiopancreatography in liver transplant recipients with abnormal liver function tests. Clin Endosc 2023;56(6):823-826. [CrossRef]
44. Choi AY, Chang KJ, Samarasena JB, Lee JG, Li X, Guo W, et al. Endoscopic Ultrasound-Guided Porto-systemic Pressure Gradient Measurement Correlates with Histological Hepatic Fibrosis. Dig Dis Sci 2022;67(12):5685-5692. [CrossRef]
45. Hüsing A, Cicinnati VR, Beckebaum S, Wilms C, Schmidt HH, Kabar I. Endoscopic ultrasound: valuable tool for diagnosis of biliary complications in liver transplant recipients? Surg Endosc 2015;29(6):1433-1438. [CrossRef]
46. Jo JH, Cho CM, Jun JH, Chung MJ, Kim TH, Seo DW, et al. Same-session endoscopic ultrasound-guided fine needle aspiration and endoscopic retrograde cholangiopancreatography-based tissue sampling in suspected malignant biliary obstruction: A multicenter experience. J Gastroenterol Hepatol 2019;34(4):799-805. [CrossRef]
47. Attwell A, Han S, Kriss M. Endoscopic retrograde cholangiopancreatography and liver biopsy in the evaluation of elevated liver function tests after liver transplantation. World J Hepatol 2021;13(1):132-143. [CrossRef]
48. Decker C, Varadarajulu S. EUS-guided drainage of an intra-abdominal abscess after liver transplantation. Gastrointest Endosc 2011;73(5):1056-1058. [CrossRef]
49. Ashat M, El-Abiad R, Shrigiriwar A, Khashab MA. Interventional Endoscopic ultrasound: current status and future frontiers. Am J Gastroenterol 2023;118(10):1768-1778. [CrossRef]
50. Lee S, Seo D-W, Paik WH, Park DH, Lee SS, Lee SK, et al. Ethanol lavage of huge hepatic cysts by using EUS guidance and a percutaneous approach. Gastrointest Endosc 2014;80(6):1014-1021. [CrossRef]
51. Shi G, Sun S, Li H, Fan Y, Liao Y, Zheng D, et al. A case of a giant cyst in the left lobe of the liver successfully treated with endoscopic ultrasound-guided fine needle aspiration. Endosc Ultrasound 2017;6(5):343-346. [CrossRef]
52. Terrin M, D'Errico F, Rotkopf H, Tuszynski T, Dumont J-L, Dehry S, et al. First-intention EUS-guided transluminal drainage with LAMS: an effective and safe method for management of fluid collections after any kind of surgery. Surg Endosc 2025;39(4):2415-2424. [CrossRef]
53. Storm AC, Levy MJ, Kaura K, Abu Dayyeh BK, Cleary SP, Kendrick ML, et al. Acute and early EUS-guided transmural drainage of symptomatic postoperative fluid collections. Gastrointest Endosc 2020;91(5):1085-1091.e1. [CrossRef]
54. Oh D, Lee H, Song TJ, Hyun Park D, Lee SK, Kim M-H, et al. Effectiveness of early endoscopic ultrasound-guided drainage for postoperative fluid collection. Surg Endosc 2022;36(1):135-142. [CrossRef]
55. Marya NB, Pawa S, Thiruvengadam NR, Ngamruengphong S, Baron TH, Bun Teoh AY, et al. American Society for Gastrointestinal Endoscopy guideline on the role of therapeutic EUS in the management of biliary tract disorders: methodology and review of evidence. Gastrointest Endosc 2024;100(6):e79-e135. [CrossRef]
56. Tanisaka Y, Mizuide M, Fujita A, Ogawa T, Suzuki M, Katsuda H, et al. Recent advances of interventional endoscopic retrograde cholangiopancreatography and endoscopic ultrasound for patients with surgically altered anatomy. J Clin Med 2021;10(8):1624. [CrossRef]
57. Mukai S, Tsuchiya T, Itoi T. Interventional endoscopic ultrasonography for benign biliary diseases in patients with surgically altered anatomy. Curr Opin Gastroenterol 2019;35(5):408-415. [CrossRef]
58. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology 2009;49(3):1017-1044. [CrossRef]
59. Rangwani S, Ardeshna DR, Mumtaz K, Kelly SG, Han SY, Krishna SG. Update on endoscopic ultrasound-guided liver biopsy. World J Gastroenterol 2022;28(28):3586-3594. [CrossRef]
60. Pineda JJ, Diehl DL, Miao CL, Johal AS, Khara HS, Bhanushali A, et al. EUS-guided liver biopsy provides diagnostic samples comparable with those via the percutaneous or transjugular route. Gastrointest Endosc 2016;83(2):360-365. [CrossRef]
61. Sarkar A, Dellatore P, Bhurwal A, Tyberg A, Shahid H, Minacapelli CD, et al. Endoscopic ultrasound-guided liver biopsy in clinical practice. Gastro Hep Adv 2022;1(6):936-941. [CrossRef]
62. Ali AH, Nallapeta NS, Yousaf MN, Petroski GF, Sharma N, Rao DS, et al. EUS-guided versus percutaneous liver biopsy: a prospective randomized clinical trial. Endosc Ultrasound 2023;12(3):334. [CrossRef]
63. Lariño-Noia J, Fernández-Castroagudín J, De La Iglesia-García D, Lázare H, Nieto L, Porto S, et al. Quality of tissue samples obtained by endoscopic ultrasound-guided liver biopsy: a randomized, controlled clinical trial. Am J Gastroenterol 2023;118(10):1821-1828. [CrossRef]
64. Arruda Do Espirito Santo P, Meine GC, Nau AL, Barbosa EC, Baraldo S, Lenz L, et al. Endoscopic ultrasound-guided versus percutaneous liver biopsy: a systematic review and meta-analysis of randomized controlled trials. Endoscopy 2025;57(1):41-48. [CrossRef]
65. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD. Liver biopsy. Hepatology 2009;49(3):1017-1044. [CrossRef]

66. Facciorusso A, Ramai D, Conti Bellocchi MC, Bernardoni L, Manfrin E, Muscatiello N, et al. Diagnostic yield of endoscopic ultrasound-guided liver biopsy in comparison to percutaneous liver biopsy: a two-center experience. Cancers 2021;13(12):3062. [CrossRef]
67. Patel H, Therapondos G, Galliano G, Romero R, Evans J, Cohen A, et al. Endoscopic ultrasound-guided liver biopsy using newer 19G FNB needles compared to percutaneous and trans-jugular liver biopsy: a tertiary center experience. Tech Innov Gastrointest Endosc 2021;24(2):127-135. [CrossRef]
68. Shuja A, Alkhasawneh A, Fialho A, Fialho A, Shukri A, Harris C, et al. Comparison of EUS-guided versus percutaneous and transjugular approaches for the performance of liver biopsies. Dig Liver Dis 2019;51(6):826-830. [CrossRef]
69. Rao W, Jiang Y-P, Cai J-Z, Xie M. Endoscopic ultrasound-guided liver biopsy in liver transplant recipients: a preliminary experience. Hepatobiliary Pancreat Dis Int 2025;24(1):108-110. [CrossRef]
70. Madhok IK, Parsa N, Nieto JM. Endoscopic ultrasound-guided liver biopsy. Clin Liver Dis 2022;26(1):127-138. [CrossRef]
71. Das A, Sivak MV, Chak A. Cervical esophageal perforation during EUS: a national survey. Gastrointest Endosc 2001;53(6):599-602. [CrossRef]
72. Buscarini E, De Angelis C, Arcidiacono PG, Rocca R, Lupinacci G, Manta R, et al. Multicentre retrospective study on endoscopic ultrasound complications. Dig Liver Dis 2006;38(10):762-767. [CrossRef]
73. Forbes N, Coelho-Prabhu N, Al-Haddad MA, Kwon RS, Amateau SK, Buxbaum JL, et al. Adverse events associated with EUS and EUS-guided procedures. Gastrointest Endosc 2022;95(1):16-26.e2. [CrossRef]
74. Jenssen C, Alvarez-Sánchez MV, Napoléon B, Faiss S. Diagnostic endoscopic ultrasonography: assessment of safety and prevention of complications. World J Gastroenterol 2012;18(34):4659-4676. [CrossRef]
75. Badaoui A, Teles De Campos S, Fusaroli P, Gincul R, Kahaleh M, Poley J-W, et al. Curriculum for diagnostic endoscopic ultrasound training in Europe: European Society of Gastrointestinal Endoscopy (ESGE) position statement. Endoscopy 2024;56(3):222-240. [CrossRef]

HEPATOLOGY FORUM
doi: 10.14744/hf.2025.11358

Role of insulin-like growth factor/receptor signaling in hepatocellular carcinoma

Sonia Bisht[1], Uma Sharma[2], Sangeetha Gupta[1]

[1]*Amity Institute of Pharmacy, Amity University Uttar Pradesh, Noida, Uttar Pradesh, India;* [2]*Department of Nuclear Magnetic Resonance, All India Institute of Medical Sciences, New Delhi, India*

Abstract

Hepatocellular carcinoma (HCC) is one of the most common and deadly forms of liver cancer worldwide. Recent research suggests that the insulin-like growth factor (IGF) system, including insulin-like growth factor-1, insulin-like growth factor-2, and their receptors, may play a critical role in the pathogenesis and progression of HCC. However, the precise mechanisms through which IGFs contribute to HCC development remain unclear. The objective of this review is to explore the association between IGF signaling and HCC, with a focus on understanding the molecular pathways through which the IGF axis influences the pathophysiology of HCC. The review also examines the potential of utilizing the IGF pathway as a therapeutic target for HCC. IGF-1R overexpression, elevated IGF-2 levels, and decreased IGF-1 levels are seen in HCC and are linked to a poor prognosis. The IGF-1R signaling pathway leads to activation of PI3K/AKT/mTOR and RAS/RAF/MEK/ERK, which increases cell growth and proliferation and inhibits apoptosis, resulting in HCC. Also, in diabetic conditions, low levels of IGF-1 contribute to a higher risk of HCC due to hyperinsulinemia, chronic inflammation, and diseases like non-alcoholic fatty liver disease (NAFLD) and its severe form, non-alcoholic steatohepatitis (NASH).

Keywords: Hepatocellular carcinoma; insulin-like growth factor-1; insulin-like growth factor-2; insulin-like growth factor-1 receptor; non-alcoholic fatty liver disease.

Introduction

Liver cancer ranks as the sixth most prevalent form of cancer, yet due to its aggressive characteristics and poor prognosis, it escalates to the third leading cause of cancer-related fatalities.[1] Primary liver cancer comprises hepatocellular carcinoma (HCC), which accounts for approximately 75%–80% of total cases, followed by intrahepatic cholangiocarcinoma, along with a few additional minor forms.[2,3]

How to cite this article: Bisht S, Sharma U, Gupta S. Role of insulin-like growth factor/receptor signaling in hepatocellular carcinoma. Hepatology Forum 2026; 7(1):59–68.

Received: January 17 2025; **Revised:** August 26, 2025; **Accepted:** September 05, 2025; **Available online:** September 26, 2025

Corresponding author: Sangeetha Gupta; Amity Institute of Pharmacy (AIP), Amity University Uttar Pradesh, Noida Campus, India
Phone: +91 991 155 85; **e-mail:** sgupta23@amity.edu

The primary risk factors for the occurrence of HCC are chronic liver disease and cirrhosis.[4] A vital phase in the HCC viral carcinogenesis process is cirrhosis. In addition, a significant risk factor for liver cancer is chronic hepatitis, which is brought on by infections with the hepatitis B virus (HBV) and hepatitis C virus (HCV). Most of the newly diagnosed cases of liver cancer happen in underdeveloped nations where HBV is prevalent.[5,6] Meanwhile, the primary cause of HCC in developed nations is non-alcoholic fatty liver disease (NAFLD).[7] Cigarettes, alcohol, and aflatoxin B1 are also linked to HCC.[8,9]

The liver function stage of the individual and the disease's current state influences the management of HCC. Surgical resection, liver transplantation, or local ablative therapy like microwave or radiofrequency ablation can all be used to treat early-stage HCC. In cases of advanced HCC, systemic medicines such as immunotherapy, chemotherapy, and targeted therapy are advised.[10,11] The Barcelona Clinic Liver Cancer (BCLC) 2022 update and recent international guidelines recommend atezolizumab plus bevacizumab or durvalumab plus tremelimumab as preferred first-line regimens in patients with preserved liver function and good performance status. When these are unsuitable, sorafenib, lenvatinib, or single-agent durvalumab may be used. Second-line options include cabozantinib, regorafenib, ramucirumab, or immune checkpoint inhibitors such as nivolumab plus ipilimumab.[11,12] Current consensus positions atezolizumab plus bevacizumab as the standard first-line therapy, while adjuvant use after resection or ablation is not recommended following recent American Association for the Study of Liver Diseases (AASLD) updates.[13]

The liver is responsible for various physiological processes, including macronutrient metabolism, blood volume regulation, immune system support, lipid and cholesterol homeostasis, and the breakdown of xenobiotic compounds, including many drugs.[14] One of the key roles of the liver is to synthesize various growth factors, one of which is insulin-like growth factors (IGFs). Liver functions such as differentiation, proliferation, and apoptosis are influenced by growth factors produced within the liver. Production of hepatic IGFs is stimulated by growth hormone (GH).[15]

The IGF family encompasses six high-affinity binding proteins (IGFBP-1 to IGFBP-6), two ligands (IGF-1 and IGF-2), and cell-surface receptors (IGF-1R and IGF-2R). Research based on animal models and *in vitro* studies indicates that components of the IGF system play a role in various cellular processes involved in hepatocarcinogenesis, including cell cycle progression, uncontrolled cell growth, survival, migration, apoptosis inhibition, protein synthesis, and overall cell growth.[16]

This review focuses on the most recent research on the association between IGF signaling and HCC, with a special focus on understanding the molecular mechanisms by which the IGF axis influences the pathophysiology of HCC. It also investigates the potential use of the IGF pathway as an HCC treatment target.

Etiology of HCC

A multiphase process resulting from the combination of environmental and genetic factors gives rise to HCC, a particular kind of cancer. In HCC, the cells are autonomous, as they produce their own growth signals (autocrine stimulation), remain insensitive to growth-inhibitory signals, are resistant to apoptotic signals, and can perform angiogenesis.[17]

In the majority of patients, normal cells convert to dysplastic cells due to the favourable condition provided by the regenerating nodule produced during cirrhosis, making cirrhosis one of the main causes of HCC. The conversion of cirrhosis to HCC is eased by various genetic and epigenetic reasons. Various factors that lead to cirrhosis include alcohol consumption and other viral pathogens such as HBV and HCV.[17,18]

In cases with chronic alcohol exposure, liver cells show increased sensitivity to the cytotoxic effects of tumour necrosis factor-α (TNFα), which leads to chronic hepatocyte destruction–regeneration, stellate cell activation, cirrhosis, and finally HCC.[19] Chronic alcohol exposure may also cause oxidative stress, which might influence HCC-relevant signaling pathways, such as the documented depletion in tyrosine phosphorylation of STAT1 (signal transducer and activator of transcription 1), decreased STAT1-directed activation of interferon-γ signaling, and the loss of the protective effects of interferon-γ with consequent hepatocyte damage. Oxidative stress might also cause the accumulation of oncogenic mutations.[20,21]

A vaccination effort against the virus has reduced the incidence rates of HCC over time; however, HBV still accounts for 54% of cases of HCC. Despite the efforts to promote vaccination against HBV, some indigenous areas still have a notably elevated risk. Approximately 31% of chronic HCV cases result in liver cirrhosis, which leads to HCC. HCV, not being inherited since birth, unlike HBV, is acquired later in life, usually through contaminated syringes or needles in drug abuse or through infected blood products.[22,23] Both host- and viral-related factors are identified as causes of HCC development. The interactions between hosts and viruses appear to play a role in the development of liver cancer in various ways. While a strong T-cell immune response is triggered to fight off the viral infection, this response also leads to the death of liver cells, inflammation, and subsequently, tissue regeneration, ultimately contributing to the onset of cancer.[3]

Another serious cause for the development of HCC is aflatoxin. It is a fungal toxin distinguished as B1, B2, G1, and G2. Out of all, aflatoxin B1 is considered a mutagen, being the most severe one.[22] Incidence of HBV infection increases the risk of HCC, as aflatoxins are known to suppress the immune system, further leading to cirrhosis.[23]

Another important cause of cirrhosis and HCC is non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH).[24] Abdominal obesity, elevated triglycerides, reduced high-density lipoprotein, hypertension, and impaired fasting glucose, collectively known as metabolic syndrome, are some of the risk factors leading to NAFLD/NASH and further developing into liver fibrosis, cirrhosis, and HCC.[25]

Type 2 diabetes mellitus (T2DM) is also considered a risk factor for HCC. Although the clear mechanism of the relationship between these two is not clearly understood, it is postulated that insulin resistance and activation of the insulin receptor and IGF-1 signaling pathways are among the main factors in the initiation and further development of HCC.[26,27] The insulin receptor has a variety of metabolic and molecular effects that lead to inflammation, oxidative stress with resultant DNA damage, and stimulation of cellular pathways that result in cellular growth and proliferation, all potentiating HCC development. The insulin receptor also leads to changes in visceral adipose tissue, including increased fatty acid oxidation and liberation, along with changes in the inflammatory and adipokine secretory profile, resulting in increased levels of tumour necrosis factor-alpha (TNF-α), interleukin-6, and leptin, which further result in states of hepatic inflammation and fibrosis, perpetuate insulin resistance, and result in carcinogenesis.[28]

Type 2 Diabetes Mellitus (T2DM), IGF, and HCC

A complex network of cellular and metabolic pathways connects IGF, HCC, and T2DM.[29] T2DM is a prevalent metabolic disorder characterized by chronic hyperglycemia due to insulin resistance and relative insulin deficiency. This condition has widespread effects on various metabolic and physiological processes in the body, including the IGF system. IGF, particularly IGF-1, plays a critical role in regulating cell growth, differentiation, and survival. In individuals with T2DM, IGF-1 levels are often found to be lower than in non-diabetic individuals.[30] This reduction in IGF-1 can be attributed to several factors, including increased insulin resistance, hyperglycemia, and alterations in the growth hormone (GH) axis, which in turn impacts IGF-1 synthesis in the liver.[30,31]

The reduction in IGF-1 has far-reaching consequences for liver physiology. IGF-1 is known to promote liver regeneration, inhibit apoptosis, and exert anti-inflammatory and anti-fibrotic effects. In T2DM, low IGF-1 levels compromise these protective mechanisms, contributing to the establishment of a pro-inflammatory and pro-fibrotic hepatic microenvironment. Over time, this environment facilitates the progression from non-alcoholic fatty liver disease (NAFLD) to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and ultimately HCC.[32] Moreover, the metabolic disturbances in diabetes, including hyperinsulinemia, dyslipidemia, and oxidative stress, enhance the activation of mitogenic and anti-apoptotic pathways downstream of the IGF-1 receptor (IGF-1R), such as PI3K/AKT and MAPK, which play key roles in hepatocarcinogenesis.[33]

Patients with type 2 diabetes had a 2–4 times greater chance of HCC recurrence, irrespective of the reason for their current liver condition or the existence of cirrhosis.[34] Dyslipidaemia and hyperinsulinemia, two metabolic disorders associated with type 2 diabetes, have been related to cancer.[35]

Anomalous lipid and carbohydrate metabolism is a hallmark of diabetes. As the condition worsens, persistent hyperglycaemia and peripheral tissue's inadequate response to circulating insulin cause IR to develop.[36] In a 2013 study, regardless of age, sex, body mass index, waist-to-height ratio, education level, smoking, or alcohol consumption, T2DM was associated with an increased incidence of both HCC and bile tract cancer over an 8-year follow-up. The study included 8,588 T2DM patients who had no cancer or metastases at baseline and 363,426 non-diabetic individuals.

The pathophysiological processes that connect HCC with T2DM are intricate and multifaceted. The main causes include inflammation, hyperinsulinemia, and chronic hyperglycemia. Furthermore, a possible contributing factor to the higher risk of HCC in diabetic patients is low levels of IGF-1.[26,37] Mechanistically, IGF-1 deficiency alters the expression of key apoptotic and cell cycle regulators (e.g., Bcl-2, Bax, cyclins), disrupts mitochondrial function, and impairs immune surveillance—making the liver more vulnerable to transformation under diabetic conditions.[38]

Table 1. IGF Family- ligands (IGF-1 and IGF-2), receptors (IGF-1R and IGF-2R) and binding proteins (IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-3, IGFBP-4, IGFBP-5 and IGFBP-6)

S. No.	Components	Role
1.	Ligands – IGF-1, IGF-2	IGF-1 promotes postnatal growth, bone development, and tissue repair, while IGF-2 is vital for prenatal development. Both ligands enhance glucose uptake, influence insulin sensitivity, and play roles in lipid metabolism. Additionally, IGF-1 supports neuroprotection and muscle regeneration.
2.	Receptors – IGF-1R, IGF-2R	IGF-1R and IGF-2R, mediate the actions of IGF ligands. IGF-2R is less directly involved in signaling compared to IGF-1R.
3.	Binding Proteins – IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, IGFBP-6	IGFBPs play essential roles in regulating the bioavailability and activity of IGF ligands. They bind to IGF-1 and IGF-2, extending their half-life, controlling their distribution in tissues, and modulating their interaction with cell surface receptors.

At the cellular level, oxidative stress and elevated pro-inflammatory cytokines—hallmarks of chronic inflammation in T2DM—drive genetic and epigenetic changes conducive to malignant transformation. Hyperglycemia can enhance the generation of reactive oxygen species (ROS), while low IGF-1 levels fail to counteract this oxidative stress, leading to DNA damage, impaired repair mechanisms, and hepatocyte senescence. These factors create a tumor-promoting niche in the liver, advancing fibrosis and carcinogenesis.[39]

In summary, the interplay between T2DM, low IGF-1 levels, and HCC is rooted in a shared pathophysiological framework involving chronic inflammation, metabolic dysregulation, and aberrant cell signaling. These insights underscore the importance of metabolic control in diabetes management, not only to prevent cardiovascular complications but also to reduce the risk of liver malignancy. Therapeutic strategies aimed at restoring IGF-1 homeostasis, mitigating insulin resistance, and controlling oxidative stress may offer promising avenues for HCC prevention in diabetic patients.[40]

IGF Ligands, Receptors, and Signaling Pathways

The IGF family comprises two ligands, IGF-1 (somatomedin C) and IGF-2 (somatomedin A), six high-affinity binding proteins, IGFBP-1 through IGFBP-6, and cell-surface receptors, IGF-1R and IGF-2R, as mentioned in Table 1 and shown in Figure 1. IGFs have a molecular weight of approximately 7.5 kDa, therefore being tiny ligands.[41,42] IGFs belong to a similar family of ligands as insulin, a dipeptide having a third disulfide bond inside the A chain and two disulfide links connecting the A and B chains. The C-terminal D-domain extension and the bridging C-domain set the two IGF ligands, IGF-1 and IGF-2, apart. Furthermore, their sequence homology with the insulin A and B chains is quite high (~45–52%). Like insulin, IGFs' three interior disulfides enable appropriate folding and allow for classical activities. The receptors that mediate the effects of IGF-1, IGF-2, and insulin include cell surface tyrosine kinases, type 1 IGFR, and insulin receptor.[43]

Peptide hormones IGF-1 and IGF-2, which resemble insulin structurally, are essential for growth and development. IGF-1 is a protein of 70 amino acids and a molecular weight of roughly 7649 Da. Its domains are like those of proinsulin. With a molecular weight of about 7500 Da, IGF-2 is significantly smaller and consists of 67 amino acids with similarly organized domains.[44] IGF-1 binds to the receptor tyrosine kinase IGF-1R, which is the main mechanism by which it affects postnatal growth and metabolic control. IGF-2 is a key player in fetal development. It primarily interacts with the mannose-6-phosphate receptor, or IGF-2R, and to a lesser extent with the IGF-1R.[45]

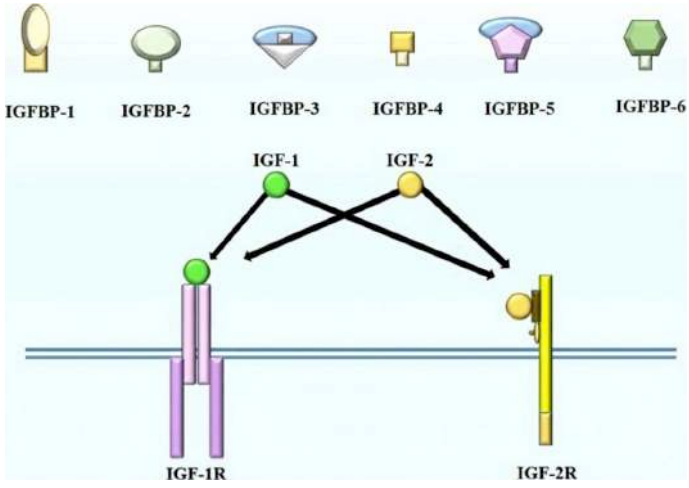

Figure 1. IGF Family. The IGF family consists of ligands IGF-1 and IGF-2, IGFBPs, and receptors IGF-1R and IGF-2R. The IGFs are bound by binding proteins in the circulation and upon release binds to the receptor.

Yet another important regulator of IGF-1 and IGF-2 activity are IGFBPs, responsible for the bioavailability and distribution of the IGF ligands. N-terminal, central, and C-terminal regions that promote IGF binding are shared by the six high-affinity IGFBPs (IGFBP-1 to IGFBP-6). By enclosing IGFs, these proteins control the way IGFs interact with IGF receptors, either by increasing or decreasing their contact. To lengthen the half-life of IGF and control systemic IGF activity, IGFBP-3, the most prevalent IGFBP in circulation, combines with IGF and the acid-labile subunit to form a ternary complex.[46] Proteases can cleave IGFBPs, releasing free IGFs that bind to their receptors and affect cell development, metabolism, and communication. Furthermore, IGFBPs interact with cell surface receptors and the extracellular matrix to influence cell signaling, apoptosis, and migration in ways that are not dependent on IGF.[47] Changes in IGFBP levels are important in both physiological and pathological situations, since they are linked to diseases such as diabetes, cancer, and growth problems. Their regulatory functions are being investigated for possible therapeutic applications in circumstances when IGF activity regulation is advantageous.[44]

Growth, development, and cellular metabolism are all significantly impacted by IGF-1R, a transmembrane receptor tyrosine kinase that is essential to the mediation of IGF-1 and IGF-2 signaling.[48] The structural makeup of IGF-1R consists of two alpha subunits and

two beta subunits that combine to create a heterotetramer. The alpha subunits are found outside of cells and are important in binding to ligands, while the beta subunits are found across the membrane and include intracellular tyrosine kinase domains.[49] When an IGF-1 or IGF-2 receptor binds, certain tyrosine residues within its intracellular domains cause the receptor to undergo autophosphorylation, which creates docking sites for adaptor proteins like IRS-1 and Shc.[50] The MAPK/ERK and PI3K/AKT signaling pathways are triggered by this activation. By phosphorylating and activating important proteins like mTOR and preventing apoptosis through the transcription factors BAD and forkhead box transcription factors (FOXO), the PI3K/AKT pathway enhances cell survival, growth, and metabolism. Simultaneously, the MAPK/ERK pathway entails a kinase cascade comprising Raf, MEK, and ERK, which ultimately leads to the control of gene expression that oversees cell division, proliferation, and survival. IGF-1R signaling is intimately controlled by feedback mechanisms to preserve cellular homeostasis. Dysregulation of this signaling has been linked to several illnesses, including cancer, making it a prime candidate for therapeutic interventions.[48,51]

Comparably, IGF-2R is a multipurpose transmembrane protein that plays important roles in controlling cell division and has a unique structure. IGF-2R is a single-chain polypeptide with a single transmembrane region, a short cytoplasmic tail, and a sizable extracellular domain with fifteen repeating motifs. Instead of having intrinsic tyrosine kinase activity like IGF-1R does, IGF-2R mainly acts by binding IGF-2, which sequesters it from IGF-1R and decreases IGF-2-mediated signaling.[52] This binding helps regulate cellular growth and development by modulating the availability of IGF-2. Additionally, IGF-2R is involved in the trafficking of lysosomal enzymes by binding mannose-6-phosphate (M6P)-tagged proteins and directing them to lysosomes. The receptor's role in IGF-2 regulation and lysosomal enzyme trafficking is crucial for maintaining cellular homeostasis and proper metabolic functioning. IGF-2R's ability to clear IGF-2 from the extracellular environment helps prevent excessive cell proliferation, which is particularly important in preventing tumor growth and progression. Dysregulation of IGF-2R expression or function can lead to pathological conditions, including cancer and developmental disorders, underscoring its significance in both normal physiology and disease states.[53]

IGF Signaling in HCC

IGF-1

The anterior pituitary cells secrete GH, which regulates the secretion of IGF-1 and IGF-2. Studies have demonstrated that GH directly stimulates IGF transcription in hepatocytes, which are the main sources of IGF-1 and IGF-2 in mice and rats.[54,55]

Hepatocytes produce the precursor of IGF-1 first after receiving the GH signal, and then cleave it to produce the mature IGF-1 peptide.[16]

Liver cell regeneration and function can be negatively impacted by IGF-1 deficiency, as it plays a crucial role in regulating cell division, growth, and survival. Low levels of IGF-1 are associated with fibrosis and chronic inflammation, two conditions that are major causes of liver carcinogenesis.[40,56,57] A pro-carcinogenic milieu is fostered by chronic inflammation, and cirrhosis—a key risk factor for HCC—can arise from fibrosis.[58,59] Furthermore, insulin resistance and hyperinsulinemia, which are prevalent in type 2 diabetes, are frequently associated with low IGF-1 levels, aggravating metabolic dysregulation and creating an environment conducive to the development of HCC.[34]

The growth and proliferation of healthy liver cells depend on IGF-1. Its absence inhibits these functions, lowering the activation of pathways including Ras/Raf/MAPK and PI3K/Akt, which are critical for survival and progression of the cell cycle. This deficiency promotes apoptosis and causes injured cells to proliferate in response, creating an environment favorable to cancer development.[60] Because low IGF-1 levels are correlated with higher levels of inflammatory cytokines, including TNF-α, IL-6, and IL-1β, they are also associated with chronic inflammation. In addition to promoting oxidative stress, cellular damage, and genetic abnormalities, chronic inflammation creates a microenvironment that aids in the development of cancer.[61,62]

IGF-2

The GH/IGF-1 axis is the main regulator of postnatal growth, even though IGF-2 appears to be important during fetal development.[63] Genetic changes such as gene amplification or loss of imprinting (LOI) frequently cause IGF-2 to become overexpressed in HCC, leading to biallelic expression. It is also possible to raise IGF-2 levels by hypomethylating the IGF-2 gene promoter.[64] Like IGF-1, IGF-2 interacts with IGF-1R and the IR isoform A to activate important signaling pathways necessary for increasing cell proliferation and preventing apoptosis, such as PI3K/AKT/mTOR and RAS/RAF/MEK/ERK.[65]

HCC cancer cells can create IGF-2, which acts in a paracrine way to affect the tumor microenvironment and in an autocrine loop to continuously promote the cancer cells' growth and survival. To further encourage tumor growth and metastasis, IGF-2 also interacts with other oncogenic pathways, including Wnt/β-catenin and HGF/c-Met.[66] IGF-2 supplies the blood supply required for tumor sustenance by promoting angiogenesis. These mechanisms highlight the possibility of employing gene silencing methods, small molecule inhibitors, or monoclonal antibodies to block the oncogenic signals by targeting the IGF-2/IGF-1R axis as a treatment approach in HCC.[67]

IGF-1R Expression

In HCC, IGF-1R is frequently found to be overexpressed. This overexpression enhances the cancer's aggressiveness by making tumor cells hypersensitive to growth-promoting signals. IGF-1R is a transmembrane tyrosine kinase receptor that plays a critical role in regulating cell growth, survival, and proliferation.[68] When its natural ligands—insulin-like growth factors IGF-1 or IGF-2—bind to the extracellular domain of IGF-1R, the receptor undergoes autophosphorylation on specific tyrosine residues within its intracellular domain. This autophosphorylation is a key step that activates the receptor's intrinsic kinase activity and initiates a cascade of downstream signaling events.[69]

One of the major signaling pathways activated by IGF-1R is the PI3K/AKT pathway. Upon activation, IGF-1R recruits and phosphorylates insulin receptor substrates (IRS-1 and IRS-2).[70] These phosphorylated substrates then serve as docking platforms for phosphoinositide 3-kinase (PI3K), which becomes activated and converts PIP2 into PIP3. PIP3, in turn, recruits AKT to the cell membrane, where it becomes activated through phosphorylation. Activated AKT promotes tumor cell survival and proliferation by phosphorylating and inactivating several pro-apoptotic proteins, including BAD and caspase-9.[71]

Additionally, AKT activates mTOR, a central regulator of protein synthesis and cell growth, further supporting cancer cell expansion and metabolic adaptation.[72]

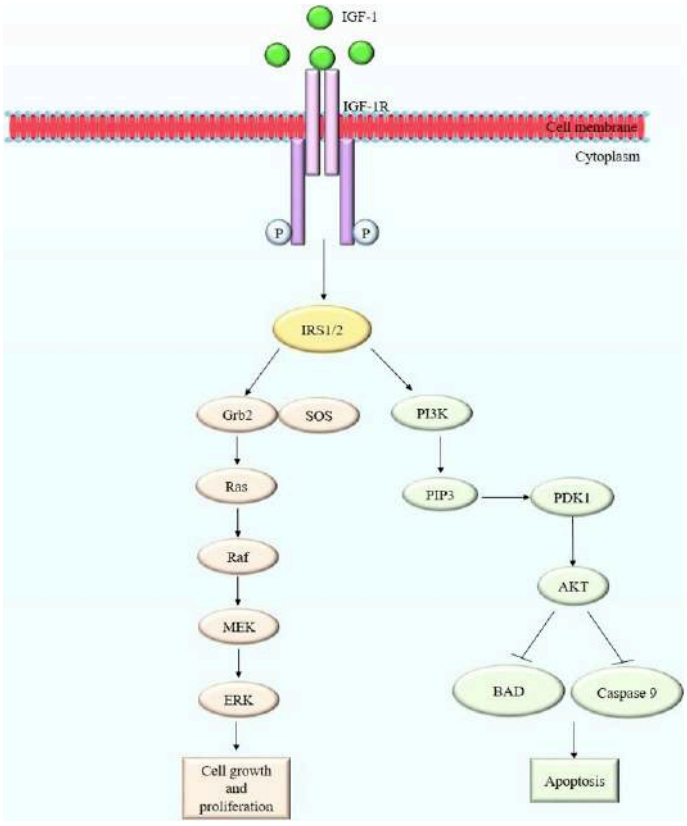

Figure 2. IGF-1 signaling. The ligand IGF-1 binds to the IGF-1R receptor which causes conformational changes in the receptor and autophosphorylation of the cytoplasmic part of the receptors. By a series of phosphorylation reactions, the signal is transduced into the nucleus. This involves the participation of many cytoplasmic proteins such as Grb2, Ras, Raf, MEK, and ERK and others such as IRS-1, PI3K, PDK1 and AKT.

Simultaneously, IGF-1R activation attracts SOS and growth factor receptor-bound protein 2 (Grb2), which in turn activates MEK, ERK, Ras, and Raf, initiating the MAPK pathway. After translocating into the nucleus, ERK regulates the expression of genes involved in cell cycle progression and division, as shown in Figure 2.[71,73]

These proliferative and anti-apoptotic pathways are continuously stimulated by IGF-1R overexpression in HCC, leading to oncogenic processes such as enhanced cell survival, proliferation, angiogenesis, and resistance to apoptosis. This aberrant signaling has been associated in HCC patients with a reduced overall survival rate and larger tumors.[74]

The persistent stimulation of these oncogenic pathways contributes to several hallmarks of cancer in HCC, including unchecked cell division, resistance to apoptosis, angiogenesis, and metastatic potential.[75] Clinically, this aberrant signaling is associated with larger tumor sizes, more aggressive disease progression, and reduced overall survival in patients. These findings highlight the central role of IGF-1R signaling in liver cancer biology and underscore its potential as a therapeutic target.[67]

To address the pathological role of IGF-1R in HCC, multiple therapeutic strategies are under investigation. Tyrosine kinase inhibitors (TKIs) have been developed to block the receptor's autophosphorylation and thereby prevent the activation of downstream signaling.[76] Additionally, monoclonal antibodies targeting the extracellular domain of IGF-1R can block ligand binding, effectively silencing the receptor's activity. Another approach involves antisense oligonucleotides or small interfering RNA (siRNA) designed to reduce IGF-1R expression by degrading its mRNA or inhibiting its translation. These therapeutic strategies aim to restore normal cell signaling dynamics, reduce tumor growth, and improve patient outcomes.[77]

Recent studies have also highlighted the intricate crosstalk between IGF-1R signaling and other key oncogenic pathways in HCC, further deepening our understanding of its tumor-promoting effects. One important interaction is with the Wnt/β-catenin pathway. IGF-1R signaling can enhance the stability and nuclear accumulation of β-catenin by inhibiting glycogen synthase kinase-3β (GSK-3β) through AKT activation. This inhibition prevents the degradation of β-catenin, allowing it to translocate into the nucleus and activate genes involved in proliferation, stemness, and dedifferentiation. The Wnt/β-catenin pathway is frequently dysregulated in HCC and plays a major role in early tumor initiation, contributing to cancer cell survival and drug resistance.[78]

Additionally, IGF-1R cooperates with the transforming growth factor-beta (TGF-β) signaling pathway, which has a dual role in liver cancer. While TGF-β initially suppresses tumor formation, it shifts toward a pro-tumorigenic role during later stages of HCC, promoting epithelial-mesenchymal transition (EMT), fibrosis, and metastasis. IGF-1R can amplify these effects by activating the PI3K/AKT and ERK pathways, which facilitate SMAD2/3 phosphorylation and further enhance TGF-β-mediated transcriptional activity that supports invasion and immune evasion.[79]

Furthermore, IGF-1R signaling intersects with the JAK/STAT pathway, particularly STAT3, which is known to drive inflammation-associated hepatocarcinogenesis. Although IGF-1R does not directly phosphorylate STAT3, it induces upstream signaling via PI3K/AKT and MAPK that results in sustained STAT3 activation. This activation promotes transcription of genes involved in survival (e.g., Bcl-2, Bcl-xL), angiogenesis (e.g., VEGF), and cell proliferation (e.g., Cyclin D1). In the context of chronic liver inflammation or cirrhosis, this synergy between IGF-1R and STAT3 signaling creates a favorable environment for tumor growth and progression.[49]

Together, these inter-pathway interactions position IGF-1R as a critical hub within a broader oncogenic network in HCC. Targeting IGF-1R alone may not be sufficient; therefore, current research is also exploring combination therapies that simultaneously inhibit IGF-1R and its interacting pathways—such as Wnt/β-catenin or STAT3—to overcome resistance and improve clinical outcomes.[77]

IGFBPs

The bioavailability and activity of IGFs, especially IGF-1 and IGF-2, which are essential for cellular growth and survival, are significantly regulated by IGFBPs.[79] IGFBPs play a major role in regulating the impact of IGFs on the formation and progression of HCC tumors. IGFBP-1 through IGFBP-6 are the six primary IGFBPs, and they all play different functions in HCC. High-affinity binding of IGFs by these proteins regulates their interaction with IGF-1R and, therefore, their biological activity.[80]

The most widely distributed IGFBP, IGFBP-3, can impede IGF-mediated signaling by isolating IGFs from IGF-1R.[49] This prevents the activation of downstream proliferative and anti-apoptotic pathways, including the MAPK and PI3K/AKT pathways. In contrast, IGFBP-3 and other IGFBPs can act without the help of IGF. IGFBP-3, for example, can internalize and translocate to the nucleus, where it affects

the transcription of genes related to apoptosis and cell cycle regulation. Through the regulation of p53 and other cell death mechanisms, it can cause apoptosis.[42]

Changes in IGFBP expression levels are frequently observed in the setting of HCC and have the potential to impact tumor behavior. For instance, decreased IGFBP-3 expression is frequently seen in HCC, which is associated with elevated IGF-1R signaling and tumor expansion. However, depending on how they interact with other cellular components and IGFs, IGFBP-1, IGFBP-2, and IGFBP-5 can have a variety of effects—sometimes limiting tumor formation and other times increasing it.[81] Depending on the tumor microenvironment and post-translational modifications, these IGFBPs can either inhibit or promote tumorigenesis. For instance, IGFBP-2 has been implicated in promoting epithelial-to-mesenchymal transition (EMT), migration, and metastasis in various cancers, including HCC, potentially through integrin signaling and interaction with the extracellular matrix.[82]

This dual nature of IGFBPs—both IGF-dependent and IGF-independent—makes them versatile regulators of tumor biology. By binding IGFs, they control proliferative and anti-apoptotic signaling through IGF-1R. Simultaneously, they engage in IGF-independent mechanisms to regulate apoptosis, differentiation, migration, and even angiogenesis through pathways involving TGF-β, integrins, nuclear hormone receptors, and epigenetic modulation. These non-canonical roles are particularly important in the context of metastasis and therapy resistance, making IGFBPs both biomarkers and potential therapeutic targets.[65]

Understanding the distinct molecular mechanisms and context-dependent behavior of individual IGFBPs in HCC could provide valuable insights into novel therapeutic strategies. Targeting their IGF-independent pathways may offer a promising approach for controlling tumor progression and overcoming resistance to conventional IGF-targeted therapies.

IGF-Related Biomarkers for Patient Stratification and Prognosis

Recent studies have shed light on the prognostic and predictive significance of insulin-like growth factor (IGF)-related biomarkers in hepatocellular carcinoma (HCC), opening new avenues for personalized treatment strategies.[83] Components of the IGF axis—including IGF-1, IGF-2, IGF-1R, and IGF-binding proteins (IGFBPs)—play not only a pathophysiological role in HCC but also hold promise as clinical indicators for patient stratification and outcome prediction.[84] Among them, serum IGF-1 levels have received particular attention. Several large cohort studies have demonstrated that reduced circulating IGF-1 levels are strongly associated with poor liver function, advanced tumor stage, and decreased overall survival in HCC patients.

Because IGF-1 is primarily synthesized in the liver, its levels also serve as a surrogate marker for hepatic reserve and are currently being evaluated for use in pre-treatment risk scoring models, including modified Child-Pugh and HCC staging systems.[85]

In contrast, elevated IGF-2 levels, often caused by loss of imprinting or promoter hypomethylation, are commonly found in early HCC and have been implicated in tumor initiation. IGF-2 overexpression may therefore serve as an early detection biomarker, especially in patients with cirrhosis or non-alcoholic steatohepatitis (NASH), where surveillance is crucial.[81] Similarly, IGF-1R overexpression has been correlated with tumor aggressiveness, poor differentiation, vascular invasion, and resistance to targeted therapies like sorafenib, making it a candidate predictive biomarker for treatment response. Moreover, IGFBPs, particularly IGFBP-3 and IGFBP-7, have shown dual roles depending on the context—either inhibiting IGF signaling by sequestering ligands or exerting IGF-independent tumor-suppressive functions, such as promoting apoptosis and modulating the tumor microenvironment. Decreased expression of IGFBP-3 has been linked with enhanced proliferation and poorer prognosis in HCC patients.[16]

Collectively, these findings underscore the potential utility of IGF-axis biomarkers in improving clinical decision-making. By integrating these biomarkers into diagnostic and therapeutic workflows, clinicians may be better equipped to identify high-risk patients, predict treatment efficacy, and personalize therapeutic strategies for improved outcomes in HCC management.

IGF signaling as a potential target for the treatment of HCC

Since the IGF signaling system is essential for tumor growth, survival, and resistance to apoptosis, targeting it as a therapeutic approach appears to be a promising approach for treating HCC. IGF-1, IGF-2, and IGF-1R interact with one another through the IGF/IGFR axis. IGF-1R undergoes autophosphorylation on tyrosine residues upon binding of IGF-1 or IGF-2, activating multiple downstream signaling pathways, including the PI3K/AKT and MAPK pathways.[16,86]

The PI3K/AKT pathway is initiated by IGF-1R activation, which then attracts and activates PI3K, which phosphorylates PIP3. AKT is brought to the plasma membrane by PIP3, which functions as a second messenger and phosphorylates it there. By phosphorylating and blocking pro-apoptotic proteins like BAD and caspase-9 and activating mTOR, a crucial regulator of cell growth and protein synthesis, activated AKT promotes cell survival and proliferation.[71,87]

Son of Sevenless (SOS) and growth factor receptor-bound protein 2 (Grb2) are recruited by IGF-1R activation in the MAPK pathway, and this helps to activate Ras. Following Ras's activation of the Raf-MEK-ERK kinase cascade, ERK is phosphorylated and activated. Once in the nucleus, ERK translocates and controls the expression of genes related to cell cycle progression and division.[71,87]

In HCC, IGF-1R is usually overexpressed and hyperactivated, contributing to the aggressiveness of the malignancy and its poor prognosis. Tumor growth, survival, angiogenesis, and metastasis are all facilitated by this overactivation, which causes proliferative and anti-apoptotic signaling pathways to be continuously stimulated.[67]

Several tactics are used to target the IGF signaling pathway in HCC to interfere with these carcinogenic signals. Monoclonal antibodies against IGF-1R can be used, which stop receptor activation. TKIs can prevent IGF-1R from autophosphorylation, which stops downstream signaling. By encouraging the mRNA of IGF-1R to degrade, antisense oligonucleotides can reduce the production of the protein.[88–90]

These targeted treatments seek to impede the growth and progression of tumors by attenuating the abnormal signaling caused by the IGF axis.[90] These medicines have the potential to significantly improve clinical results by precisely targeting the mechanisms underlying the formation and progression of HCC, offering a more accurate and efficient means of treating this difficult-to-treat malignancy. There is still hope for better management and therapy of HCC thanks to continuous research and development of various therapeutic approaches, which may also increase patient quality of life and survival rates.[89]

Table 2. Pharmacological interventions in clinical trials that target IGF-1R for treatment of HCC

Compound	Targets	Phase	ID	Reference
Ganitumab	Monoclonal anitibody targeting IGF-1R	Phase II	NCT01204177	[95]
OSI-906 (Linsitinib)	Tyrosine kinase inhibitor targeting IGF-1R	Phase II	NCT01100931	[102]
CP-751871 (Figitumumab)	Monoclonal antibody targeting IGF-1R	Phase II	NCT01013300	[103]
MK-0646 (Dalotuzumab)	IGF-1R inhibitor	Phase I/ II	NCT01051080	[104]
XL288	Multi-kinase inhibitor targeting IGF-1R	Phase I	NCT00788219	[105]
Dalotuzumab (MK-0646) and MK-2206	IGF-1R inhibitor and akt inhibitor	Phase II/III	NCT01483027	[104]
R1507	Monoclonal antibody targeting IGF-1R	Phase II	NCT00596830	[106]
Ficlatuzumab (AV-299)	Anti-HGF antibody that may indirectly affect IGF signaling	Phase I	NCT01631717	[107]

HCC: Hepatocellular carcinoma.

Numerous medications aimed at this route vary in their clinical development stages. Monoclonal antibodies that are specially made to bind to the IGF-1R include figitumumab (CP-751,871), cixutumumab (IMC-A12), and dalotuzumab (MK-0646). These antibodies inhibit receptor activation and subsequent downstream signaling through pathways important for cell growth and survival, such as PI3K/AKT/mTOR and Ras/Raf/MEK/ERK.[91,92]

Linsitinib (OSI-906) and BMS-754807 are two TKIs that specifically target the intracellular kinase domain of IGF-1R. For example, linsitinib suppresses both the IR and IGF-1R's kinase activity, inhibiting their autophosphorylation and subsequent signaling pathway activation. In HCC, where compensatory mechanisms can activate IR in the absence of IGF-1R signaling, this dual inhibition is especially advantageous.[93]

A different approach is provided by small molecule inhibitors such as NVP-AEW541 and picropodophyllin (PPP), which bind to the IGF-1R's ATP-binding site to stop its activation. By attaching to another location on the receptor, PPP, a non-ATP-competitive inhibitor, inhibits the receptor's function without going up against ATP directly. These inhibitors diminish IGF-1R-mediated signaling, which in turn causes angiogenesis, apoptosis, and decreased tumor cell proliferation.[92,94]

These IGF/IGFR-related medications not only directly stop tumor growth but also negatively impact the tumor microenvironment by lowering angiogenesis and boosting the body's defenses against cancerous cells. Clinical trials have brought to light issues such as possible toxicities and medication resistance, which might result from compensatory processes or mutations.[95] As a result, current research is concentrated on improving existing medications, either by creating next-generation inhibitors with increased specificity and fewer side effects or by combining treatments with other targeted therapies.[96]

Emerging data suggest that resistance to IGF-targeted therapies is frequently mediated through compensatory activation of parallel signaling cascades, including the insulin receptor (IR), epidermal growth factor receptor (EGFR), and MET pathways. Even when IGF-1R is successfully inhibited, these alternative receptors can maintain activation of downstream effectors such as PI3K/AKT or MAPK, sustaining tumor proliferation and survival. Additionally, feedback loops within the mTOR pathway and upregulation of insulin receptor substrate (IRS) proteins may re-stimulate oncogenic signaling, further complicating treatment efficacy.[91]

To address these limitations, combination therapy is gaining attention as a rational strategy. Co-targeting IGF-1R along with other pathways—such as mTOR inhibitors (e.g., everolimus), EGFR inhibitors, or immune checkpoint inhibitors like anti-PD-1/PD-L1—can help circumvent resistance and provide synergistic anti-tumor effects.[97] These combinations not only suppress tumor-intrinsic signaling but also modulate the tumor microenvironment and immune evasion mechanisms, offering a more holistic therapeutic approach in HCC.[98]

Furthermore, personalized medicine strategies are being explored to identify biomarkers that predict response to IGF-targeted therapy. Stratifying patients based on IGF-1R expression, gene mutations, or activation of compensatory pathways could optimize treatment selection and improve outcomes. Continued preclinical and clinical efforts are essential to refine these strategies, develop fewer toxic agents, and ultimately translate IGF pathway inhibition into durable responses in HCC management.[99]

Agents in Clinical Trials for HCC

Only a few medications are available for the clinical treatment of HCC, even though it is one of the deadliest health problems in the world. However, rigorous basic research and multiple clinical trials in HCC have led to significant advances in the development of new medications in recent years. There are currently over a thousand active clinical trials pertaining to HCC, indicating a thriving environment in the field of HCC medication research.[100,101] Table 2 mentions the pharmacological interventions in clinical trials that target IGF-1R for the treatment of HCC.

Conclusion

This review includes evidence for dysregulated IGF/IGF-1R signaling in HCC. Many factors, such as hepatitis virus infection, diabetes, and imbalance of IGF-1R modulators, can start carcinogenesis in the pathophysiology of HCC. In conclusion, there is an increase in IGF-1R expression in HCC tissues, which is influenced by a few clinical variables, along with an increase in IGF-2 levels and a decrease in IGF-1 levels. When combined, IGF-1R has the potential to be a useful prognostic biomarker for HCC. While some IGF-1R-targeting drug trials have demonstrated limited efficacy or safety concerns, more research into this combination of anti-cancer medications and agents that block IGF/IGF-1R signaling is hoped to result in a successful treatment for HCC.

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 – SG; Design – SG; Supervision – SG; Data Collection and/or Processing – SB; Literature Search – SB, TP; Writing – SB; Critical Review – US.

Peer-review: Externally peer-reviewed.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71(3):209-249. [CrossRef]
2. Kinsey E, Lee HM. Management of Hepatocellular Carcinoma in 2024: The Multidisciplinary Paradigm in an Evolving Treatment Landscape. Cancers (Basel) 2024;16:666. [CrossRef]
3. Kim DY. Changing etiology and epidemiology of hepatocellular carcinoma: Asia and worldwide. J Liver Cancer 2024;24(1):62-70. [CrossRef]
4. Baek M, Chai JC, Choi HI, Yoo E, Binas B, Lee YS, et al. Comprehensive transcriptome profiling of BET inhibitor-treated HepG2 cells. PLoS One 2022;17(4):e0266966. [CrossRef]
5. Liu X, Liu F, Yu H, Zhang Q, Liu F. Development and validation of a prediction model for predicting the prognosis of postoperative patients with hepatocellular carcinoma. Int J Gen Med 2022;15:3625-3637. [CrossRef]
6. Ge XY, Sun MC, Wang TY, Wang XM, Liu G, Yang T, et al. Analysis of risk factors of hepatocellular carcinoma and establishment of a clinical prognosis model. Front Oncol 2023;13:1067353. [CrossRef]
7. Velliou RI, Legaki AI, Nikolakopoulou P, Vlachogiannis NI, Chatzigeorgiou A. Liver endothelial cells in NAFLD and transition to NASH and HCC. Cell Mol Life Sci 2023;80(11):314. [CrossRef]
8. Llovet JM, Kelley RK, Villanueva A, Singal AG, Pikarsky E, Roayaie S, et al. Hepatocellular carcinoma. Nat Rev Dis Primers 2021;7(1):6. [CrossRef]
9. Zhu Q, Ma Y, Liang J, Wei Z, Li M, Zhang Y, et al. AHR mediates the aflatoxin B1 toxicity associated with hepatocellular carcinoma. Signal Transduct Target Ther 2021;6(1):299. Erratum in: Signal Transduct Target Ther 2021;6(1):432. [CrossRef]
10. Addissouky TA, El Sayed IET, Ali MMA, Wang Y, El Baz A, Khalil AA, et al. Latest advances in hepatocellular carcinoma management and prevention through advanced technologies. Egypt Liver J 2024;14(1):2. [CrossRef]
11. Cerreto M, Cardone F, Cerrito L, Stella L, Santopaolo F, Pallozzi M, et al. The new era of systemic treatment for hepatocellular carcinoma: from the first line to the optimal sequence. Curr Oncol 2023;30(10):8774-8792. [CrossRef]
12. Shin H, Yu SJ. A concise review of updated global guidelines for the management of hepatocellular carcinoma: 2017-2024. J Liver Cancer 2025;25(1):19-30. [CrossRef]
13. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. J Hepatol 2022;76(3):681-693. [CrossRef]
14. Goel C, Monga SP, Nejak-Bowen K. Role and regulation of Wnt/β-catenin in hepatic perivenous zonation and physiological homeostasis. Am J Pathol 2022;192(1):4-17. [CrossRef]
15. Dichtel LE, Cordoba-Chacon J, Kineman RD. Growth hormone and insulin-like growth factor 1 regulation of nonalcoholic fatty liver disease. J Clin Endocrinol Metab 2022;107(7):1812-1824. [CrossRef]
16. Ngo MHT, Jeng HY, Kuo YC, Diony Nanda J, Brahmadhi A, Ling TY, et al. The role of IGF/IGF-1R signaling in hepatocellular carcinomas: stemness-related properties and drug resistance. Int J Mol Sci 2021;22(4):1931. [CrossRef]
17. Panneerselvam S, Wilson C, Kumar P, Abirami D, Pamarthi J, Reddy MS, et al. Overview of hepatocellular carcinoma: from molecular aspects to future therapeutic options. Cell Adh Migr 2023;17(1):1-21. [CrossRef]
18. Suresh D, Srinivas AN, Kumar DP. Etiology of hepatocellular carcinoma: special focus on fatty liver disease. Front Oncol 2020;10:601710. [CrossRef]
19. Wang X, Wang J, Peng H, Zuo L, Wang H. Role of immune cell interactions in alcohol-associated liver diseases. Liver Res 2024;8(2):72-82. [CrossRef]
20. Wang H, Mehal W, Nagy LE, Rotman Y. Immunological mechanisms and therapeutic targets of fatty liver diseases. Cell Mol Immunol 2021;18(1):73-91. [CrossRef]
21. Chen L, Ye X, Yang L, Zhao J, You J, Feng Y. Linking fatty liver diseases to hepatocellular carcinoma by hepatic stellate cells. J Natl Cancer Cent 2024;4(1):25-35. [CrossRef]
22. Tümen D, Heumann P, Gülow K, Demirci CN, Cosma LS, Müller M, et al. Pathogenesis and current treatment strategies of hepatocellular carcinoma. Biomedicines 2022;10(12):3202. [CrossRef]
23. Rizzo GEM, Cabibbo G, Craxì A. Hepatitis B virus-associated hepatocellular carcinoma. Viruses 2022;14(5):986. [CrossRef]
24. Pal Chaudhary S, Reyes S, Chase ML, Govindan A, Zhao L, Luther J, et al. Resection of NAFLD/NASH-related hepatocellular carcinoma (HCC): clinical features and outcomes compared with HCC due to other etiologies. Oncologist 2023;28(4):341-350. [CrossRef]
25. Radu F, Potcovaru CG, Salmen T, Filip PV, Pop C, Fierbințeanu-Braticievici C. The link between NAFLD and metabolic syndrome. Diagnostics (Basel) 2023;13(4):614. [CrossRef]
26. Shi Z, Xiao Z, Hu L, Gao Y, Zhao J, Liu Y, et al. The genetic association between type 2 diabetic and hepatocellular carcinomas. Ann Transl Med 2020;8(6):380. [CrossRef]
27. Onikanni SA, Lawal B, Bakare OS, Ajiboye BO, Ojo OA, Farasani A, et al. Cancer of the liver and its relationship with diabetes mellitus. Technol Cancer Res Treat 2022;21:15330338221119744. [CrossRef]
28. Jaffe A, Taddei TH, Giannini EG, Ilagan-Ying YC, Colombo M, Strazzabosco M. Holistic management of hepatocellular carcinoma: the hepatologist's comprehensive playbook. Liver Int 2022;42(12):2607-2619. [CrossRef]
29. Vella V, Lappano R, Bonavita E, Maggiolini M, Clarke RB, Belfiore A, et al. Insulin/IGF axis and the receptor for advanced glycation end products: role in meta-inflammation and potential in cancer therapy. Endocr Rev 2023;44(4):693-723. [CrossRef]
30. Dilworth L, Facey A, Omoruyi F. Diabetes mellitus and its metabolic complications: the role of adipose tissues. Int J Mol Sci 2021;22(14):7644. [CrossRef]
31. Nijenhuis-Noort EC, Berk KA, Neggers SJCM, van der Lely AJ. The fascinating interplay between growth hormone, insulin-like growth factor-1, and insulin. Endocrinol Metab 2024;39(1):83-89. [CrossRef]
32. Talamantes S, Lisjak M, Gilglioni EH, Llamoza-Torres CJ, Ramos-Molina B, Gurzov EN. Non-alcoholic fatty liver disease and diabetes mellitus as growing aetiologies of hepatocellular carcinoma. JHEP Rep 2023;5(9):100811. [CrossRef]
33. Szablewski L. Insulin resistance: the increased risk of cancers. Curr Oncol 2024;31(2):998-1027. [CrossRef]
34. Vetrano E, Rinaldi L, Mormone A, Giorgione C, Galiero R, Caturano A, et al. Non-alcoholic fatty liver disease (NAFLD), type 2 diabetes, and non-viral hepatocarcinoma: pathophysiological mechanisms and new therapeutic strategies. Biomedicines 2023;11(2):468. [CrossRef]
35. Kim DS, Scherer PE. Obesity, diabetes, and increased cancer progression. Diabetes Metab J 2021;45(6):799-812. [CrossRef]
36. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci 2020;21(17):6275. [CrossRef]
37. Ghazanfar H, Javed N, Qasim A, Zacharia GS, Ghazanfar A, Jyala A, et al. Metabolic dysfunction-associated steatohepatitis and progression to hepatocellular carcinoma: a literature review. Cancers (Basel) 2024;16(6):1214. [CrossRef]
38. Kasprzak A. Insulin-like growth factor 1 (IGF-1) signaling in glucose metabolism in colorectal cancer. Int J Mol Sci 2021;22(12):6434. [CrossRef]

39. Dey S, Murmu N, Mondal T, Saha I, Chatterjee S, Manna R, et al. Multi-faceted entrancing role of glucose and its analogue, 2-deoxy-D-glucose in cancer cell proliferation, inflammation, and virus infection. Biomed Pharmacother 2022;156:113801. [CrossRef]
40. Shan Y, Lu C, Wang J, Li M, Ye S, Wu S, et al. IGF-1 contributes to liver cancer development in diabetes patients by promoting autophagy. Ann Hepatol 2022;27(4):100697. [CrossRef]
41. Tzanakakis GN, Giatagana EM, Berdiaki A, Spyridaki I, Hida K, Neagu M, et al. The role of IGF/IGF-IR-signaling and extracellular matrix effectors in bone sarcoma pathogenesis. Cancers (Basel) 2021;13(10):2478. [CrossRef]
42. LeRoith D, Holly JMP, Forbes BE. Insulin-like growth factors: ligands, binding proteins, and receptors. Mol Metab 2021;52:101245. [CrossRef]
43. Osher E, Macaulay VM. Therapeutic targeting of the IGF axis. Cells 2019;8(8):895. [CrossRef]
44. Baxter RC. Signaling pathways of the insulin-like growth factor binding proteins. Endocr Rev 2023;44(5):753-778. [CrossRef]
45. Blyth AJ, Kirk NS, Forbes BE. Understanding IGF-II action through insights into receptor binding and activation. Cells 2020;9(10):2276. [CrossRef]
46. Bailes J, Soloviev M. Insulin-like growth factor-1 (IGF-1) and its monitoring in medical diagnostic and in sports. Biomolecules 2021;11(2):217. [CrossRef]
47. Miller BS, Rogol AD, Rosenfeld RG. The history of the insulin-like growth factor system. Horm Res Paediatr 2022;95(6):619-630. [CrossRef]
48. Galal MA, Alouch SS, Alsultan BS, Dahman H, Alyabis NA, Alammar SA, et al. Insulin receptor isoforms and insulin growth factor-like receptors: implications in cell signaling, carcinogenesis, and chemoresistance. Int J Mol Sci 2023;24(19):15006. [CrossRef]
49. Werner H. The IGF1 signaling pathway: from basic concepts to therapeutic opportunities. Int J Mol Sci 2023;24(19):14882. [CrossRef]
50. Hakuno F, Takahashi SI. 40 years of IGF1: IGF1 receptor signaling pathways. J Mol Endocrinol 2018;61(1):T69-T86. [CrossRef]
51. Liu Z, Yang L, Wu W, Chen Z, Xie Z, Shi D, et al. Prognosis and therapeutic significance of IGF-1R-related signaling pathway gene signature in glioma. Front Cell Dev Biol 2024;12:1375030. [CrossRef]
52. Scalia P, Giordano A, Williams SJ. The IGF-II-insulin receptor isoform-A autocrine signal in cancer: actionable perspectives. Cancers (Basel) 2020;12(2):366. [CrossRef]
53. Torrente Y, Bella P, Tripodi L, Villa C, Farini A. Role of insulin-like growth factor receptor 2 across muscle homeostasis: implications for treating muscular dystrophy. Cells 2020;9(2):441. [CrossRef]
54. Catellani C, Ravegnini G, Sartori C, Angelini S, Street ME. GH and IGF system: the regulatory role of miRNAs and lncRNAs in cancer. Front Endocrinol (Lausanne) 2021;12:701246. [CrossRef]
55. Al-Samerria S, Radovick S. The role of insulin-like growth factor-1 (IGF-1) in the control of neuroendocrine regulation of growth. Cells 2021;10(10):2664. [CrossRef]
56. de la Garza RG, Morales-Garza LA, Martin-Estal I, Castilla-Cortazar I. Insulin-like growth factor-1 deficiency and cirrhosis establishment. J Clin Med Res 2017;9(4):233-247. [CrossRef]
57. Kaseb AO, Guan Y, Gok Yavuz B, Abbas AR, Lu S, Hasanov E, et al. Serum IGF-1 scores and clinical outcomes in the phase III IMbrave150 study of atezolizumab plus bevacizumab versus sorafenib in patients with unresectable hepatocellular carcinoma. J Hepatocell Carcinoma 2022;9:1065-1079. [CrossRef]
58. Johnson PJ, Kalyuzhnyy A, Boswell E, Toyoda H. Progression of chronic liver disease to hepatocellular carcinoma: implications for surveillance and management. BJC Rep 2024;2(1):39. [CrossRef]
59. Bahar ME, Kim HJ, Kim DR. Targeting the RAS/RAF/MAPK pathway for cancer therapy: from mechanism to clinical studies. Signal Transduct Target Ther 2023;8(1):455. [CrossRef]
60. Yoon JS, Lee CW. Protein phosphatases regulate the liver microenvironment in the development of hepatocellular carcinoma. Exp Mol Med 2022;54(11):1799-1813. [CrossRef]
61. Püschel GP, Klauder J, Henkel J. Macrophages, low-grade inflammation, insulin resistance and hyperinsulinemia: a mutual ambiguous relationship in the development of metabolic diseases. J Clin Med 2022;11(15):4358. [CrossRef]
62. Racine HL, Serrat MA. The actions of IGF-1 in the growth plate and its role in postnatal bone elongation. Curr Osteoporos Rep 2020;18(3):210-227. [CrossRef]
63. He Y, Sun MM, Zhang GG, Yang J, Chen KS, Xu WW, et al. Targeting PI3K/Akt signal transduction for cancer therapy. Signal Transduct Target Ther 2021;6(1):425. [CrossRef]
64. Belfiore A, Rapicavoli RV, Le Moli R, Lappano R, Morrione A, De Francesco EM, et al. IGF2: a role in metastasis and tumor evasion from immune surveillance. Biomedicines 2023;11(1):229. [CrossRef]
65. Liu ZL, Chen HH, Zheng LL, Sun LP, Shi L. Angiogenic signaling pathways and anti-angiogenic therapy for cancer. Signal Transduct Target Ther 2023 May;8(1):198. [CrossRef]
66. Zheng J, Rapicavoli RV, Le Moli R, Lappano R, Morrione A, De Francesco EM, et al. Hepatocellular carcinoma: signaling pathways and therapeutic advances. Signal Transduct Target Ther 2025;10(1):35. [CrossRef]
67. Cai W, Ma Y, Song L, Cao N, Gao J, Zhou S, et al. IGF-1R down regulates the sensitivity of hepatocellular carcinoma to sorafenib through the PI3K/akt and RAS/raf/ERK signaling pathways. BMC Cancer 2023;23(1):87. [CrossRef]
68. Hua H, Kong Q, Yin J, Zhang J, Jiang Y. Insulin-like growth factor receptor signaling in tumorigenesis and drug resistance: a challenge for cancer therapy. J Hematol Oncol 2020;13(1):64. [CrossRef]
69. Khan MZ, Zugaza JL, Torres Aleman I. The signaling landscape of insulin-like growth factor 1. J Biol Chem 2025;301(1):108047. [CrossRef]
70. Kearney AL, Norris DM, Ghomlaghi M, Kin Lok Wong M, Humphrey SJ, Carroll L, et al. Akt phosphorylates insulin receptor substrate to limit PI3K-mediated PIP3 synthesis. Elife 2021;10:e66942. [CrossRef]
71. Glaviano A, Foo ASC, Lam HY, Yap KCH, Jacot W, Jones RH, et al. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Mol Cancer 2023;22(1):138. [CrossRef]
72. Dillon M, Lopez A, Lin E, Sales D, Perets R, Jain P. Progress on Ras/MAPK signaling research and targeting in blood and solid cancers. Cancers (Basel) 2021;13(20):5059. [CrossRef]
73. Kouroumalis E, Tsomidis I, Voumvouraki A. Pathogenesis of hepatocellular carcinoma: the interplay of apoptosis and autophagy. Biomedicines 2023;11(4):1166. [CrossRef]
74. Tufail M, Hu JJ, Liang J, He CY, Wan WD, Huang YQ, et al. Hallmarks of cancer resistance. iScience 2024;27(6):109979. [CrossRef]
75. Tomuleasa C, Tigu AB, Munteanu R, Moldovan CS, Kegyes D, Onaciu A, et al. Therapeutic advances of targeting receptor tyrosine kinases in cancer. Signal Transduct Target Ther 2024;9(1):201. [CrossRef]
76. Kotsifaki A, Maroulaki S, Karalexis E, Stathaki M, Armakolas A. Decoding the role of insulin-like growth factor 1 and its isoforms in breast cancer. Int J Mol Sci 2024;25(17):9302. [CrossRef]
77. Ma S, Meng G, Liu T, You J, He R, Zhao X, et al. The Wnt signaling pathway in hepatocellular carcinoma: regulatory mechanisms and therapeutic prospects. Biomed Pharmacother 2024;180:117508. [CrossRef]
78. Wang XL, Yang M, Wang Y. Roles of transforming growth factor-β signaling in liver disease. World J Hepatol 2024;16(7):973-979. [CrossRef]
79. Afradiasbagharani P, Hosseini E, Allahveisi A, Bazrafkan M. The insulin-like growth factor and its players: their functions, significance, and consequences in all aspects of ovarian physiology. Middle East Fertil Soc J 2022;27(1):27. [CrossRef]
80. Kerr A, Baxter RC. Noncoding RNA actions through IGFs and IGF binding proteins in cancer. Oncogene 2022;41(25):3385-3393. [CrossRef]
81. Jo Y, Lim E, Park J, Kang K, Shin MY, Choi JW, et al. Epigenetic dysregulation of H19/IGF2 in hepatic cells exposed to toxic metal mixtures *in vitro*. Sci Rep 2024;14(1):29413. [CrossRef]

82. Liu Y, Shen S, Yan Z, Yan L, Ding H, Wang A, et al. Expression characteristics and their functional role of IGFBP gene family in pan-cancer. BMC Cancer 2023;23(1):371. [CrossRef]
83. Mohamed AA, Sahin C, Berres ML, Beetz O, Websky MV, Vogel T, et al. The prognostic utility of IGF-1 in hepatocellular carcinoma treated with stereotactic body radiotherapy. Clin Transl Radiat Oncol 2025;50:100887. [CrossRef]
84. Perks CM. Role of the insulin-like growth factor (IGF) axis in diseases. Int J Mol Sci 2023;24(23):16969. [CrossRef]
85. Liu Y, Xue H, Liu Y, Li H, Liang Q, Ma L, et al. Serum insulin-like growth factor 1 and the prognosis of patients with advanced liver diseases: a meta-analysis. Clin Transl Gastroenterol 2025;16(7):e00829. [CrossRef]
86. Mabrouk NMK, Elkaffash DM, Abdel-Hadi M, Abdelmoneim SE, Saad ElDeen S, Gewaifel G, et al. Identification of the possible therapeutic targets in the insulin-like growth factor 1 receptor pathway in a cohort of Egyptian hepatocellular carcinoma complicating chronic hepatitis C type 4. Drug Target Insights 2020;14:1-11. [CrossRef]
87. Rocca A, Braga L, Volpe MC, Maiocchi S, Generali D. The predictive and prognostic role of RAS-RAF-MEK-ERK pathway alterations in breast cancer: revision of the literature and comparison with the analysis of cancer genomic datasets. Cancers Basel 2022;14(21):5306. [CrossRef]
88. Dimri M, Satyanarayana A. Molecular signaling pathways and therapeutic targets in hepatocellular carcinoma. Cancers Basel 2020;12(2):491. [CrossRef]
89. Luo X, He X, Zhang X, Zhao X, Zhang Y, Shi Y, et al. Hepatocellular carcinoma: signaling pathways, targeted therapy, and immunotherapy. MedComm (2020) 2024;5(2):e474. [CrossRef]
90. Chen YM, Qi S, Perrino S, Hashimoto M, Brodt P. Targeting the IGF-axis for cancer therapy: development and validation of an IGF-trap as a potential drug. Cells 2020;9(5):1098. [CrossRef]
91. Soni UK, Jenny L, Hegde RS. IGF-1R targeting in cancer - does sub-cellular localization matter? J Exp Clin Cancer Res 2023;42(1):273. [CrossRef]
92. Peng Y, Tan J. The relationship between IGF pathway and acquired resistance to tyrosine kinase inhibitors in cancer therapy. Front Biosci Landmark 2023;28(8):163. [CrossRef]
93. Fuentes-Baile M, Ventero MP, Encinar JA, García-Morales P, Poveda-Deltell M, Pérez-Valenciano E, et al. Differential effects of IGF-1R small molecule tyrosine kinase inhibitors BMS-754807 and OSI-906 on human cancer cell lines. Cancers Basel 2020;12(12):3717. [CrossRef]
94. Vishwamitra D, George SK, Shi P, Kaseb AO, Amin HM. Type I insulin-like growth factor receptor signaling in hematological malignancies. Oncotarget 2017;8(1):1814-1844. [CrossRef]
95. Tap WD, Demetri G, Barnette P, Desai J, Kavan P, Tozer R, et al. Phase II study of ganitumab, a fully human anti-type-1 insulin-like growth factor receptor antibody, in patients with metastatic Ewing family tumors or desmoplastic small round cell tumors. J Clin Oncol 2012;30(15):1849-1856. [CrossRef]
96. Nwabo Kamdje AH, Seke Etet PF, Kipanyula MJ, Vecchio L, Tagne Simo R, Njamnshi AK, et al. Insulin-like growth factor-1 signaling in the tumor microenvironment: carcinogenesis, cancer drug resistance, and therapeutic potential. Front Endocrinol Lausanne 2022;13:927390. [CrossRef]
97. Ou X, Gao G, Habaz IA, Wang Y. Mechanisms of resistance to tyrosine kinase inhibitor-targeted therapy and overcoming strategies. MedComm Beijing 2024;5(9):e694. [CrossRef]
98. Chen C, Wang Z, Ding Y, Qin Y. Tumor microenvironment-mediated immune evasion in hepatocellular carcinoma. Front Immunol 2023;14:1133308. [CrossRef]
99. Duan XP, Qin BD, Jiao XD, Liu K, Wang Z, Zang YS. New clinical trial design in precision medicine: discovery, development and direction. Signal Transduct Target Ther 2024;9(1):57. [CrossRef]
100. Luo XY, Wu KM, He XX. Advances in drug development for hepatocellular carcinoma: clinical trials and potential therapeutic targets. J Exp Clin Cancer Res 2021;40(1):172. [CrossRef]
101. Zheng S, Chan SW, Liu F, Liu J, Chow PKH, Toh HC, et al. Hepatocellular carcinoma: current drug therapeutic status, advances and challenges. Cancers (Basel) 2024;16(8):1582. [CrossRef]
102. Barata P, Cooney M, Tyler A, Wright J, Dreicer R, Garcia JA. A phase 2 study of OSI-906 (linsitinib, an insulin-like growth factor receptor-1 inhibitor) in patients with asymptomatic or mildly symptomatic (non-opioid requiring) metastatic castrate resistant prostate cancer (CRPC). Invest New Drugs 2018;36(3):451-457. [CrossRef]
103. Schmitz S, Kaminsky-Forrett MC, Henry S, Zanetta S, Geoffrois L, Bompas E, et al. Phase II study of figitumumab in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck: clinical activity and molecular response (GORTEC 2008-02). Ann Oncol 2012;23(8):2153-2161. [CrossRef]
104. Sclafani F, Kim TY, Cunningham D, Kim TW, Tabernero J, Schmoll HJ, et al. A randomized phase II/III study of dalotuzumab in combination with cetuximab and irinotecan in chemorefractory, KRAS wild-type, metastatic colorectal cancer. J Natl Cancer Inst 2015;107(12):djv258. [CrossRef]
105. Huang SL, Wang YM, Wang QY, Feng GG, Wu FQ, Yang LM, et al. Mechanisms and clinical trials of hepatocellular carcinoma immunotherapy. Front Genet 2021;12:691391. [CrossRef]
106. Pappo AS, Vassal G, Crowley JJ, Bolejack V, Hogendoorn PC, Chugh R, et al. A phase 2 trial of R1507, a monoclonal antibody to the insulin-like growth factor-1 receptor (IGF-1R), in patients with recurrent or refractory rhabdomyosarcoma, osteosarcoma, synovial sarcoma, and other soft tissue sarcomas: results of a Sarcoma Alliance for Research Through Collaboration study. Cancer 2014;120(16):2448-2456. [CrossRef]
107. Bauman JE, Ohr J, Gooding WE, Ferris RL, Duvvuri U, Kim S, et al. Phase I study of ficlatuzumab and cetuximab in cetuximab-resistant, recurrent/metastatic head and neck cancer. Cancers Basel 2020;12(6):1537. [CrossRef]

Review

HEPATOLOGY FORUM

MASLD and viral hepatitis: Dual burden

doi: 10.14744/hf.2025.88386

MASLD and viral hepatitis overlap: An emerging dual burden in chronic liver disease

Maham Ejaz, Kirsh Kumar, Daniyal Sohail, Imteshal Sarfaraz, Hafsa Azam, Fatima Yaseen

Department of Medicine, Jinnah Sindh Medical University, Karachi, Pakistan

Abstract

The coexistence of metabolic dysfunction-associated steatotic liver disease (MASLD) and viral hepatitis has gained greater focus due to the global increase in chronic liver diseases. This convergence of conditions creates a unique clinical entity characterized by complex molecular interactions, difficult diagnosis, and treatment issues. The frequency of MASLD alongside viral hepatitis is becoming more prevalent. Overlapping pathogenic mechanisms, such as insulin resistance, activation of pro-inflammatory cytokines, hepatic steatosis, and persistent viral infection, establish a synergistic pathophysiological relationship that exacerbates fibrosis and liver damage. Non-invasive fibrosis assessments, multimodal imaging, and, in certain cases, liver biopsies are often required to achieve diagnostic accuracy. This review intends to examine the epidemiological overlap, shared pathophysiological mechanisms, diagnostic hurdles, and management challenges associated with the concurrent manifestation of MASLD and viral hepatitis.

Keywords: Coinfection; hepatitis B; hepatitis C; hepatocellular carcinoma; liver fibrosis; MASLD; viral hepatitis.

Introduction

Overview of Liver Disease

Liver disease is a significant global health issue, causing nearly two million deaths each year, which accounts for about 4 percent of all global mortality. It is one of the top causes of death worldwide.[1] Among the chronic liver disorders, chronic viral hepatitis (hepatitis B virus [HBV] and hepatitis C virus [HCV]) and metabolic dysfunction-associated steatotic liver disease (MASLD) are significant. In the past, people viewed viral hepatitis as an infectious disease. They saw MASLD as a liver problem tied to metabolic syndrome. However, it is now clear that both conditions can occur together. Despite the widespread use of HBV vaccines and the availability of effective direct-acting antivirals for HCV, it is still a major cause of morbidity and mortality.[2] This trend is largely due to increasing rates of obesity, type 2 diabetes, and sedentary lifestyles.[3]

Chronic Viral Hepatitis

Chronic viral hepatitis is a long-lasting infection caused by the HBV or the HCV. HBV chronically infects an estimated 350 to 400 million individuals globally and stays in liver cells as covalently closed circular DNA (cccDNA). This cccDNA acts as a stable viral template, posing a significant barrier to eradication.[2,4] HCV affects approximately 58 million people globally.[5] Both viruses lead to ongoing liver damage that can result in fibrosis, cirrhosis, and liver cancer. HBV infection alone increases the risk of liver-related death by more than three times, with an adjusted hazard ratio of 3.35.[6] This risk rises more than twelvefold when MASLD is also present, highlighting the importance of early diagnosis and comprehensive management.[6] In Pakistan, where HBV and HCV rates are moderate and hepatitis A and E are common, poor sanitation and inadequate healthcare systems hinder effective disease control.[7]

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)

In 2023, international societies (EASL, AASLD, ALEH, etc.) adopted a new nomenclature, replacing non-alcoholic fatty liver disease (NAFLD) with MASLD. According to the consensus definition, MASLD is diagnosed when there is evidence of hepatic steatosis (by imaging, histology, or non-invasive biomarker), at least one cardiometabolic risk factor (such as obesity or overweight, type 2 diabetes, elevated blood pressure, high triglycerides, or low HDL-cholesterol), and exclusion of harmful alcohol intake above established thresholds. MASLD is embedded under the umbrella term steatotic liver disease (SLD), which also includes related subtypes such as metabolic dysfunction- and alcohol-associated liver disease (MetALD) and cryptogenic steatotic liver disease. By using this definition, most patients previously labeled NAFLD meet criteria for MASLD.[8,9] It is considered a hepatic manifestation of metabolic syndrome and is closely linked to obesity, insulin resistance, type 2 diabetes, high cholesterol, and high blood pressure. Worldwide, MASLD affects about 29.8 percent of adults in the general population, and prevalence is significantly higher in individuals with metabolic comorbidities—58.5 percent in those with diabetes, 74.1 percent in those with high blood pressure, and 47.4 percent in those who are obese.[3] The global burden of this disease has nearly doubled in the past thirty years, increasing from 561 million cases in 1990 to 1.24 billion by 2019, and over 80 percent of countries have reported a rise in prevalence.[10]

How to cite this article: Ejaz M, Kumar K, Sohail D, Sarfaraz I, Azam H, Yaseen F. MASLD and Viral Hepatitis Overlap: An Emerging Dual Burden in Chronic Liver Disease. Hepatology Forum 2026; 7(1):69–76.

Received: September 02, 2025; **Revised:** October 05, 2025; **Accepted:** October 29, 2025; **Available online:** December 10, 2025

Corresponding author: Maham Ejaz; Department of Medicine, Jinnah Sindh Medical University, Karachi, Pakistan
Phone: +92-324-8037054; **e-mail:** maham2343791@gmail.com

The disease can range from simple fat accumulation to metabolic dysfunction-associated steatohepatitis (MASH), which may lead to fibrosis, cirrhosis, and liver cancer. At present, no medications have wide regulatory approval for treating MASLD. Lifestyle changes and managing metabolic risk factors remain the main approach to treatment.[11]

Epidemiological Overlap and Synergistic Burden

Recent studies show that chronic viral hepatitis and MASLD frequently occur together and worsen liver damage.[2,12] Among 425 inactive chronic hepatitis B (CHB) patients, 47.8% had concurrent MASLD, with 10.5% showing significant fibrosis compared to only 1.4% of those without fat in the liver.[13] This indicates a much higher risk of cirrhosis when both conditions are present.[13] Similarly, HCV genotype 3a-infected individuals show steatosis in nearly 48% of cases, associated with higher viral loads, more severe liver inflammation, and faster fibrosis progression.[14] Mechanically, HBV's X protein disrupts lipid metabolism, while HCV hinders lipid export. Insulin resistance and fat toxicity in MASLD trigger the release of inflammatory cytokines and activate stellate cells.[5,15] Clinically, patients with both chronic viral hepatitis and MASLD experience faster scarring, significantly greater risks of cirrhosis and hepatocellular carcinoma, and higher liver-related death rates than those with single infections. This also presents greater challenges in diagnosis and treatment.[6,16,17]

Regional and Demographic Variations

The prevalence of MASLD and its overlap with chronic viral hepatitis varies significantly across different populations. In Pakistan, MASLD impacts 75 percent of adults with type 2 diabetes. Of these, 22.5 percent progress to MASH. There are clear ethnic differences. Pathans have the highest rates of steatosis at 58.5 percent and NASH at 19.5 percent, compared to Punjabis at 44.5 percent and 10 percent, and Sindhis at 35.3 percent.[18] These patterns reflect the country's high metabolic burden, with 26.7 percent of adults having diabetes, and one in four considered obese.[19] This variation, influenced by genetic, metabolic, and lifestyle factors, emphasizes the need for region-specific screening methods and combined antiviral and metabolic management strategies.[16,20]

Knowledge Gaps and Rationale

Despite increasing evidence that CHB/HCV and MASLD together accelerate fibrosis, cirrhosis, and liver cancer, most studies still examine these conditions separately. There are significant gaps in understanding how they interact, identifying the best diagnostic methods—especially for non-obese MASLD in CHB—and developing effective combined treatment plans.[21–23] Additionally, modeling studies indicate that cirrhosis linked to MASLD and liver-related deaths could more than double by 2030, especially in older populations.[16]

Materials and Methods

A narrative review was conducted to explore the combined impact of MASLD and viral hepatitis in the same patient population. The focus was to illuminate their combined effects on liver pathology, the diagnostic challenges they present, and the management strategies available. The primary objective was to gather and synthesize current evidence from a variety of sources, including pre-clinical studies, clinical trials, systematic reviews, population-based analyses, and established clinical guidelines that pertain to this dual condition. A detailed literature search was done through electronic databases including PubMed, Scopus, ScienceDirect, and Google Scholar using specific keywords like ["MASLD," "viral hepatitis," "HCV," "HBV," "liver fibrosis," "coexisting liver diseases," "hepatocellular carcinoma," "coexisting pathologies," "dual etiology"] and Boolean operators ["AND" and "OR"] to refine the results. Additionally, "NAFLD" was also included as a keyword to capture relevant articles published before the 2023 nomenclature change, ensuring a comprehensive review.

Articles published in English from 2015–2023 involving patients having both NAFLD and viral hepatitis and from 2023–2025 having both MASLD and viral hepatitis were included, along with studies emphasizing clinical outcomes, diagnostic challenges, and therapeutic strategies; studies containing human subjects were also focused on. Conversely, studies having animal subjects with insufficient data on dual pathologies, editorials, case reports, studies exploring complications like hepatocellular carcinoma without the context of MASLD or viral hepatitis, and studies exploring liver diseases unrelated to MASLD or viral hepatitis were excluded.

Among the selected literature, particular attention was given to articles detailing the pathological interactions between these diseases, diagnostic methodologies, and the clinical consequences or complications that may arise. Relevant data from these included studies were thoroughly analyzed and categorized based on population characteristics, reported clinical and histological outcomes, diagnostic tools (such as liver biopsy, imaging, and biomarkers), and intervention strategies. All the data were compiled to identify the existing patterns, knowledge gaps, and potential clinical approaches for the management of patients suffering from both etiologies. This review also highlights the importance of future research and the need for updated clinical guidelines for this dual pathology.

Pathophysiological Crossroads in MASLD and Viral Hepatitis Coexistence

Chronic liver disease (CLD) is a serious health concern worldwide. The two primary causes of CLD around the world are viral hepatitis (HBV and HCV) and MASLD.[24] Typically, viral hepatitis and MASLD have been studied separately, but several studies highlight the collaborative effect of viral hepatitis and MASLD. Higher complication rates and more complicated management of either disease arise when MASLD coexists with HBV or HCV in the same person.[25]

The "Multiple-Hit" Pathogenesis of MASLD

MASLD includes a range of liver damage, from simple accumulation of fat in liver cells—steatosis—to more advanced forms of the disease, steatohepatitis, which can lead to fibrosis, cirrhosis, end-stage liver disease, and even hepatocellular carcinoma (HCC).[26] It progresses according to the "multiple-hit" theory:

1. The "first hit" in MASLD is insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. After the initial impact, the liver stores free fatty acids as triglycerides, which eventually results in typical steatosis.
2. "Multi-hits," such as oxidative stress, inflammatory mediators, apoptosis, and mitochondrial dysfunction, cause disease progression and chronic liver damage (Fig. 1).[27] The gut microbiota, as well as genetic and epigenetic factors, may also play an essential role; thus, the two-hit hypothesis is insufficient to explain the progression mechanism.[28]

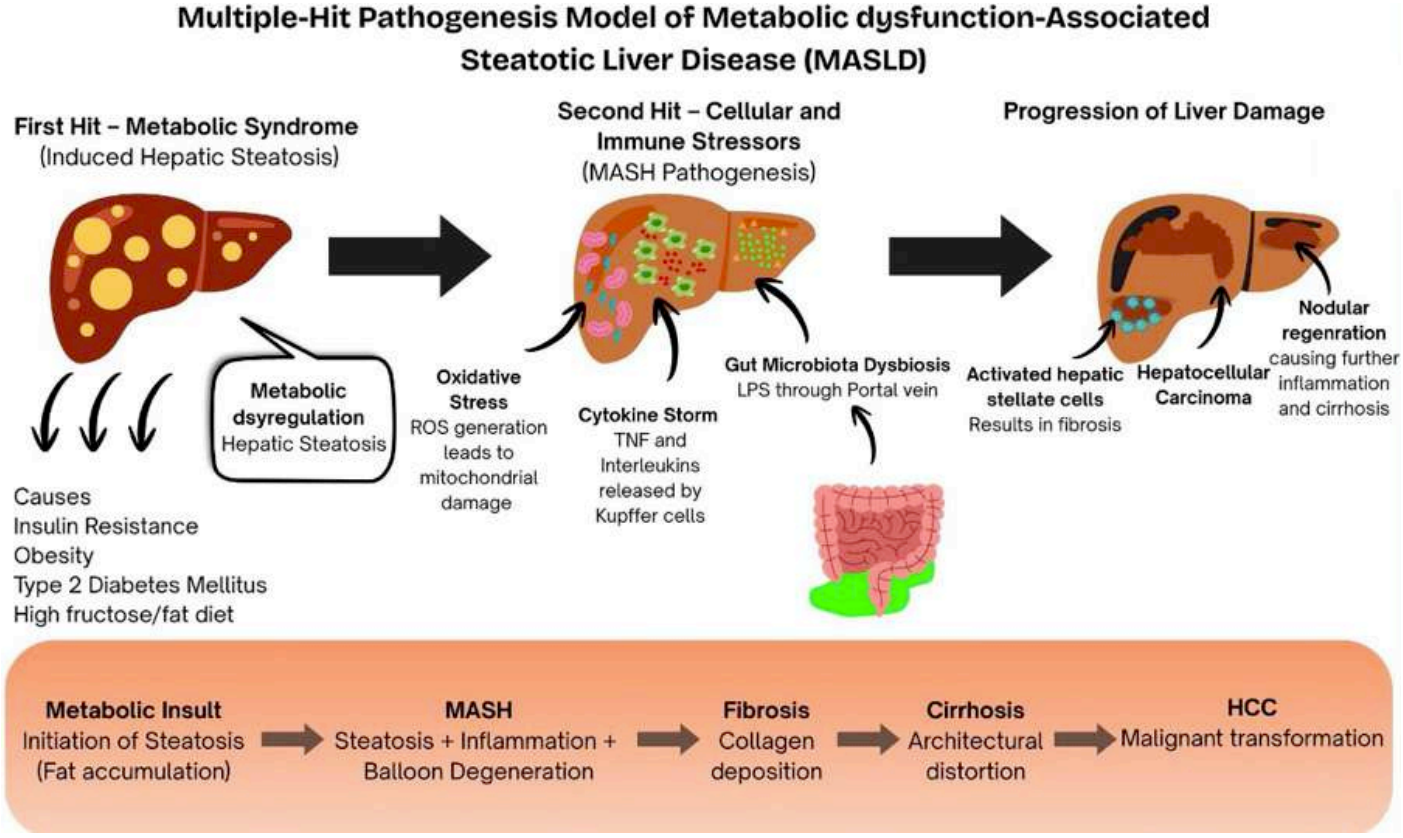

Figure 1. Multiple-hit model depicting the interplay of metabolic insults, oxidative stress, and cytokine-mediated injury leading to fibrosis and eventual hepatocellular carcinoma (HCC) in metabolic dysfunction-associated steatotic liver disease (MASLD).

Immune Dysregulation and Inflammatory Pathways in MASLD

Activation of immune cells could exacerbate liver damage and inflammation in MASLD. Both the innate and adaptive immune systems play a significant role. The innate immune system cells include Kupffer cells, monocytes, macrophages, hepatic dendritic cells, neutrophils, and natural killer cells.[27] In MASLD, innate immunity—particularly macrophages—plays a major role in promoting liver inflammation. MASH is caused by the activation of resident Kupffer cells (KCs) and the recruitment of monocytes, which both produce nitric oxide, ROS, and cytokines like TNF, IL-1β, IL-6, and TGF-β.[29]

Adaptive immune system cells include CD4+ and CD8+ T cells (Th1, Th17, and regulatory T cells), B cells, and platelets.[27] Additionally, KCs may stimulate Th17 differentiation by generating IL-23 or IL-6. Parallel to this, pathogen-associated molecular patterns (PAMPs) produced by the intestine activate B cells through TLR4, which can then either transform into plasma cells or be linked with MHC-II and trigger CD4+ T cells to produce interferon (IFN)-γ. In MASH, lipotoxicity can also change the Th17/Treg ratio by decreasing the frequency of intrahepatic CD4+ T cells. When Th17 activates neutrophils, they contribute to the inflammatory response by producing IL-17 and accumulating in the white adipose tissue (WAT), where they encourage lipolysis.[30] The pathophysiology of MASLD is also influenced by insulin resistance, which is mainly caused by pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6 (Fig. 2).[31]

Viral Immune Escape and Immune Exhaustion

Viral hepatitis exacerbates immunological imbalance through immune escape and exhaustion. Immunological imbalance at the Th17/IL-17 axis level plays a significant role in liver fibrogenesis after initial HCV or HBV injury. By recruiting neutrophils and monocytes, and by inducing the expression and production of interleukin-23 and IL-6 in the liver or peripheral cells, the Th17/IL-17 axis drives a chain of events that encourages a proinflammatory and profibrotic environment.[32] Persistent exposure to viral factors, including hepatitis B and hepatitis C (HCV), causes CD8+ T cells to become functionally fatigued. The overexpression of inhibitory receptors such as PD-1 (programmed cell death protein 1) and/or Tim-3 (T-cell immunoglobulin and mucin domain-containing molecule-3) leads to immune exhaustion and subsequent downregulation of the host response by setting up chronic infection (Fig. 2).[33,34]

Shared Molecular Mechanisms: Lipid Metabolism Disruption

Both HBV and HCV cause steatosis in MASLD patients by interfering with the liver's lipid metabolism.

HCV: HCV affects multiple mechanisms of lipid metabolism within hepatocytes. It increases lipid biosynthesis, inhibits mitochondrial oxidation, and consequently lipid degradation. It also lowers the export of apolipoproteins, particularly very low-density lipoproteins (VLDL), leading to significant intracellular lipid accumulation and circulatory hypocholesterolemia and hypolipoproteinemia.[35]

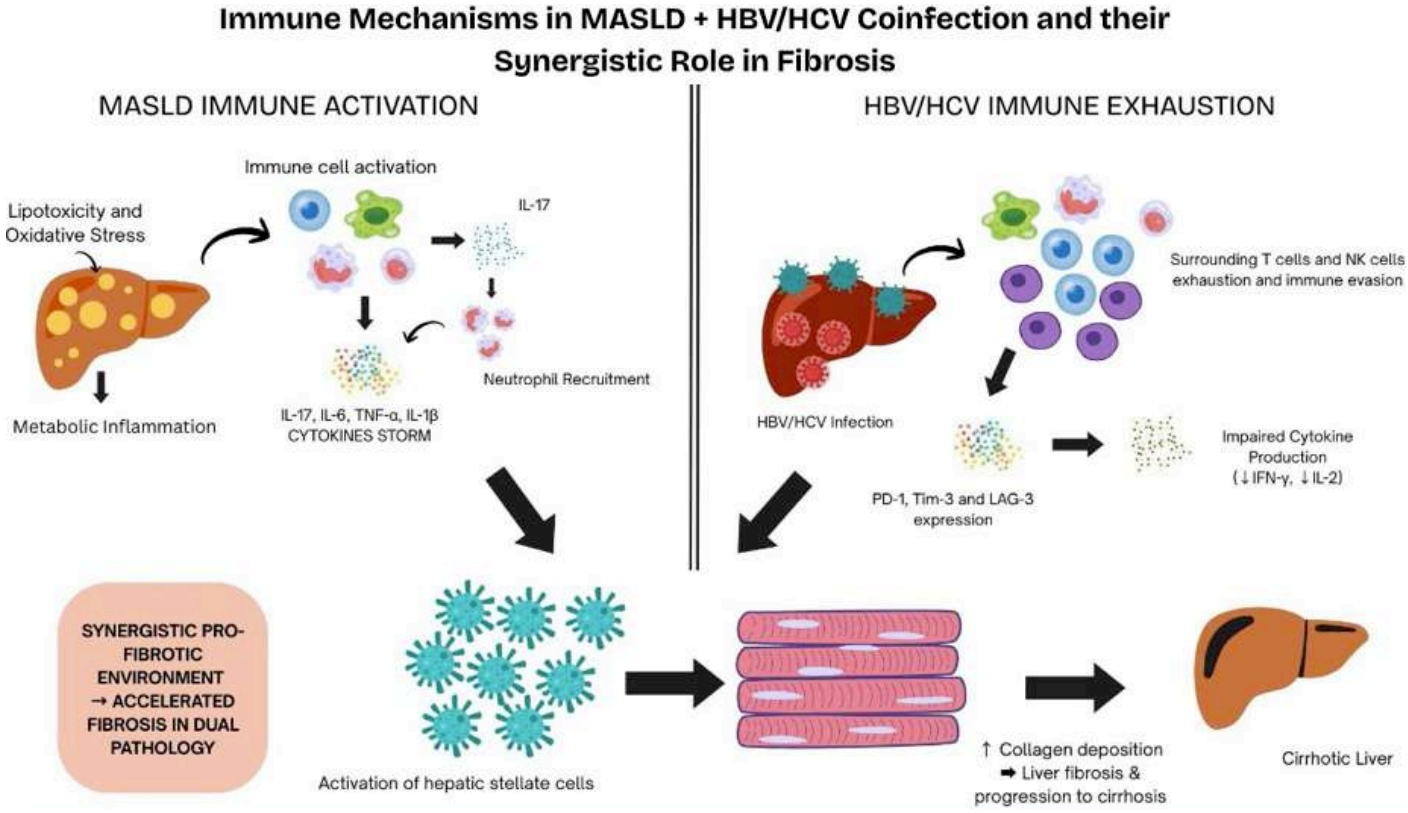

Figure 2. Illustrating distinct immunopathogenic pathways for MASLD and Hepatitis B/C virus and their synergistic contribution to the development and progression of liver fibrosis.

HBV: Hepatic lipogenesis, oxidative conversion of cholesterol to bile acids, hepatic lipid homeostasis, and therefore hepatic steatosis can all be impacted by the inhibition of peroxisome proliferator-activated receptors (PPARs) and signaling pathways (PI3K/AKT, LXR/SREBP, NF-κβ) by the HBV HBx protein. When the pre-S1 protein attaches to sodium taurocholate co-transporting polypeptide (NTCP), it most likely causes hepatic steatosis and changes in the metabolism of cholesterol. By influencing hepatic lipogenesis and hepatic stellate cells (HSCs) proliferation and survival, a differential expression of IL-13, G-CSF, CCL11, IL-6, and IL-4 may be linked to the development of hepatic steatosis and fibrosis in HBV patients.[36]

Interplay Between MASLD and HBV/HCV Infection

Effect of MASLD on HBV/HCV Infection

Activation of the TLR4/Myd88 pathway in MASLD prevents HBV replication, and TLR (Toll-like receptors) induction contributes to HSC activation, thereby triggering inflammation-fibrosis-carcinoma (IFC). Palmitic acid, a saturated fatty acid, suppresses HBV-specific immunocytes, leading to insufficient immunological responses, which may be linked to a more severe course of HBV-related illness.[36] The fatty liver has a sophisticated metabolic network that controls HCV replication. HCV uses lipid droplets for virion assembly and replication. Moreover, after being released from hepatocytes, mature HCVs in circulation are complexed with lipoproteins.[37]

Effect of HBV/HCV on MASLD

The transcription of HBV DNA involves several transcription factors, such as CEBP, CREB, HNF3, HNF4, FXR, RXR, and PPAR. These transcription factors are involved in the metabolism of hepatic glucose, lipid, bile acid, and xenobiotics, and can either promote or inhibit hepatic cell regeneration, inflammation, fibrosis, and malignant transformation.[37] As compared to patients with CHC alone, a study found that patients with simultaneous CHC and MASLD characteristics were more likely to have higher degrees of fibrosis.[38]

Lipotoxicity and Hepatic Immune Modulation

The liver transforms triglycerides and free fatty acids into fatty acyl-CoA, which is subsequently carried to the mitochondria for β-oxidation, producing acetyl-CoA. However, a greater buildup of FFA (free fatty acids) results in:

1. Insufficient hepatic β-oxidation
2. Production of reactive oxygen species
3. Mitochondrial damage and mitophagy
4. Hepatocellular inflammation and oxidative stress[27]

Reactive oxygen species (ROS) and lipid metabolites stimulate immune system cells, such as Kupffer cells, monocytes, and macrophages, which in turn release pro-inflammatory cytokines, including TNF-α, IL-10, and IL-17. By activating hepatic stellate cells, these cytokines exacerbate hepatic inflammation and promote the development of liver fibrosis.[33]

Gut-Liver Axis and Systemic Inflammation

According to the recently proposed "intestinal-liver axis" notion, there is a connection between digestive tract disorders and liver illness.[39] Due to intestinal damage and increased permeability caused by

changes in gut microbiota, inflammatory factors (TNF-α, IL-1β, and IL-6) and lipopolysaccharides (LPS) are able to enter the bloodstream and make their way to the liver. Additionally, bile acid metabolism is disrupted by altered gut microbiota, which worsens oxidative stress and hepatic inflammation. This buildup of ROS triggers nuclear factor kappa B (NF-κB) signaling through TLR4, which leads to hepatocyte death and inflammation.[40]

Clinical Implications of Dual Pathology

Patients with fatty liver who were infected with HBV were more likely to have advanced liver fibrosis, hepatic steatosis, hepatic inflammation, and hepatic ballooning than those with a simple chronic HBV infection. While fatty liver could predict considerable liver inflammation in chronic HBV infection on its own, it was not a risk factor for significant or advanced fibrosis.[41] In patients with CHB undergoing antiviral therapy with nucleoside analogs (NAs), the coexistence of MASLD may reduce the virological response.[17]

Diagnostic Challenges

Over the past decade, extensive research has evaluated many diagnostic techniques for staging chronic liver diseases and revealed their pros and cons.[42]

Diagnostic Confusion / Overlapping Symptoms

In a clinical setting, there are several overlaps between the symptoms of MASLD and viral hepatitis. Despite a vast difference in the pathologic mechanisms of both diseases, patients often present with symptoms like fatigue, abdominal discomfort, icterus, ascites, and pruritus. These similar symptoms pose a challenge in diagnosing and contrasting both diseases.[43,44] When comparing biomarkers, elevation of AST and ALT is a presentation of both diseases, which is why liver enzymes are not considered a useful diagnostic tool for MASLD in real-life practice.[43] Moreover, oftentimes patients have advanced histological MASLD but are asymptomatic with normal liver function test (LFT) levels.[42] In some patients, viral infections and MASLD act as a catalyst for disease progression, working in synergy and hastening the progression towards advanced liver pathologies.[45,46] Secondly, viral infections may mimic the clinical presentations of MASLD, hindering the process of accurate diagnosis.[42,47] In some cases, medications designed for MASLD management may interact with antiviral therapies, leading to a potential loss of efficacy and viral pathogenesis, which can lead to more severe consequences.[45,47]

Imaging and Biomarkers in the Context of Coexisting Pathologies

Non-invasive markers are the first choice in the prediction of the severity of chronic liver diseases. This helps doctors to come up with a plan for treating the patient, such as deciding on aggressive treatments or simple monitoring.[42] Other diagnostic tools, such as CTs or MRIs, are more sensitive and specific for advanced MASLD, but their main limitation is the fact that these tools cannot differentiate between MASLD and viral hepatitis, and cannot pinpoint the cause of these diseases, especially if they are secondary to some other pathology. CT is also contraindicated in pregnant women due to its harmful radiation.[42,43,45]

The Role of Liver Biopsy and Non-Invasive Fibrosis Scores / When is the Liver Biopsy Justified?

Now the question arises, which tools are better at diagnosing liver pathologies than others? The answer to that is liver biopsy, which is considered the perfect gold standard test for MASLD. If these tests suggest a high-risk patient, i.e., they may have fibrosis or cirrhosis, then the next plan of action would be to go for a liver biopsy for definitive diagnosis.[42,45] However, common practice is to use a combination of biomarkers and imaging techniques for accurate diagnosis, whereas liver biopsy is retained only for those patients who are at maximum severity.[42,48] A liver biopsy accurately tells the staging, disease progression, and extent of the disease. However, it also has some downsides, such as being a very expensive and time-consuming procedure. It also poses a rare but life-threatening risk of complications and is not ideal in patients who are not at high risk.[49]

Second in the list of better techniques is FibroScan or transient elastography. This technique uses ultrasound waves for diagnosis. With decent sensitivity, specificity, and its non-invasive nature, it is usually recommended.[42,48,49] However, it is less effective in obese patients, and given that obesity is a risk factor for MASLD or any liver disease, the test often becomes insignificant.[49] Fibrosis scores such as FIB-4, MASLD Fibrosis Score, and APRI (AST to platelet ratio index) are also proving to be a very useful diagnostic resource for liver diseases.[50,51] Research shows that the MASLD Fibrosis Score is a validated biomarker, but it seems to perform better in the white population than in Asians, considering its limitations.[42,50,52]

Treatment Challenges

Managing Antiviral Therapy in Metabolic Context

The management plans for patients with concurrent MASLD and viral infections also pose some serious challenges, as studies have shown that the treatment strategies for CHB may have adverse metabolic interactions with MASLD. For example, the standard treatment regimen for hepatitis B involves antivirals like tenofovir and entecavir. Tenofovir has been associated with kidney dysfunction, hypophosphatemia, and reduced bone mineral density.[53] While some studies suggest entecavir may be associated with weight gain and glucose metabolism impairment, both of which may indirectly cause metabolic dysfunction.[54] Similarly, HCV antivirals like ribavirin and interferon worsen insulin resistance.[55,56] By contrast, direct-acting antivirals are generally associated with minimal adverse effects, but rapid HCV clearance may exacerbate underlying steatosis progression and unmask underlying MASLD.[57] Moreover, the progression of one disease may impact the treatment of the other and vice versa, leading to unpredictability of the effect.[25] Studies have stated that the impact of MASLD on antiviral treatments in CHB patients is controversial. Some argue that MASLD has a positive impact by increasing the clearance of HBsAg, while others suggest that MASLD has a negative impact by reducing HBV DNA suppression. While many studies found no clinically relevant association. Hence, close and timely monitoring of HBV DNA and ALT should be done for better intervention.[58]

Lifestyle and Pharmacological Approaches in Dual Disease

Due to the complexities of management strategies in patients with concurrent MASLD and viral hepatitis, lifestyle modifications remain the best option, with weight loss being the first-line treatment.[48] Other lifestyle modifications include exercise, cognitive behavioral therapy, and dietary changes such as hypocaloric diets and low fructose intake.

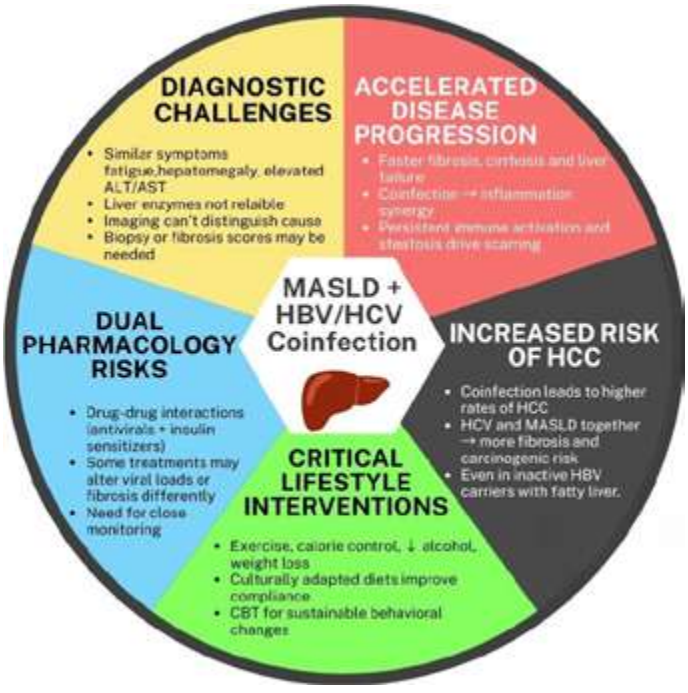

Figure 3. Comprehensive framework of MASLD and HBV/HCV, illustrating disease evolution, oncogenic potential, and the key diagnostic, therapeutic, and preventive considerations.

Alcohol intake increases the chances of HCC and should be avoided.[45,59] These lifestyle modifications should be emphasized and closely monitored in patients receiving long-term antiviral treatment. CHB or CHC antiviral therapy has been shown to adversely affect lipid metabolism, potentially aggravating the steatohepatic burden of these patients.[60,61] As for therapeutic plans, there are no approved drugs for concurrent MASLD and viral hepatitis, but some drugs are given to support metabolic improvements, such as GLP agonists, which have demonstrated favorable effects on liver functional markers, reducing fibrosis, and reducing hepatic fat content in clinical trials,[62] ezetimibe in reducing liver fat, and metformin for increasing insulin sensitivity.[59] In addition, many patients with concurrent MASLD and CHB also have other comorbidities such as diabetes, hypertension, or dyslipidemia. Administration of these drugs along with those for liver disease may cause the phenomenon of polypharmacy, raising concerns regarding drug-drug interactions and cumulative hepatotoxicity. This risk should be carefully monitored and minimized in a clinical setting.[63,64]

Future Targets: Dual-Action Therapeutics and Clinical Trials

Several investigations are currently underway in clinical trial phases, which may show promising results. One such study is the development of a drug named Lanifibranor, a pan-PPAR agonist, which has shown improvements in both MASLD and fibrosis.[65] Another study is considering pegylated interferon, lamivudine (a reverse transcriptase inhibitor), and entecavir as a combination therapy for the treatment of CHB in MASLD patients. Some clinical trials have also investigated the role of FXR agonists in concurrent liver conditions, with positive outcomes reported. FXR agonists like tropifexor and obeticholic acid are shown to target steatosis, reduce viral replication, and have favorable results.[66,67] Multiple other studies are also underway, and early data suggest potential benefits in the future (Fig. 3).[68]

Study Gaps and Future Research

Although increasing focus has been placed on the overlap between MASLD and viral hepatitis, some major aspects of the disease interaction are still not fully understood. Firstly, while previous experimental work has shown that HBV can interfere with metabolic pathways inside liver cells, including those related to glucose and amino acids, these findings have mostly been limited to laboratory studies and need further confirmation in human model.[69] Secondly, some studies based on liver biopsy findings suggest that fatty liver may slow down the progression of fibrosis in HBV-infected individuals, which goes against earlier beliefs.[21] These gaps highlight the need for well-designed, long-term studies that look at how both conditions interact over time, ideally using combined clinical, molecular, and imaging data. Research efforts should also focus on finding reliable tools for diagnosis and on testing treatment strategies that address both metabolic and viral factors at once.

Conclusion

As the prevalence of liver disease continues to grow globally, it has become increasingly crucial to comprehend the interaction between MASLD and viral hepatitis. These conditions have common underlying mechanisms, such as insulin resistance and the accumulation of fat in the liver, that not only speed up disease progression but also complicate diagnosis and treatment. When these diseases co-occur, the likelihood of severe complications, including liver cancer, rises significantly. Regrettably, existing diagnostic tools and treatments often do not adequately address both conditions simultaneously. There is a clear demand for a more integrated approach that aligns expertise from various fields of care to better assist patients dealing with this intricate overlap.

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

Financial Disclosure: The authors received no financial support for the research, authorship, and/or publication of this article.

Use of AI for Writing Assistance: The authors declare that no artificial intelligence (AI)-assisted technologies were used in the production of this manuscript.

Author Contributions: ME, IS, HA; Design – ME, KK; Supervision – ME; Data Collection and/or Processing – ME, DS; Analysis and/or Interpretation – ME, DS, KK; Literature Search – KK, HA, FY; Writing – ME, DS, IS, HA, FY; Critical Reviews KK, IS, HA, FY.

Peer-review: Externally peer-reviewed.

References

1. 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]
2. Zhang J, Lin S, Jiang D, Li M, Chen Y, Li J, Fan J. Chronic hepatitis B and non-alcoholic fatty liver disease: Conspirators or competitors? Liver Int 2020;40(3):496-508. [CrossRef]
3. Hassan F, Farman M, Khan KA, Awais M, Akhtar S. Prevalence of nonalcoholic fatty liver disease in Pakistan: A systematic review and meta-analysis. Sci Rep 2024;14(1):19573. [CrossRef]
4. Revill PA, Chisari FV, Block JM, Dandri M, Gehring AJ, Guo H, et al. A global scientific strategy to cure hepatitis B. Lancet Gastroenterol Hepatol 2019;4(7):545-558. [CrossRef]
5. Hasanoglu I, Rivero-Juárez A, Özkaya Şahin G, ESCMID Study Group for Viral Hepatitis. When metabolic dysfunction-associated steatotic liver disease meets viral hepatitis. J Clin Med 2025;14(10):3422. [CrossRef]

6. Makuza JD, Jeong D, Binka M, Adu PA, Cua G, Yu A, et al. Impact of hepatitis B virus infection, non-alcoholic fatty liver disease, and hepatitis C virus co-infection on liver-related death. Viruses 2022;14(11):2579. [CrossRef]
7. Subhan Butt A. Epidemiology of viral hepatitis and liver diseases in Pakistan. Euroasian J Hepato Gastroenterol 2015;5(1):43-48. [CrossRef]
8. Tacke F, Horn P, Wai-Sun Wong V, Ratziu V, Bugianesi E, Francque S, et al. EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease. J Hepatol 2024;81(3):492-542. [CrossRef]
9. Loomba R, Wong VW. Implications of the new nomenclature of steatotic liver disease and definition of metabolic dysfunction-associated steatotic liver disease. Aliment Pharmacol Ther 2024;59(2):150-156. [CrossRef]
10. Paik JM, Henry L, Younossi Y, Ong J, Alqahtani S, Younossi ZM. The burden of nonalcoholic fatty liver disease is rapidly growing in every region of the world from 1990 to 2019. Hepatol Commun 2023;7(10):e0251. [CrossRef]
11. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67(1):328-357. [CrossRef]
12. Tong X, Wan Y, Yin S, Shao L, Yao R, Ma X, et al. Comprehensive analysis of chronic hepatitis B concurrent with non-alcoholic fatty liver disease: A proteomics report based on clinical liver samples. Clin Proteomics 2025;22(1):19. [CrossRef]
13. Al-Busafi SA, Al Balushi AS, Al Shuaili HH, Mahmood DA, Al Alawi AM. Prevalence of non-alcoholic fatty liver disease and its impact on fibrosis risk in inactive chronic hepatitis B patients. J Clin Med 2024;13(16):4738. [CrossRef]
14. Adinolfi LE, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific genotype and visceral obesity. Hepatology 2001;33(6):1358-1364. [CrossRef]
15. NAFLD and HBV interplay related mechanisms underlying liver disease progression. Front Immunol 2022;13:965548. [CrossRef]
16. Zeng G, Holmes BR, Alqahtani SA, Gill US, Kennedy PTF. The co-existence of NAFLD and chronic hepatitis B is associated with suboptimal viral and biochemical response to antiviral therapy: A systematic review and meta-analysis. Front Gastroenterol 2024;3:1333988. [CrossRef]
17. Li HD, Liu YN, Wu S, Quan XF, Wang XY, Xiang TD, et al. Influence of non-alcoholic fatty liver disease on the therapeutic effect of nucleoside analogs for hepatitis B virus. World J Hepatol 2024;16(12):1395-1406. [CrossRef]
18. Shah AS, Khan S, Rahim H, Chishti KA, Khan AG. Prevalence of nonalcoholic fatty liver and nonalcoholic steatohepatitis in Peshawar Cantonment, Pakistan. Pak J Pharm Sci 2018;31(1):193-198.
19. Khurshid Bhatti T, Kamani L. Fatty liver disease in Pakistan: An underestimated threat. World Gastroenterol Organ 2024;29(3).
20. Huang SC, Liu CJ. Chronic hepatitis B with concurrent metabolic dysfunction-associated fatty liver disease: Challenges and perspectives. Clin Mol Hepatol 2023;29(2):320-331. [CrossRef]
21. Yao R, Lu S, Xue R, Wang J, Qiu Y, Chen Y, et al. NAFLD is associated with less severe liver fibrosis in chronic hepatitis B: A multicenter retrospective study. Ann Hepatol 2024;29(1):101155. [CrossRef]
22. Wong YJ, Nguyen VH, Yang HI, Li J, Le MH, Wu WJ, et al. Impact of fatty liver on long-term outcomes in chronic hepatitis B: a systematic review and matched analysis of individual patient data meta-analysis. Clin Mol Hepatol 2023;29(3):705-720. [CrossRef]
23. Hu D, Wang P, Wang X, Hu X, Huang D, Yan W, et al. Disease severity and antiviral response in patients with chronic hepatitis B with non-obese NAFLD. J Formos Med Assoc 2024;123(7):773-780. [CrossRef]
24. De Siervi S, Cannito S, Turato C. Chronic liver disease: Latest research in pathogenesis, detection and treatment. Int J Mol Sci 2023;24(13):10633. [CrossRef]
25. Fernandez CJ, Alkhalifah M, Afsar H, Pappachan JM. Metabolic dysfunction-associated fatty liver disease and chronic viral hepatitis: The interlink. Pathogens 2024;13(1):68. [CrossRef]
26. Geh D, Manas DM, Reeves HL. Hepatocellular carcinoma in non-alcoholic fatty liver disease: A review of an emerging challenge facing clinicians. Hepatobiliary Surg Nutr 2021;10(1):59-75. [CrossRef]
27. Petagine L, Zariwala MG, Patel VB. Non-alcoholic fatty liver disease: Immunological mechanisms and current treatments. World J Gastroenterol 2023;29(32):4831-4850. [CrossRef]
28. Ziolkowska S, Binienda A, Jabłkowski M, Szemraj J, Czarny P. The interplay between insulin resistance, inflammation, oxidative stress, base excision repair and metabolic syndrome in nonalcoholic fatty liver disease. Int J Mol Sci 2021;22(20):11128. [CrossRef]
29. Mao T, Yang R, Luo Y, He K. Crucial role of T cells in NAFLD-related disease: A review and prospect. Front Endocrinol 2022;13:1051076. [CrossRef]
30. Ramadori P, Kam S, Heikenwalder M. T cells: Friends and foes in NASH pathogenesis and hepatocarcinogenesis. Hepatology 2022;75(4):1038-1049. [CrossRef]
31. Rafaqat S, Gluscevic S, Mercantepe F, Rafaqat S, Klisic A. Interleukins: Pathogenesis in non-alcoholic fatty liver disease. Metabolites 2024;14(3):153. [CrossRef]
32. Paquissi FC. Immunity and fibrogenesis: The role of Th17/IL-17 axis in HBV and HCV-induced chronic hepatitis and progression to cirrhosis. Front Immunol 2017;8:1195. [CrossRef]
33. Khanam A, Chua JV, Kottilil S. Immunopathology of chronic hepatitis B infection: Role of innate and adaptive immune response in disease progression. Int J Mol Sci 2021;22(11):5497. [CrossRef]
34. Osuch S, Laskus T, Perlejewski K, Berak H, Bukowska-Ośko I, Pollak A, et al. CD8+ T-cell exhaustion phenotype in chronic hepatitis C virus infection is associated with epitope sequence variation. Front Immunol 2022;13:832206. [CrossRef]
35. Elgretli W, Chen T, Kronfli N, Sebastiani G. Hepatitis C virus-lipid interplay: Pathogenesis and clinical impact. Biomedicines 2023;11(2):271. [CrossRef]
36. Tourkochristou E, Assimakopoulos SF, Thomopoulos K, Marangos M, Triantos C. NAFLD and HBV interplay: Related mechanisms underlying liver disease progression. Front Immunol 2022;13:965548. [CrossRef]
37. Metabolic dysfunction-associated fatty liver disease and chronic viral hepatitis: The interlink. Pathogens 2024;13(1):68. [CrossRef]
38. Patel A, Harrison SA. Hepatitis C virus infection and nonalcoholic steatohepatitis. Gastroenterol Hepatol (N Y) 2012;8(5):305-312.
39. Liu J, Wu A, Cai J, She ZG, Li H. The contribution of the gut-liver axis to the immune signaling pathway of NAFLD. Front Immunol 2022;13:968799. [CrossRef]
40. Zhou M, Lv J, Chen X, Shi Y, Chao G, Zhang S. From gut to liver: Exploring the crosstalk between gut-liver axis and oxidative stress in metabolic dysfunction-associated steatotic liver disease. Ann Hepatol 2025;30(1):101777. [CrossRef]
41. Dai YN, Xu CF, Pan HY, Chen MJ, Yu CH. Fatty liver is associated with significant liver inflammation and increases the burden of advanced fibrosis in chronic HBV infection. BMC Infect Dis 2023;23:637. [CrossRef]
42. Chen JYS, Chua D, Lim CO, Ho WX, Tan NS. Lessons on drug development: A literature review of challenges faced in nonalcoholic fatty liver disease clinical trials. Int J Mol Sci 2022;24(1):158. [CrossRef]
43. Megahed FAK, Zhou X, Sun P, Elmaghrabi MM. The interplay between non-alcoholic fatty liver disease and innate immunity in hepatitis B virus patients. Egypt Liver J 2021;11(1):16. [CrossRef]
44. Azarkar G, Doosti Z, Osmani F, Ziaee M. Analysis of risk factors for non-alcoholic fatty liver disease in hepatitis B virus infection: A case-control study. Hepat Med 2019;11:153-158. [CrossRef]
45. Cleveland E, Bandy A, VanWagner LB. Diagnostic challenges of non-alcoholic fatty liver disease/nonalcoholic steatohepatitis. Clin Liver Dis 2018;11(4):98-104. [CrossRef]

46. Tao X, Chen L, Zhao Y, Liu Y, Shi R, Jiang B, et al. A novel noninvasive diagnostic model of HBV-related inflammation in chronic hepatitis B virus infection patients with concurrent nonalcoholic fatty liver disease. Front Med 2022;9:862879. [CrossRef]
47. Impact of NAFLD on the outcome of patients with chronic hepatitis B in Asia. Liver Int 2022;42:15252. [CrossRef]
48. European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH clinical practice guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol 2015;63(1):237-264. [CrossRef]
49. Li Q, Huang C, Xu W, Hu Q, Chen L. Accuracy of FibroScan in analysis of liver fibrosis in patients with concomitant chronic hepatitis B and nonalcoholic fatty liver disease. Medicine (Baltimore) 2020;99(23):e20616. [CrossRef]
50. Unalp-Arida A, Ruhl CE. Liver fibrosis scores predict liver disease mortality in the United States population. Hepatology 2017;66(1):84-95. [CrossRef]
51. Prasad M, Gupta S, Kashyap N, Kapil U. Diagnostic performance of non-invasive liver fibrosis risk scores in biopsy-proven non-alcoholic fatty liver disease patients in India. Indian J Gastroenterol 2023;42(2):192-198. [CrossRef]
52. Hadizadeh F, Faghihimani E, Adibi P. Nonalcoholic fatty liver disease: Diagnostic biomarkers. World J Gastrointest Pathophysiol 2017;8(2):11. [CrossRef]
53. Athish K, Nayak Rao S, Marimuthu VH, Krishna V, Arun A. Tenofovir-associated kidney dysfunction and bone fracture: A case report and literature review. Cureus 2024;16(6):e61562. [CrossRef]
54. He MW, Cui L, Chen DD, Zhao Y, Luo WZ, Jia YF, et al. Efficacy and safety of switching from entecavir to tenofovir alafenamide in chronic hepatitis B patients with low-level viremia: A real-world 48-week extension study. Antimicrob Agents Chemother 2025;69(3):e01827-24. [CrossRef]
55. Conjeevaram HS, Wahed AS, Afdhal N, Howell CD, Everhart JE, Hoofnagle JH, et al. Changes in insulin sensitivity and body weight during and after peginterferon and ribavirin therapy for hepatitis C. Gastroenterology 2011;140(2):469-477. [CrossRef]
56. Jung HJ, Kim YS, Kim SG, Lee YN, Jeong SW, Jang JY, et al. The impact of pegylated interferon and ribavirin combination treatment on lipid metabolism and insulin resistance in chronic hepatitis C patients. Clin Mol Hepatol 2014;20(1):38-46. [CrossRef]
57. Cespiati A, Coelho Rodrigues I, Santos I, Policarpo S, Carvalhana S, Fracanzani AL, et al. Effect of HCV eradication by DAAs on liver steatosis, carotid atherosclerosis, and associated metabolic comorbidities: A systematic review. Liver Int 2024;44(5):1075-1092. [CrossRef]
58. Liu L, Li H, Zhang Y, Zhang J, Cao Z. Hepatitis B virus infection combined with nonalcoholic fatty liver disease: Interaction and prognosis. Heliyon 2023;9(1):e13113. [CrossRef]
59. Hanif H, Khan MM, Ali MJ, Shah PA, Satiya J, Lau DTY, et al. A new endemic of concomitant nonalcoholic fatty liver disease and chronic hepatitis B. Microorganisms 2020;8(10):1526. [CrossRef]
60. Gitto S, Cicero AFG, Loggi E, Giovannini M, Conti F, Grandini E, et al. Worsening of serum lipid profile after direct acting antiviral treatment. Ann Hepatol 2018;17(1):64-75. [CrossRef]
61. Hashem Sultan A, Sharaf-Eldin MAE, Mosaad Soliman S, Elkhouly RAE. Glucose and lipid profile changes in hepatitis C patients after direct acting antivirals therapy. Int J Trop Dis Health 2021;12-24. [CrossRef]
62. Njei B, Al-Ajlouni Y, Lemos SY, Ugwendum D, Ameyaw P, Njei LP, et al. Efficacy and safety of GLP-1 receptor agonists in patients with metabolic dysfunction-associated steatotic liver disease: A systematic review and meta-analysis of randomized controlled trials. Cureus 2024;16(10):e71366. [CrossRef]
63. Noor S, Ismail M, Haider I, Khadim F. Drug-drug interactions in hepatitis patients: Do these interactions matter in clinical perspectives? Ann Hepatol 2018;17(6):1001-1011. [CrossRef]
64. Farooq J, Sana MM, Chetana PM, Almuqbil M, Prabhakar Bhat N, Sultana R, et al. Polypharmacy in chronic liver disease patients: Implications for disease severity, drug-drug interaction, and quality of life. Saudi Pharm J 2023;31(8):101668. [CrossRef]
65. Francque SM, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, et al. A randomized, controlled trial of the pan-PPAR agonist lanifibranor in NASH. N Engl J Med 2021;385(17):1547-1558. [CrossRef]
66. Lin C, Yu B, Chen L, Zhang Z, Ye W, Zhong H, et al. Obeticholic acid induces hepatotoxicity via FXR in NAFLD mice. Front Pharmacol 2022;13:880508. [CrossRef]
67. Sanyal AJ, Lopez P, Lawitz EJ, Lucas KJ, Loeffler J, Kim W, et al. Tropifexor for nonalcoholic steatohepatitis: An adaptive, randomized, placebo-controlled phase 2a/b trial. Nat Med 2023;29(2):392-400. [CrossRef]
68. Sutradhar R, Dalal DC. Combination therapy for chronic hepatitis B using capsid recycling inhibitor. Arxiv 2024. Preprint. doi: 10.48550/arXiv.2402.07701 [CrossRef]
69. Xie Q, Fan F, Wei W, Liu Y, Xu Z, Zhai L, et al. Multi-omics analyses reveal metabolic alterations regulated by hepatitis B virus core protein in hepatocellular carcinoma cells. Sci Rep 2017;7:41089. [CrossRef]

Case Report

Hepatic granulomas heralding vasculitides

HEPATOLOGY FORUM

doi: 10.14744/hf.2025.45561

Hepatic granulomas heralding eosinophilic granulomatosis with polyangiitis overlapping with Sjögren's syndrome

Tayssir Ben Achour[1,2], Fatma Saïd[1,2], Abir Chérif[1,2], Maysam Jridi[1,2], Imed Ben Ghorbel[1,2], Ines Naceur[1,2], Monia Smiti[1,2]

[1]Departement of Internal Medicine, University Hospital La Rabta, Tunisia; [2]University Tunis El Manar, Faculty of Medicine of Tunisia, Tunisia

Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAVs) encompass a group of rare autoimmune diseases characterized by granuloma formation and/or inflammation of small vessels. The clinical spectrum of AAV varies widely. Liver involvement is exceptional, posing diagnostic challenges. Moreover, AAV can co-exist with other systemic diseases, further complicating the diagnosis. We herein present a unique case of AAV overlapping with Sjögren's syndrome (SS) with an uncommon onset of the disease. A 47-year-old female was admitted for hiatal hernia surgery. During the intervention, nodular hepatomegaly was observed. A liver biopsy was performed, showing non-necrotizing epithelioid and central giant cell granulomas. Computed tomography (CT) scan showed perilymphatic pulmonary micronodules with bilateral hilar lymphadenopathies, raising the suspicion of sarcoidosis. Minor salivary gland biopsy revealed Chisholm grade 3 sialadenitis, which, along with the patient's dry eye and mouth symptoms, confirmed SS. Immunological workup showed negative antinuclear antibodies and positive anti-myeloperoxidase (MPO) antibodies. A year later, the patient presented with asthma flare-ups and ear, nose, and throat (ENT) symptoms. A nasal biopsy showed signs of eosinophilic leukocytoclastic vasculitis, confirming the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA). Oral steroid therapy was initiated, which resulted in clinical improvement. We present a case highlighting that EGPA is a protean disease, possibly mimicking or co-occurring with other autoimmune disorders. Thus, it is important to consider the differential diagnoses and carefully monitor for any new symptom or organ dysfunction.

Keywords: ANCA-associated vasculitis; hepatic granuloma; late-onset asthma; leukocytoclastic vasculitis; Sjögren's syndrome.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) are a group of rare autoimmune diseases belonging to the small vessel vasculitis group, according to the Chapel Hill classification, characterized by the formation of granulomas and/or inflammation of small vessels. The clinical spectrum of AAV is large, ranging from benign skin lesions to potentially fatal multisystem dysfunction. The most commonly affected organs are the kidneys, lungs, and peripheral nerves. Yet almost any organ can be affected, often making the diagnosis challenging. Hepatic granulomatosis is an atypical localization during eosinophilic granulomatosis with polyangiitis (EGPA). In addition to its frequently misleading presentations, possibly mimicking other conditions, AAV can co-occur with different systemic diseases, thus further delaying and complicating the diagnosis. Herein, we present a case of an unusual revealing mode of an AAV overlapping with Sjögren's syndrome (SS).

Case Report

A 47-year-old female with a history of benign breast tumor resection was admitted to the surgical department for symptomatic hiatal hernia. During the surgery, nodular hepatomegaly was discovered and biopsied. Extemporaneous examination showed non-necrotizing epithelioid and central giant cell granulomas (Fig. 1a). Sarcoidosis was suspected; thus, the patient was referred to the internal medicine ward.

Patient interrogation revealed a history of allergic rhinitis and late-onset asthma with frequent flare-ups, treated by bronchodilators and inhaled steroids for over four years. Physical examination revealed papulonodular lesions of the eyelids resembling sarcoid. Blood and urine tests were strictly normal, including liver work-up, inflammation markers, and blood eosinophil count. Tuberculin skin test and liquid mycobacterial cultures were negative.

Chest X-ray showed an apical left lung partially excavated opacity and an interstitial lung pattern. Computed tomography (CT) of the chest, abdomen, and pelvis showed perilymphatic pulmonary micronodules consistent with diffuse interstitial lung disease, a "Galaxy sign" of the left upper lobe, bilateral hilar lymphadenopathies, and an enlarged liver. The total cell count in the bronchoalveolar lavage fluid was slightly higher than normal (250,000 cells per ml), and the CD4/CD8 ratio was 2.3. Spirometry showed a slightly restrictive pattern with a forced expiratory volume in 1 second of 68% and a forced vital capacity of 74%.

In addition to pulmonary symptoms, the patient complained of dry mouth and dry eye sensation, polyarthralgia, and tingling sensation of the feet. The unstimulated whole saliva flow rate and Schirmer's test

How to cite this article: Ben Achour T, Saïd F, Cherif A, Jridi M, Ghorbel IB, Naceur I, Smiti M. Hepatic granulomas heralding eosinophilic granulomatosis with polyangiitis overlapping with Sjögren's syndrome. Hepatology Forum 2026; 7(1):77–80.

Received: February 12, 2025; **Revised:** July 29, 2025; **Accepted:** August 11, 2025; **Available online:** September 24, 2025

Corresponding author: Tayssir Ben Achour; Departement of Internal Medicine, University Hospital La Rabta, Tunis; Faculty of Medicine of Tunis, University Tunis El Manar, Tunisia

Phone: +21655235180; **e-mail:** tayssir.benachour2017@gmail.com

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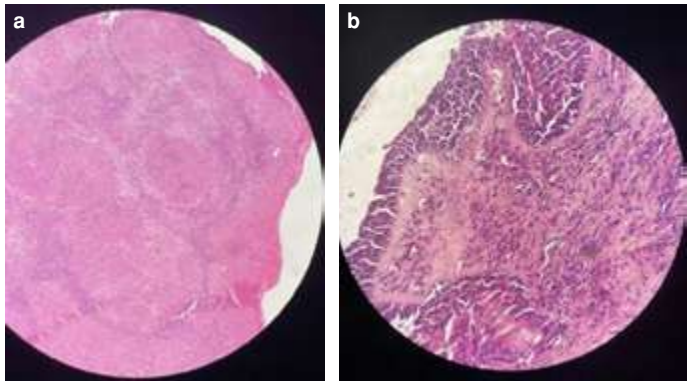

Figure 1. (a) Extemporaneous examination showed non-necrotizing epithelioid and central giant cell granulomas. **(b)** Nasal biopsy revealed eosinophilic leukocytoclast.

were both abnormal. A minor salivary gland biopsy was performed and revealed Chisholm grade 3 sialadenitis with no granuloma. Immunologic work-up showed negative antinuclear antibodies and positive perinuclear ANCA (P-ANCA), myeloperoxidase (MPO). Transthoracic echocardiogram and electromyography were normal.

The patient was diagnosed with SS. She was prescribed eye drops and bromhexine. A year later, she presented with epistaxis, and an ENT examination showed a hypertrophied nasal mucosa with multiple ulcerations and signs of nasal obstruction. A nasal biopsy revealed eosinophilic leukocytoclastic vasculitis (Fig. 1b).

Maxillofacial CT showed a deviated nasal septum with a left concha bullosa with middle and inferior turbinate swelling and hypertrophy (Fig. 2). Therefore, the diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) was confirmed according to the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria. The patient was treated with oral steroid therapy at a dose of 0.5 mg/kg/day. She showed significant clinical improvement with no recurrence of asthma flare-ups.

Discussion

AAVs have witnessed a significant and obvious increase in incidence and prevalence during the last few years, which is most likely explained by a better understanding of the disease and better case definition due to standardized diagnostic criteria. Recent studies, however, have reported a prevalence of 300–421 cases per million persons[1] and an annual incidence of 33 cases per million persons, only four of which are EGPA (12% of all AAVs).[2]

According to a recent US study comparing the incidence and prevalence of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA), it is certain that EGPA is the rarest among all AAVs, with an incidence of 0.5–2.3 per 1 million person-years vs. 0.4–11.9 for GPA and 0.5–24 for MPA, and a prevalence of EGPA of 2–22 per million persons vs. 2.9–146 for GPA and 9–94 for MPA.[3]

The mean age of onset of AAVs is reported to be 65 years, with extremes in GPA between 8 and 99 years. According to a Tunisian study, the mean age is 56 years, with extremes between 5 and 72. It is important to mention that the mean age of EGPA onset is generally lower than that in other AAVs. Moreover, patients with ANCA (usually anti-MPO)-positive EGPA are older than those with ANCA-negative EGPA.[3]

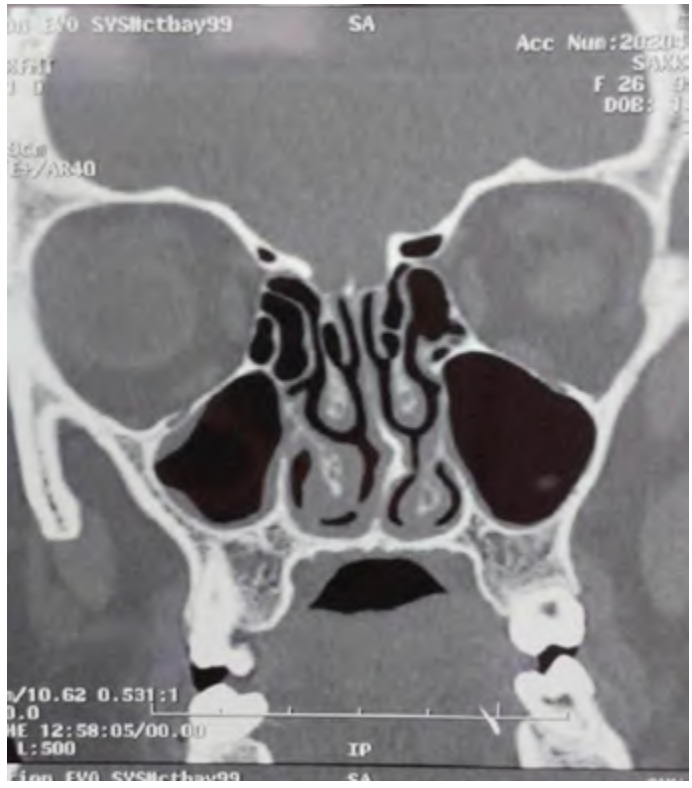

Figure 2. Maxillofacial computed tomography showed a deviated nasal septum with a left concha bullosa with middle and inferior turbinate swelling and hypertrophy.

For all AAVs, no significant sex difference has been reported, with a sex ratio varying between 1:1 and 1.9:1. For EGPA, however, the sex ratio was 6:1 in a Latin American study. In contrast, males had higher disease activity in EGPA.[3]

ANCA-activated neutrophils release autoantigens from vulnerable microvascular beds and present them to antigen-presenting cells. These autoantigens are recognized by effector T cells, thus causing further injury.

As for EGPA, pathogenesis is substantially different from that of GPA and MPA. EGPA can be ANCA negative; in this case, it is the role of the genes affecting the barrier function and causing mucosal dysfunction. Lyons et al.[4] reported 11 loci associated with EGPA, influencing eosinophil count and underlying asthma. In this case, interleukin 5 (IL-5) is the main cytokine involved, and serum IL-5 levels may be increased. As for ANCA-positive EGPA, it is an eosinophilic autoimmune disease similar to other AAVs, but a direct relationship between anti-MPO and eosinophils has not yet been demonstrated.

The clinical spectrum of EGPA varies widely, but it typically involves the upper and lower respiratory tract, manifesting as nasal polyps, chronic sinusitis, allergic rhinitis, and late-onset asthma. EGPA-related asthma is typically resistant to inhaled steroids and necessitates continuous use of oral corticosteroids, which may have severe side effects. Other respiratory manifestations include pulmonary nodules, interstitial lung disease, and pleural effusion, further underlying the importance of chest CT in diagnosing and monitoring disease activity for prognostic purposes. The second most common organ dysfunction is in the peripheral nervous system, which is polyneuropathy or mononeuritis multiplex, which can be severe.

As supported by the literature, the liver is not typically one of the target organs of AAV. Hepatic involvement in AAV is more associated with GPA than with MPA or EGPA and ranges from asymptomatic elevation of liver enzymes and subclinical liver fibrosis to severe events such as acute or necrotizing hepatitis, hepatic thrombosis, hepatic aneurysms potentially responsible for hemorrhagic shock, and fatal hepatic encephalopathy.[5]

There have been rare reports of hepatic granulomas associated with AAV, most of which are about GPA. Shah et al.[6] reported a case of post-mortem diagnosis of GPA based on the presence of "perivascular and periportal non-caseating granuloma with multinucleated and Langhans' type giant cells" and "necrotizing vasculitis of a small vein" in a liver pathology at autopsy. Grigoriou et al.[7] reported a case of a 22-year-old female with a history of asthma presenting with severe abdominal pain and vomiting, elevated transaminases, positive ANCA antibodies, patchy areas of liver attenuation on CT, and liver biopsy consistent with EGPA. Darnall et al.[8] reported a case of a 66-year-old female with a history of EGPA who presented with abdominal fullness and lower limb edema, liver cirrhosis on CT angiography, and liver biopsy revealing granulomatous formation, eosinophilic infiltration, and vasculitis.

Gastrointestinal manifestations are very rare in EGPA. They are due to eosinophilic infiltration and may vary from abdominal pain to severe intestinal hemorrhage, obstruction, or perforation.

SS is a connective tissue disorder that frequently overlaps with other connective tissue disorders, notably rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic scleroderma (SSc). On the other hand, it rarely overlaps with vasculitis such as AAV. The 44 cases of overlapping AAV and primary SS (pSS) reported in the literature showed that, in addition to the possible positivity of ANCA antibodies in SS, authentic AAV may occur in patients with pSS. Most cases had positive p-ANCA with anti-MPO specificity, and the vast majority presented with SS previously or concomitantly with AAV, as was the case with our patient.

Bilateral hilar lymphadenopathies are typically associated with infections and malignancies. When these are ruled out, sarcoidosis is the most likely diagnosis, especially when biopsy reveals non-caseating granulomas, as was the case with our patient. Although the co-existence of all three diseases seems very unlikely, we found one similar Japanese case reported by Tsuji et al.[9] AAV and SS are among the rare causes of hilar lymphadenopathies. In this situation, particular attention should be paid to patients with SS because they are at a higher risk of lymphoma.

Morbidity and mortality rates in patients with EGPA are related to the severity of respiratory and cardiac manifestations. However, in this study, we aimed to assess the prognosis of patients with hepatic lesions. As mentioned, hepatic manifestations in AAVs vary widely, from asymptomatic hepatic granuloma or liver function test (LFT) abnormalities to liver fibrosis and fulminant hepatitis. Studies showed that increased gamma-GT values were correlated with an increased disease activity score and were more associated with pulmonary and renal involvement and a longer time to remission, but data are limited to patients with GPA. Classical oral corticosteroid treatment alone relieved the symptoms of our patient.

Based on this case and according to the literature, it seems that asthma in ANCA-positive EGPA is less severe than that in seronegative EGPA. In the latter case, mepolizumab (anti-IL5 monoclonal antibody) seems to be the most effective treatment. Hepatic involvement can present with various clinical manifestations. It may be completely asymptomatic, as in our patient, associated with abnormalities in LFTs, or manifest as a severe presentation with hepatocellular failure.[5]

Conclusion

Initial presentation can be strongly misleading, as was the case with our patient whose liver biopsy and chest CT scan indicated sarcoidosis. However, even with a positive ANCA antibody titer, we could not confirm the diagnosis of EGPA until the patient developed other, more typical disease manifestations. Therefore, it is crucial to consider all the differential diagnoses and to closely monitor key symptoms. If such symptoms emerge, physicians may need to reassess the diagnosis and consequently the therapeutic options, especially when a vital organ is involved.

Our observation highlighted a rare mode of presentation of EGPA and encourages clinicians to consider this diagnosis when faced with hepatic granulomatosis. It allowed us to address the difficulty of establishing the etiological diagnosis in the case of granulomatosis, given the variety of possible diagnoses. Association of a connective tissue disease (such as Sjögren's syndrome) and a vasculitis is possible, as in our case.

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 was obtained from participants.

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: No artificial intelligence (AI)–assisted technologies (such as Large Language Models, chatbots, or image generators) were used in the production of this manuscript.

Author Contributions: Concept – TBA, AC; Design – FS; Supervision – MS; Data Collection and/or Processing – MJ; Analysis and/or Interpretation – AC; Literature Search – IBG; Writing – TBA; Critical Reviews – IN.

Peer-review: Externally peer-reviewed.

References

1. Watts RA, Mahr A, Mohammad AJ, Gatenby P, Basu N, Flores-Suárez LF. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Nephrol Dial Transplant 2015;30(Suppl 1):i14-i22. [CrossRef]
2. Mohammad AJ, Jacobsson LT, Mahr AD, Sturfelt G, Segelmark M. Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg-Strauss syndrome within a defined population in southern Sweden. Rheumatology (Oxford) 2007;46(8):1329-1337. [CrossRef]
3. Berti A, Cornec D, Crowson CS, Specks U, Matteson EL. The epidemiology of antineutrophil cytoplasmic autoantibody-associated vasculitis in Olmsted County, Minnesota: A twenty-year US population-based study. Arthritis Rheumatol 2017;69(12):2338-2350. [CrossRef]
4. Lyons PA, Peters JE, Alberici F, Liley J, Coulson RMR, Astle W et al. Genome-wide association study of eosinophilic granulomatosis with polyangiitis reveals genomic loci stratified by ANCA status. Nat Commun 2019;10(1):5120. [CrossRef]
5. Pimentel-Quiroz VR, Sánchez-Torres A, Acevedo-Vásquez E, Gamboa-Cárdenas RV, Reátegui-Sokolova C, Medina-Chinchón M, et al. Demographic and clinical features of ANCA-associated vasculitides in a peruvian tertiary center. J Clin Rheumatol 2021;27(6S):S246-S251. [CrossRef]

6. Shah IA, Holstege A, Riede UN. Bioptic diagnosis of Wegener's granulomatosis in the absence of vasculitis and granulomas. Pathol Res Pract 1984;178(4):407-415. [CrossRef]
7. Grigoriou A, Endean A, Sangle SR, D'Cruz DP. B cell depletion therapy and eosinophilic granulomatosis with polyangiitis with hepatic involvement. Rheumatol (Oxford) 2014;53(10):1741. [CrossRef]
8. Darnall A, Parker K, Gburek S. Rare case of hepatic involvement caused by eosinophilic granulomatosis with polyangiitis. Clin Rheumatol 2023;42(9):2519-2520. [CrossRef]
9. Tsuji K, Okuyama Y, Asano Y, Yamaoka K, Kitamura S, Wada J. Co-occurrence of three systemic diseases: ANCA-associated vasculitis, Sjögren's syndrome and sarcoidosis. Intern Med 2023;62(15):2215-2221. [CrossRef]

Case Report

Hepatic steatosis after portal vein thrombosis

HEPATOLOGY FORUM

doi: 10.14744/hf.2025.76132

Focal hepatic steatosis as a rare complication of microwave ablation-induced portal vein thrombosis: A radiologic case report

Bisar Akbas, Ferhat Can Piskin, Hasan Bilen Onan, Ipek Yolay, Ege Gormez, Mustafa Kolkiran, Hazal Guleryuz, Senol Durak

Department of Radiology, Cukurova University School of Medicine, Adana, Turkiye

Abstract

Microwave ablation (MWA) is a widely used treatment for liver metastases, particularly for lesions smaller than 3 cm. Although generally safe, rare complications such as segmental or lobar portal vein thrombosis (PVT) can occur. We present a unique case of tumor-like focal fat deposition in the left hepatic lobe following left PVT, a rare complication of MWA, in a 59-year-old female with pancreatic adenocarcinoma liver metastasis. Post-ablation imaging revealed geographic-shaped areas of focal hepatic steatosis confined to the left lobe, accompanied by left PVT. Dual-echo MRI, a routine but highly effective imaging sequence for liver fat characterization, was instrumental in distinguishing benign fat deposition from tumor recurrence. This case highlights the importance of recognizing focal hepatic steatosis as a rare but significant complication of MWA and PVT, with implications for clinical management and follow-up strategies.

Keywords: Focal hepatic steatosis; microwave ablation; portal vein thrombosis.

Introduction

Microwave ablation (MWA) is an established, minimally invasive treatment for liver metastases, offering high efficacy for lesions smaller than 3 cm.[1] While generally well tolerated, rare complications such as segmental or lobar portal vein thrombosis (PVT) have been reported.[2] Hepatic steatosis following PVT is an exceedingly rare phenomenon, with only one reported case in the context of liver transplantation.[3] Focal hepatic steatosis and sparing are frequently encountered in radiology practice and are often related to regional perfusion alterations. Dual-echo MRI, a routine sequence in liver imaging, is crucial for identifying fat-containing hepatic lesions and differentiating them from tumor recurrence. This report presents a rare instance of focal hepatic steatosis following left PVT, a complication of MWA performed for liver metastasis from pancreatic adenocarcinoma. In addition to presenting the clinical and imaging findings, we discuss the underlying pathophysiology of steatosis in the context of altered hepatic perfusion and portal venous flow.

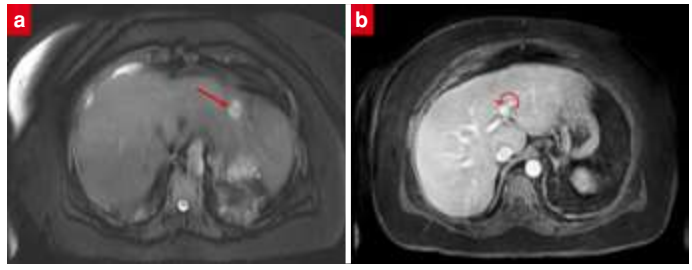

Figure 1. Pre-procedure T2-weighted MR imaging reveals a metastatic lesion in segment 2 (arrow) **(a)**. Portal phase MRI demonstrates that the left portal vein remains patent (curved arrow) **(b)**.

Case Report

A 59-year-old female patient underwent distal pancreatectomy and splenectomy for pancreatic adenocarcinoma. During routine follow-up one year later, a metastatic lesion measuring 23 × 18 mm was detected in liver segment 2 on abdominal magnetic resonance imaging (MRI) (Fig. 1). MWA was performed on the lesion (2+1 minutes, 150 watts) using a Covidien-brand antenna under ultrasound guidance by an interventional radiologist with over 9 years of experience. The procedure was performed under general anesthesia. Written informed consent was obtained from the patient, who voluntarily agreed to participate in the study.

Post-procedure abdominal CT was obtained on the same day to assess ablation efficacy and complications. The same-day CT confirmed the patency of the portal vein and inclusion of the metastatic lesion within the ablation zone. The patient was discharged the following day without complications. One month later, dynamic contrast-enhanced MRI and CT were performed as part of our institutional routine follow-up protocol. MRI revealed newly developed, T2 mildly hyperintense, geographic-shaped areas confined to the left lobe, without enhancement or diffusion restriction. Additionally, left PVT was observed. Fat suppression on out-of-phase images in the dual-echo sequence supported the diagnosis of focal hepatic steatosis (Fig. 2).

The patient exhibited a striking post-procedural elevation in CA 19-9 levels (>200-fold above ULN), which may be related to

How to cite this article: Akbas B, Piskin FC, Onan HB, Yolay I, Gormez E, Kolkiran M, et al. Focal hepatic steatosis as a rare complication of microwave ablation-induced portal vein thrombosis: A radiologic case report. Hepatology Forum 2026; 7(1):81–83.

Received: February 15, 2025; **Revised:** May 10, 2025; **Accepted:** June 19, 2025; **Available online:** November 14, 2025

Corresponding author: Bisar Akbas; Department of Radiology, Cukurova University School of Medicine, Adana, Turkiye
Phone: +90 546 404 44 33; **e-mail:** bisarakbas20@gmail.com

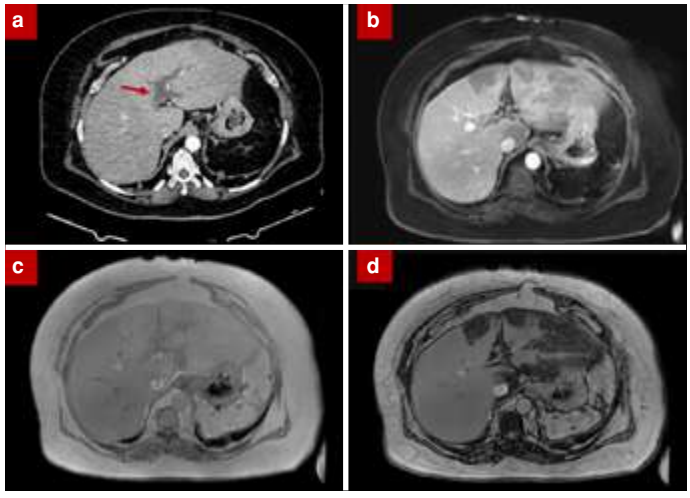

Figure 2. CT imaging demonstrates left portal vein thrombosis (arrow) **(a)**. MR images **(b–d)** reveal patchy, nonenhancing areas **(b)**, observed on dual-echo in-phase images **(c)**, corresponding to focal fatty infiltration in the left liver lobe, confirmed by out-of-phase imaging **(d)**.

emerging pulmonary metastases, although this remains speculative without confirmatory imaging. No local tumor recurrence or new hepatic lesions were identified. Elevated GGT and AST levels post-procedure, along with thrombocytosis, may reflect a combination of hepatic stress and systemic inflammatory response. The timing of laboratory tests ranged from one week before to one week after the procedure. A table summarizing laboratory values is provided (Table 1).

Discussion

Focal hepatic steatosis is a common imaging finding and is often related to regional alterations in hepatic perfusion.[3] In this rare case, focal hepatic steatosis developed in the left hepatic lobe following PVT induced by MWA. The pathophysiology likely involves decreased portal venous flow leading to localized hypoxia, impairment of lipid metabolism, and compensatory increase in hepatic arterial flow.[4,5] These changes may result in hepatocyte lipid accumulation and focal fatty infiltration. Experimental studies have supported the notion that regional hypoperfusion can induce hepatic steatosis by disrupting lipoprotein transport and altering hepatocellular metabolism.[6,7]

Although dual-echo MRI is a routine liver imaging sequence, its importance in characterizing focal hepatic fat is underscored in this case. The absence of enhancement and diffusion restriction, along with the presence of fat suppression in out-of-phase images, was key in differentiating benign steatosis from tumor recurrence, guiding appropriate clinical management.

MWA is generally safe, but PVT may occur due to thermal injury to adjacent vascular structures or the thrombogenic effects of ablated tissue. To minimize the risk of PVT, meticulous technique is crucial: maintaining a safe distance from major portal branches, using lower power settings near vascular structures, and ensuring proper needle placement are recommended. Routine follow-up after MWA in our institution includes an abdominal CT on the day of the procedure and dynamic contrast-enhanced MRI at 1 month to assess treatment response and detect early complications.

Table 1. Comparative analysis of laboratory parameters in pre- and post-ablation follow-up evaluations

Laboratory parameters	Pre-procedure	Post-procedure follow up
AST (U/L)	23	46
ALT (U/L)	15	35
GGT (U/L)	239	266
CA 19–9 (U/mL)	113	9397
Platelet count (cells/μL)	649000	434000
Bilirubin (mg/dL)	0.36	0.61
INR	0.97	1.03

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; INR: International normalized ratio.

In this case, the left portal vein was patent on immediate post-procedure CT. The subsequent development of PVT at 1 month suggests a delayed thrombotic process, possibly related to endothelial injury or local inflammation induced by the ablation. Laboratory parameters are typically not discussed in detail in the case presentation section. Here, they are summarized in Table 1 for clarity. While CA 19-9 elevation may indicate disease progression or distant metastasis (e.g., pulmonary), a definitive link requires further imaging. Further follow-up in this patient includes serial imaging to monitor for tumor recurrence and resolution or progression of PVT. MRI with dual-echo and diffusion-weighted imaging, in combination with laboratory markers, remains the mainstay of follow-up.

Conclusion

This case underscores the importance of recognizing focal hepatic steatosis as a rare but significant complication following MWA-induced PVT. Although dual-echo MRI is a routine imaging tool, its utility in differentiating fat deposition from tumor recurrence is critical for clinical decision-making. Awareness of this rare complication, combined with thoughtful imaging follow-up and careful procedural planning, can help optimize patient outcomes. Further research is needed to clarify the mechanisms linking altered portal perfusion to focal fat deposition and to refine post-ablation monitoring protocols.

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 was obtained from the patient, who voluntarily agreed to participate in the study.

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 study did not use AI-enabled technology.

Author Contributions: Concept – BA, FCP; Design – BA; Supervision – FCP, HBO; Fundings – IY; Materials – MK; Data Collection and/or Processing – HG, IY; Analysis and/or Interpretation – BA; Literature Search – EG, SD; Writing – BA, HG, IY; Critical Review – BA.

Peer-review: Externally peer-reviewed.

References

1. Crocetti L, de Baére T, Pereira PL, Tarantino FP. CIRSE standards of practice on thermal ablation of liver tumours. Cardiovasc Intervent Radiol 2020;43(7):951-962. [CrossRef]
2. Fang C, Cortis K, Yusuf GT, Gregory S, Lewis D, Kane P, et al. Complications from percutaneous microwave ablation of liver tumours: a pictorial review. Br J Radiol 2019;92(1099):20180864. [CrossRef]
3. Ogita K, Taguchi T, Soejima Y, Ieiri S, Katsura S, Takada N, et al. Fatty liver caused by portal vein thrombosis after living donor liver transplantation: a case report. J Pediatr Surg 2005;40(8):e7-e9. [CrossRef]
4. Taguchi S, Masumoto K, Yamanouchi T, Suita S. Decrease in hepatic circulation induces hepatic fibrosis in a neonatal piglet model with short bowel syndrome. J Pediatr Surg 2005;40(10):1592-1597. [CrossRef]
5. Zahmatkeshan M, Geramizadeh B, Eshraghian A, Nikeghbalian S, Bahador A, Salahi H, et al. *De novo* fatty liver due to vascular complications after liver transplantation. Transplant Proc 2011;43(2):615-617. [CrossRef]
6. Hashimoto N, Ishii H, Kitada T, Utsunomiya J. Significance of venous drainage for small-bowel allografts. Hepatogastroenterology 1992;39(6):511-514.
7. Starzl TE. Portal vein thrombosis and portal diversion. J Pediatr (Rio J) 1983;103:741-742. [CrossRef]