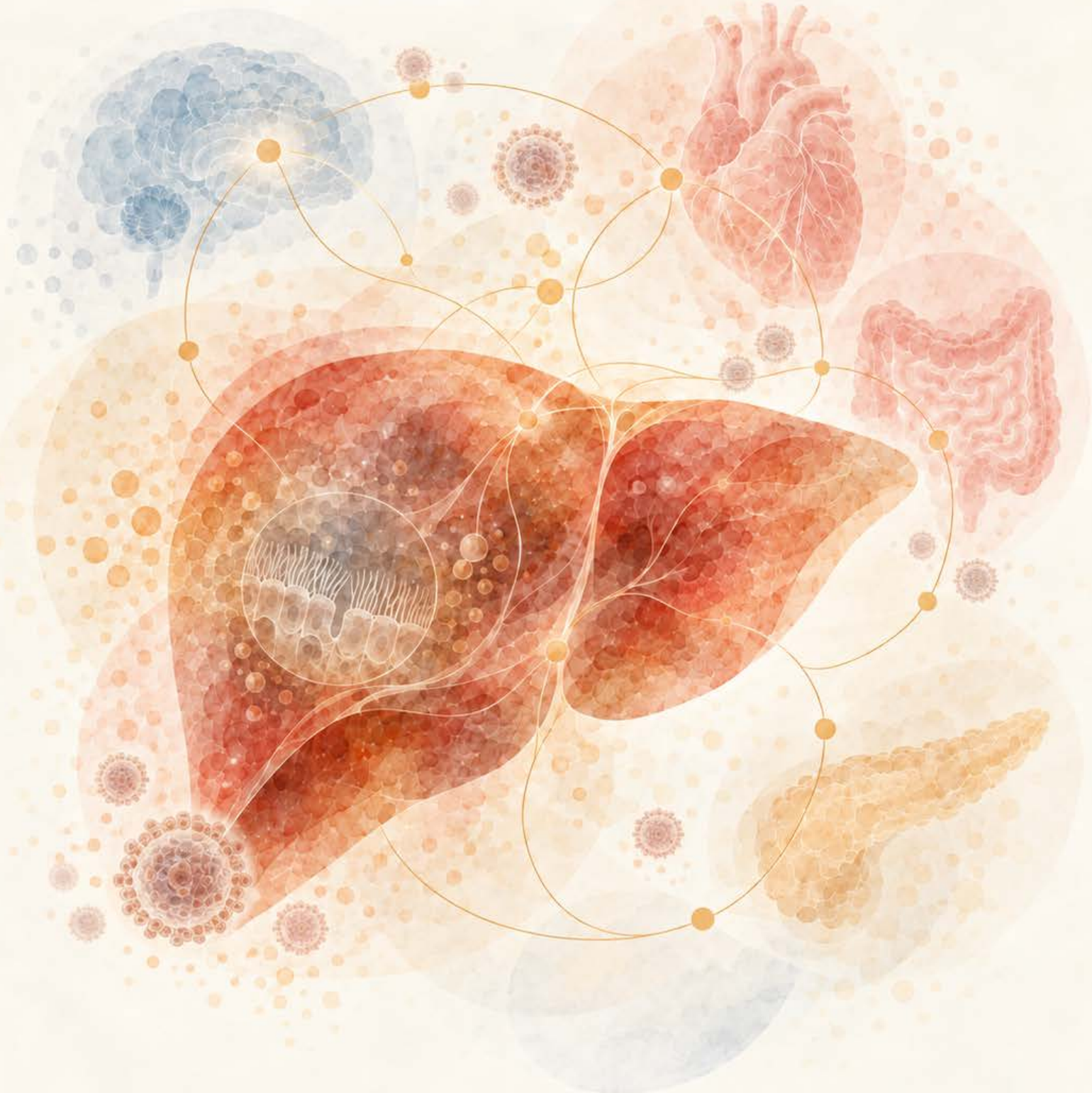
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HEPATOLOGY FORUM

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ORIGINAL RESEARCH

Efficacy of tenofovir alafenamide in patients with chronic hepatitis B undergoing chronic hemodialysis and kidney transplantation: A real-world data study

Abdullah Tokuc[1], Dinc Dincer[2], Digdem Ozer Etik[3], Abdullah Emre Yildirim[4], Shahin Mehdiyev[5], Derya Ari[6], Arif Mansur Cosar[7], Haydar Adanir[2], Hale Gokcan[8], Suna Yapali[9], Feyza Dilber[5], Sabite Kacar[6], Meral Akdogan[6], Nurdan Tozun[9], Sedat Boyacioglu[3], Ramazan Idilman[8], and TASL Viral Hepatitis Special Interest Group (SIG)

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Highlights & Insights

- **Scientific Gap:** Data on the efficacy and safety of TAF in patients undergoing chronic hemodialysis and in kidney transplant recipients remain limited.
- **Key Finding:** Virological response rates were 78.9% at month 12 and 94.7% at month 24, with improved serum ALT levels in patients with elevated baseline ALT levels, while renal function remained stable.
- **Clinical Impact:** These real-world findings support TAF as an effective and well-tolerated treatment option for these high-risk populations.

ABSTRACT

Background and Aim: This study evaluated the efficacy and safety of tenofovir alafenamide (TAF) in chronic hepatitis B virus-infected patients undergoing chronic hemodialysis and kidney transplant recipients.

Materials and Methods: Between January 2019 and January 2023, patients receiving TAF who were undergoing chronic hemodialysis or were kidney transplant recipients were included in a multicenter retrospective study at 17 tertiary care centers across Türkiye.

Results: A total of 58 patients were included (13 receiving hemodialysis and 45 kidney transplant recipients). The mean age of patients was 50.1±12.5 years, with a predominantly male gender (71%). At baseline, 19 patients were hepatitis B virus DNA-positive; 11 of whom were antiviral treatment-naïve. The virological response rate was 78.9% (15/19) at 12 months of TAF treatment and increased to 94.7% (18/19) by 24 months. Patients with elevated baseline alanine aminotransferase levels exhibited significant improvement after initiation of TAF. Overall, TAF was well tolerated throughout the study period, with no serious adverse events or drug discontinuations due to adverse effects.

Conclusion: TAF was associated with effective virological suppression and favorable biochemical response in patients with chronic HBV infection undergoing chronic hemodialysis and kidney transplant recipients. TAF was generally well tolerated in such patients.

Keywords: Chronic hepatitis B, hemodialysis, kidney transplantation, real-world data, tenofovir alafenamide.

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Introduction

Hepatitis B virus (HBV) infection is a major global public health concern, affecting over 250 million individuals.[1,2] HBV accounts for the majority of adult cases of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC) in Türkiye.[3–5] However, its prevalence has decreased over time. At present, interferons and nucleos(t)ide analogs (NAs) with high genetic barriers are recommended for the treatment of chronic hepatitis B (CHB).[1,2,6] NA treatment provides effective long-term viral suppression, reduces fibrosis, slows disease progression, and prevents HCC development in patients with CHB. The primary goal of antiviral treatment for HBV is to eliminate hepatitis B surface antigen (HBsAg) and achieve seroconversion to antibody to hepatitis B surface antigen (anti-HBs).[1–3] Current guidelines recommend high-genetic-barrier NAs, including entecavir, tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF), as first-line antiviral agents.[6]

TAF demonstrates efficacy comparable to TDF, showing non-inferior viral suppression and high rates of aminotransferase normalization. In addition, TAF is associated with fewer adverse effects, including reduced renal toxicity, a lower risk of hypophosphataemia, and less loss of bone mineral density. For these reasons, it is particularly preferred in patients at risk for chronic kidney disease or osteoporosis.[6,7] Several studies have investigated the efficacy and tolerability of TAF therapy in patients with CHB with or without cirrhosis.[1,7–10] However, data on the efficacy and safety of TAF treatment in hemodialysis patients and kidney transplant recipients are limited. The present study aimed to evaluate the efficacy and tolerability of TAF in chronic HBV-infected patients undergoing chronic hemodialysis and kidney transplant recipients.

Materials and Methods

This multicenter retrospective study included non-cirrhotic patients who were receiving hemodialysis or kidney transplantation and were followed at liver disease outpatient clinics at 17 tertiary care centers across Türkiye. All patients received TAF either as prophylaxis against HBV reactivation or as treatment for CHB. Medical records covering the period from January 2019 to January 2023 were retrospectively reviewed. Patients with cirrhosis were excluded from the study. A specific electronic case report form was developed for data collection and documentation. Data were collected and entered into the CRF at each center. This study was approved by the Marmara University Ethics Committee of the Marmara Medical School (June 12, 2020/09.2020.698), and written informed consent was waived due to the retrospective nature of the study. The study was conducted in accordance with the principles of the Declaration of Helsinki. TAF was administered at a dosage of 25 mg/day. In patients receiving chronic hemodialysis, TAF was administered after the dialysis session, and the timing of administration relative to the dialysis session was not otherwise standardized; this practice is consistent with pharmacokinetic data supporting TAF use in patients on dialysis.[11,12]

The laboratory investigations included serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase, total bilirubin, creatinine, fasting glucose levels, lipid profile (serum total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], very-low-density lipoprotein [VLDL], and triglyceride), and prothrombin time. Complete blood cell counts were obtained using the local central laboratory of each unit. HBsAg, anti-HBs, HBeAg, antibody to hepatitis B e antigen (anti-HBe), antibody to hepatitis B core antigen, and anti-delta were measured. HBV DNA levels were measured using the Roche COBAS TaqMan assay (lower limit of quantitation of 20 IU/mL). Patients with HBV DNA below the lower limit of quantitation at baseline were analyzed separately from patients with detectable baseline HBV DNA. Biochemical and serological test results obtained at treatment initiation and during follow-up were recorded.

The primary endpoint was to evaluate the efficacy of TAF in chronic HBV-infected patients undergoing chronic hemodialysis and in kidney transplant recipients. The secondary endpoint was to evaluate the tolerability and adverse effects of TAF in this population.

Safety

Safety and tolerability analyses were assessed during TAF treatment. Adverse events (AE), serious AEs, laboratory abnormalities, drug discontinuation due to AE, and deaths were evaluated. Serum creatinine levels 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 in the outpatient clinic at 3- or 6-month intervals after initiation of TAF treatment. Available clinical assessments, laboratory findings, treatment adherence data, and HBV virological and serological markers documented at baseline and during follow-up were recorded. Blood was drawn to determine the metabolic, biochemical, and serological parameters. HBV viral markers were all monitored. Follow-up data for up to 24 months after TAF initiation were evaluated. Complete virological response was defined as undetectable serum HBV DNA (<20 IU/mL).

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences, version 23 (IBM Corp., Armonk, NY, USA). Normality of distribution was assessed using the Shapiro-Wilk Test. The categorical data were analyzed by groups using Fisher's Exact Test and Fisher's Exact Test with Monte Carlo Correction, and multiple comparisons were made using the Bonferroni-corrected Z-test. The Independent Samples T-Test was used to compare normally distributed data across groups, and the Mann–Whitney U-Test was used to compare variables that did not meet normality assumptions. Repeated Measures Analysis of Variance was used to compare dependent data with a normal distribution measured at different times within each group, and the Friedman Test was used to compare dependent data

that did not conform to a normal distribution. Analysis results are presented as frequencies (percentages) for categorical variables and as means±standard deviations and medians (minimum–maximum) for quantitative variables. The level of significance was set at p<0.050.

Results

A total of 58 patients were included in the study: 13 receiving hemodialysis and 45 who had undergone kidney transplantation. All patients in the hemodialysis group were HBsAg-positive. Among the kidney transplant recipients, 10 were HBsAg-negative and anti-HBc-positive and received TAF prophylaxis against HBV reactivation during immunosuppressive therapy. The mean age of the participants was 50.1±12.5 years, with a predominantly male gender (71%). Among the patients, 8 of the 12 hemodialysis patients with available data and 11 of 45 kidney transplant recipients were antiviral treatment-naïve. Of the 45 transplant patients, six were receiving a single immunosuppressant, while 39 were on multiple therapies. HBeAg was positive in 9 of 42 patients (21.4%). Tacrolimus was the most commonly used single agent, whereas the multiple-therapy regimen consisted of tacrolimus, mycophenolate mofetil, and steroids. Immunosuppressive drug levels were not available in this cohort; therefore, no data on immunosuppressant dose adjustments during TAF treatment could be provided. The baseline characteristics of all patients are given in Table 1.

Nineteen patients were HBV DNA-positive at baseline; 11 of these were antiviral treatment-naïve (eight in the hemodialysis group and three in the transplant group). Baseline HBV DNA positivity rates were 84.6% (11/13) in the hemodialysis group and 17.8% (8/45) in the transplant group. Eleven patients (4 receiving hemodialysis and 7 post-kidney transplantation) had elevated baseline serum ALT levels (>40 U/L). When baseline laboratory values were compared between the two groups, mean serum phosphorus and creatinine levels were significantly higher in the hemodialysis group. In contrast, serum total cholesterol and HDL levels were significantly higher in the transplant group (Table 1). The remaining 39 patients (67.2%) had undetectable HBV DNA (<20 IU/mL) at the time of switching to TAF and were analyzed separately from the 19 patients with detectable baseline HBV DNA. Baseline and follow-up HBV serological and virological markers are summarized in Table 2.

Among the 19 patients with detectable HBV DNA at baseline, the complete virological response rates at 12 and 24 months were 78.9% (15/19) and 94.7% (18/19), respectively. Among the 11 hemodialysis patients with high baseline HBV DNA levels, 10 achieved HBV DNA undetectability during TAF treatment, while the remaining patient showed a marked reduction in HBV DNA – from 19,756,248 IU/mL at baseline to 450,000 IU/mL at month 12 and 23,000 IU/mL at month 24. This patient was anti-HBe positive at baseline. No HBeAg seroconversion occurred during TAF treatment. In the kidney transplantation group, all eight patients with high baseline HBV DNA levels became HBV DNA undetectable during TAF treatment. Serum ALT levels improved significantly in patients with elevated baseline ALT levels during TAF treatment (Table 3).

Fasting plasma glucose levels remained stable from baseline to the end of follow-up (median [min–max]: 91 [73–322] mg/dL vs. 95 [56–206] mg/dL; p=0.69). TAF was associated with a slight increase in serum lipid parameters. From baseline to end of follow-up visit, total cholesterol increased from 168.8±46.4 mg/dL to 172.5±48.1 mg/dL (p=0.41), HDL cholesterol increased from 41.4±14.2 mg/dL to 42.7±14.8 mg/dL (p=0.52), LDL cholesterol increased from 103.4±38.6 mg/dL to 106.1±39.7 mg/dL (p=0.47), and triglycerides increased from 158.6±70.2 mg/dL to 162.4±72.5 mg/dL (p=0.55) (Table 3).

Safety

TAF treatment was well tolerated. Headache, fatigue, and nausea were the most common adverse effects. No drug discontinuation was observed due to adverse effects. No significant clinical side effects or serious AE were reported. Renal function parameters were analyzed separately for the hemodialysis and kidney transplant groups. In the kidney transplant group, the mean eGFR-MDRD was 50.12±22.52 mL/min/1.73 m^2 at baseline (n=44), 63.86±22.69 mL/min/1.73 m^2 at month 12 (n=36), and 60.86±25.27 mL/min/1.73 m^2 at month 24 (n=29). Although eGFR-MDRD increased numerically over time, this change was not statistically significant (Friedman test, $\chi^2(2)=1.813$, p=0.404; Kendall's W=0.034).

In the hemodialysis group, the mean eGFR-MDRD was 10.71±5.38 mL/min/1.73 m^2 at baseline, 9.38±3.48 mL/min/1.73 m^2 at month 12, and 16.13±9.83 mL/min/1.73 m^2 at month 24 (Friedman test, $\chi^2(2)=0.200$, p=0.905; Kendall's W=0.010).

In the 10 hemodialysis patients with serum phosphorus measurements available at baseline, month 12, and month 24, the estimated mean serum phosphorus levels were 5.434 mg/dL (95% confidence interval [CI], 4.207–6.661) at baseline, 5.504 mg/dL (95% CI, 4.456–6.552) at month 12, and 5.624 mg/dL (95% CI, 4.937–6.311) at month 24; Bonferroni-adjusted pairwise comparisons indicated no significant differences between baseline and month 12 (mean difference: -0.070 mg/dL; adjusted p=1.000), baseline and month 24 (mean difference: -0.190 mg/dL; adjusted p=1.000), or months 12 and 24 (mean difference: -0.120 mg/dL; adjusted p=1.000). In the kidney transplant group, Bonferroni-adjusted pairwise comparisons showed no significant differences in serum phosphorus levels between baseline and month 12 (mean difference: 0.244 mg/dL, 95% CI: -0.300–0.788; adjusted p=0.775), baseline and month 24 (mean difference: 0.162 mg/dL, 95% CI: -0.325–0.650; adjusted p=1.000), or months 12 and 24 (mean difference: -0.082 mg/dL, 95% CI: -0.520–0.357; adjusted p=1.000).

Discussion

This multicenter study evaluated the efficacy and tolerability of TAF in chronic HBV-infected patients undergoing chronic hemodialysis or who had received a kidney transplant. Among patients with detectable HBV DNA at baseline, TAF treatment was associated with a high virological response rate, improved serum aminotransferase levels in both patient groups. These findings are consistent with

Table 1. Baseline characteristics of patients receiving TAF undergoing chronic hemodialysis and kidney transplant recipients

Parameter	Overall	Group		p
		Kidney transplant recipient	Hemodialysis	
Gender				0.494
Male	41 (70.7)	33 (73.3)	8 (61.5)	
Female	17 (29.3)	12 (26.7)	5 (38.5)	
Age	50.1±12.5 52.5 (26–77)	49.3±11.6 50.0 (26–77)	52.8±15.4 59.0 (27–70)	0.102
Hypertension	50 (86.2)	38 (84.4)	12 (92.3)	0.669
Diabetes mellitus	15 (27.3)	11 (25.6)	4 (33.3)	0.370
Coronary artery disease	9 (15.8)	6 (13.6)	3 (23.1)	0.671
Osteoporosis	11 (19.6)	11 (25.6)	0 (0)	0.098
Antiviral therapy before TAF initiation	38 (66.7)	34 (75.6)	4 (33.3)	**0.013**
Type of antiviral agent before TAF initiation				
TDF	23 (60.5)	21 (61.8)	2 (50)	0.447
Entecavir	9 (23.7)	7 (20.6)	2 (50)	
Lamivudine	6 (15.8)	6 (17.6)	0 (0)	
Baseline HBV DNA positivity (n)	19 (32.8)	8 (17.8)	11 (84.6)	**<0.001**
Serum HBV DNA Level (Log10 IU/ml)	3.4 (1.50–8.33)	2.8 (1.62–8.03)	3.7 (1.5–8.33)	0.102
Serum ALT (U/L)	42.1±98.5 18 (4–746)	29.7±28.6 18 (4–121)	85.0±201.3 16 (5–746)	0.538
Serum AST (U/L)	30.1±56.8 18 (7–422)	21.2±11.3 18 (8–66)	58.2±112.6 20 (7–422)	0.612
Fasting plasma glucose (mg/dL)	91 (73–322)	92 (73–322)	90 (75–146)	0.79
Total cholesterol (mg/dL)	168.8±46.4 172 (90–248)	177.6±45.6 184 (94–248)	143.3±40.5 143 (90–232)	**0.033**
HDL (mg/dL)	41.4±14.2 38 (10.5–80)	44.1±14.3 40 (10.5–80)	32.6±9.9 31 (21–53)	**0.005**
LDL (mg/dL)	103.4±38.6 101 (19.4–177)	108.9±38.5 107 (19.4–177)	85.9±35.0 79 (40–153)	0.085
Triglyceride (mg/dL)	158.6±70.2 147 (58–356)	159.5±76.8 142.5 (58–356)	155.73±44.9 156 (88–233)	0.811
Serum creatinine (mg/dL)	3.1±2.6 1.6 (0.8–10.1)	2±1.5 1.5 (0.8–7)	6.6±2.4 6.5 (3.1–10.1)	**<0.001**
Serum phosphorus (mg/dL)	3.8±1.5 3.5 (1.9–7.9)	3.3±0.9 3.3 (1.9–6.0)	5.7±1.7 6.0 (3.4–7.9)	**<0.001**

Data are presented as n (%), mean±standard deviation and median (minimum–maximum), or, for fasting plasma glucose, median (minimum–maximum) only. Percentages and continuous variables were calculated using patients with available data. Missing data: diabetes mellitus, 3 patients (2 kidney transplant recipients, 1 hemodialysis patient); coronary artery disease, 1 kidney transplant recipient; osteoporosis, 2 kidney transplant recipients; prior antiviral therapy, 1 hemodialysis patient; fasting plasma glucose, 4 kidney transplant recipients. HDL: High-density lipoprotein; LDL: Low-density lipoprotein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; HBV: Hepatitis B virus; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate.

prior studies demonstrating a high virological response rate following initiation of TAF therapy in both immunocompetent and immunosuppressed populations.[1,9,13]

Long-term treatment with NA, particularly TDF, has been associated with renal dysfunction in some studies.[9,12–15] Consequently, TAF treatment is often preferred over TDF for older patients, those with renal impairment, and those with bone disease.[1,8-10,16] In the present study, no significant changes were observed in mean eGFR or serum creatinine levels from baseline to 24 months of TAF treatment in either the hemodialysis or the kidney transplant group. Serum phosphate levels were stable in most patients, and no major TAF-related renal AE were detected among kidney transplant

Table 2. HBV serological and virological markers at baseline and during follow-up

HBV marker	Baseline positive n/N (%)	Month 12 positive n/N (%)	Month 24 positive n/N (%)
HBsAg	46/56 (82.1)	17/21 (81.0)	11/13 (84.6)
Anti-HBc	47/52 (90.4)	13/15 (86.7)	4/4 (100.0)
HBeAg	9/42 (21.4)	2/13 (15.4)	1/5 (20.0)
Anti-HBe	29/40 (72.5)	10/13 (76.9)	4/5 (80.0)
Anti-HBs	3/22 (13.6)	4/15 (26.7)	0/7 (0.0)
HBV DNA	19/58 (32.8)	4/45 (8.9)	2/44 (4.5)

Data are presented as n/N (%), where N represents the number of patients with a known positive or negative test result at the corresponding time point. Unknown and missing results were excluded from percentage calculations. HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; anti-HBc: Antibody to hepatitis B core antigen; HBeAg: Hepatitis B e antigen; anti-HBe: Antibody to hepatitis B e antigen; Anti-HBs: Antibody to hepatitis B surface antigen; DNA: Deoxyribonucleic acid.

recipients. These findings support the renal safety and stability of TAF treatment in these high-risk populations.

Some studies have demonstrated that TAF treatment, particularly a switch from TDF to TAF, is associated with weight gain, adverse changes in lipid profiles, and increases in cardiovascular risk scores.[6–8,12,15] However, other studies have not confirmed these findings.[1,9,17–19] Calcineurin inhibitors, including cyclosporine and tacrolimus, suppress hepatic LDL receptor expression and reduce LDL clearance, contributing to hyperlipidemia; this effect is particularly pronounced with cyclosporine.[20] Corticosteroids induce hyperlipidemia through multiple mechanisms, including promotion of insulin resistance with increased hepatic free fatty acid reuptake and augmented VLDL synthesis.[20] They also lower LDL receptor activity and promote VLDL-to-LDL conversion. Mammalian target of rapamycin inhibitors, such as sirolimus and everolimus, impair lipolysis by inhibiting lipoprotein lipase activity, further contributing to dyslipidemia.[20] As expected, in the present study, total serum cholesterol and HDL levels were higher in the transplant group than in the hemodialysis group, likely reflecting the effects of immunosuppressive therapy. TAF did not significantly change lipid profiles in either the hemodialysis or kidney transplant group from baseline to the end of the follow-up period.

The multicenter, real-world design of this study enhances the clinical generalizability and reliability of the findings. However, several limitations should be acknowledged. These include the retrospective design, insufficient data to classify the natural-history phases of chronic HBV infection, missing laboratory data at certain time points, irregular follow-up in some patients who did not return to the center regularly, a relatively small sample size, and the lack of bone mineral density data during TAF treatment. In addition, the uncontrolled study design, without a comparator arm, limits causal inference regarding the observed renal outcomes attributable to TAF treatment.

Table 3. Changes in laboratory values over 24 months by group

Variables	Group	Baseline	3-months	6-months	12-months	24-months	p
ALT (U/L), patients with baseline ALT >40 U/L*	Overall	229.4±290.4	26.2±9.3	26.2±15.2	27.6±13.7	22.6±9.0	**0.024**
ALT (U/L)	Overall	42.1±98.5	28.3±34.1	26.2±29.8	27.6±31.5	24.8±28.4	**0.001**
Fasting plasma glucose levels (mg/dL)	Overall	91 (73–322)	93 (69–239)	90 (65–205)	93 (71–264)	95 (56–206)	0.69
Total cholesterol (mg/dL)	Overall	168.8±46.4	170.2±47.1	171.4±48.0	173.0±49.2	172.5±48.1	0.41
LDL (mg/dL)	Overall	103.4±38.6	104.5±39.2	105.3±39.8	106.8±40.5	106.1±39.7	0.47
HDL (mg/dL)	Overall	41.4±14.2	41.9±14.5	42.3±14.9	42.8±15.2	42.7±14.8	0.52
Triglyceride (mg/dL)	Overall	158.6±70.2	160.1±71.5	161.8±72.4	163.5±73.2	162.4±72.5	0.55
Creatinine (mg/dL)							
Kidney transplant recipients		2.0±1.5	1.4±0.5	1.5±0.6	1.5±0.5	1.5±0.6	0.826
Hemodialysis patients		6.6±2.4	4.8±2.7	6.3±2.7	6.7±2.2	5.4±3.2	0.419
eGFR-MDRD (mL/min/1.73 m^2)							
Kidney transplant recipients		50.1±22.5	58.9±22.1	61.8±21.7	63.9±22.7	60.9±25.3	0.404
Hemodialysis patients		10.7±5.4	15.3±9.3	10.7±6.3	9.4±3.5	16.1±9.8	0.905
Phosphorus (mg/dL)							
Kidney transplant recipients		3.2±1.2	3.3±0.8	3.0±0.7	3.1±0.5	3.3±0.7	0.321
Hemodialysis patients		5.4±1.7	4.8±1.3**	5.5±1.2	5.5±1.5	5.6±1.0	0.944

Data are presented as mean±standard deviation (SD), except fasting plasma glucose, which is presented as median (minimum–maximum). *This subgroup includes 11 patients with baseline ALT levels >40 U/L; the values and p-value shown are for the 5 patients with measurements at all time points. Follow-up values were available in 8, 7, 10, and 7 of the 11 patients at months 3, 6, 12, and 24, respectively. Fasting plasma glucose values were available in 54, 28, 41, 43, and 37 patients at baseline and at months 3, 6, 12, and 24, respectively; the p-value was calculated in the 21 patients with measurements at all time points. Phosphorus values in the hemodialysis group are based on the 10 patients with measurements at baseline, month 12, and month 24. **The 3-month phosphorus measurement was unavailable in one patient (9 patients). Baseline values in Table 1 include all 12 patients with available data and therefore differ slightly. HDL: High-density lipoprotein; LDL: Low-density lipoprotein; ALT: Alanine aminotransferase; eGFR-MDRD: Estimated glomerular filtration rate - modification of diet in renal disease.

Conclusion

TAF treatment was associated with effective virological suppression and favorable biochemical responses in patients with chronic HBV infection receiving chronic hemodialysis and in kidney transplant recipients. TAF was well tolerated in these patients.

Ethics Committee Approval: The study protocol was approved by the Marmara University Clinical Research Ethics Committee (date: June 12, 2020, number: 09.2020.698) and the study was conducted in accordance with the principles of the Declaration of Helsinki.

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

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ORIGINAL RESEARCH

Cardiometabolic index and central adiposity as non-invasive markers of hepatic steatosis and elevated liver stiffness in chronic hepatitis B

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Highlights & Insights

- **Scientific Gap:** Whether the cardiometabolic index and simple anthropometric measures are associated with hepatic steatosis and liver stiffness in nucleos(t)ide-treated chronic hepatitis B has not been established.
- **Key Finding:** CMI was associated with CAP-defined hepatic steatosis but not with elevated liver stiffness, whereas waist circumference showed the highest discrimination for elevated liver stiffness (AUC 0.75) and exceeded FIB-4 and APRI.
- **Clinical Impact:** Part of the waist circumference signal may reflect the influence of obesity on VCTE measurement, so anthropometry complements rather than replaces existing non-invasive tests.

ABSTRACT

Background and Aim: Residual liver disease in chronic hepatitis B (CHB) under long-term antiviral therapy is increasingly metabolic. We assessed whether the cardiometabolic index (CMI), modified CMI (MCMI) and simple anthropometry are associated with hepatic steatosis and elevated liver stiffness.

Materials and Methods: In a two-part cross-sectional study, CMI and MCMI were compared between inactive hepatitis B virus carriers (n=21) and matched controls (n=27). Separately, 92 nucleos(t)ide-treated CHB patients underwent vibration-controlled transient elastography (VCTE). Significant steatosis was a controlled attenuation parameter (CAP) ≥268 dB/m and elevated liver stiffness a liver stiffness measurement ≥7.0 kPa. No biopsy was performed. Areas under the curve (AUC) were compared by the DeLong test, and cutoff performance was internally validated by bootstrap.

Results: CMI and MCMI did not differ between carriers and controls (p>0.6). Significant steatosis occurred in 44 of 91 (48%) and elevated liver stiffness in 48 of 90 (53%). CMI correlated with CAP (rho=0.37, p<0.001) and increased across CAP grades (p=0.009). Its AUC for steatosis was 0.70, comparable with waist circumference (0.70, p=0.96). For elevated liver stiffness, waist circumference had the highest AUC (0.75; 95% confidence interval, 0.65–0.85), exceeding fibrosis-4 index (FIB-4) (0.57, p=0.023), aspartate aminotransferase-to-platelet ratio index (APRI) (0.56, p=0.022) and CMI (0.58, p=0.006), and remained associated after age and sex adjustment (odds ratio 2.94/10 cm, p<0.001).

Conclusion: In long-term nucleos(t)ide-treated CHB, CMI was associated with CAP-defined hepatic steatosis, whereas waist circumference showed the highest discrimination for elevated liver stiffness and exceeded FIB-4 and APRI. Part of this may reflect obesity-related effects on VCTE.

Keywords: Adiposity, cardiometabolic risk factors, chronic hepatitis B, hepatic steatosis, vibration-controlled transient elastography, waist circumference.

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Introduction

Chronic hepatitis B (CHB) remains a leading cause of cirrhosis and hepatocellular carcinoma worldwide, yet the clinical landscape has shifted as potent nucleos(t)ide analogues achieve durable viral suppression in most treated patients.[1] In this context, the drivers of residual liver injury are increasingly metabolic rather than virologic. Metabolic dysfunction-associated steatotic liver disease (MASLD), the term adopted in 2023 to replace non-alcoholic fatty liver disease, now affects roughly a third of adults globally and is defined by hepatic steatosis in the presence of cardiometabolic risk factors.[2–4]

The coexistence of hepatic steatosis and CHB is common and clinically consequential, and concurrent steatosis has been linked with accelerated fibrosis progression and with a higher risk of cirrhosis and hepatocellular carcinoma.[5,6] Concurrent steatosis may also complicate non-invasive assessment, although the evidence is more limited than is sometimes stated. Shen et al.[7] reported that moderate to severe steatosis was associated with a higher liver stiffness measurement (LSM) by vibration-controlled transient elastography (VCTE) in patients with CHB who did not have significant fibrosis, whereas no such effect was seen at more advanced fibrosis stages. Con et al.[8] reported that aspartate aminotransferase-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4) performed less well in patients with CHB and concurrent MASLD, but they did not establish that steatosis itself reduces the accuracy of these scores. Both scores incorporate aminotransferases and platelet count, which are influenced by necroinflammatory activity, alcohol intake, medication and other factors that are not specific to fibrosis. The independent contribution of steatosis therefore remains uncertain.

Simple and inexpensive metabolic indices may add value in this setting. The cardiometabolic index (CMI), proposed by Wakabayashi and Daimon, multiplies the triglyceride (TG)-to-high-density lipoprotein-cholesterol (HDL-C) ratio by the waist-to-height ratio and combines atherogenic dyslipidemia with central adiposity in a single number.[9,10] In MASLD populations, a higher CMI is associated with the degree of hepatic fat, with liver fibrosis and with long-term mortality.[11–13] Whether these relationships hold in treated CHB, where metabolic and viral processes overlap, has not been established.

We hypothesized that metabolic indices would show no significant difference between inactive hepatitis B virus (HBV) carriers and HBV-negative controls, that they would be associated with VCTE-defined hepatic steatosis and elevated liver stiffness in treated CHB, and that they would complement rather than replace conventional fibrosis scores. We therefore conducted a two-part cross-sectional study to quantify these associations.

Materials and Methods

Study Design and Participants

This cross-sectional study was conducted at a secondary-care center (Etimesgut Şehit Sait Ertürk State Hospital) and comprised two separate and non-overlapping samples. The diagnostic-comparison sample included 21 patients with inactive HBV carriage (hepatitis B surface antigen positive for more than 6 months, persistently normal aminotransferases, low or undetectable HBV DNA, no antiviral therapy) and 27 age- and sex-matched volunteers without known liver disease. The staging cohort included 92 consecutive patients with CHB receiving nucleos(t)ide analogue therapy who underwent VCTE during routine follow-up. No participant contributed to both samples. The two samples are presented together because they address complementary questions, namely, whether cardiometabolic indices differ in untreated inactive carriage and whether they track hepatic steatosis and liver stiffness during long-term nucleos(t)ide analogue therapy. All analyses were performed separately in each sample, and no pooled analysis was undertaken.

Exclusion criteria, applied to protect the interpretability of metabolic and blood-count-derived indices, were coinfection with hepatitis C, hepatitis D or human immunodeficiency virus, significant alcohol intake, other chronic liver disease, active infection, hematologic disease or malignancy, and pregnancy. The study was conducted in accordance with the Declaration of Helsinki and ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Ankara Provincial Health Directorate (approval number 04-10-2025, dated April 10, 2025).

Measurements and Exposures

Anthropometry (height, weight, and waist circumference), fasting lipids, glycated hemoglobin (HbA1c), aminotransferases and platelet count were recorded. Waist circumference was measured at the midpoint between the lowest rib and the iliac crest at the end of a normal expiration. Body-mass index (BMI) and the waist-to-height ratio were derived. CMI was calculated as (TG/HDL-C) × (waist circumference/height).[9]

Fasting plasma glucose was not available in this dataset. An estimated average glucose was therefore derived from HbA1c using the published relationship (estimated average glucose in mg/dL=28.7×HbA1c-46.7) for the two glucose-dependent measures, which are reported as exploratory throughout.[14] These were the modified CMI (MCMI)=(TG×estimated average glucose/HDL-C)×(waist circumference/height), and a TG-to-estimated-glucose ratio calculated as TG/(estimated average glucose/2). The latter is not the conventional logarithmic TG-glucose (TyG) index of Simental-Mendia et al.,[15] which requires a directly measured fasting glucose, and it is not interpretable against published TyG thresholds. It is therefore reported only as a descriptive exploratory variable in the carrier-versus-control comparison and was not used in any diagnostic or regression analysis of the CHB cohort. APRI was calculated as ([aspartate aminotransferase [AST]/upper limit of normal AST]/platelet count in 10^9/L)×100 with an upper limit of normal of 40 U/L, and FIB-4 as (age × AST)/(platelet count in 10^9/L × square root of alanine aminotransferase [ALT]).[16,17]

VCTE

LSM and controlled attenuation parameter (CAP) were obtained simultaneously by VCTE (FibroScan, Echosens, Paris, France) by a single experienced operator who was unaware of the laboratory results. Pa-

tients fasted for at least 3 h before the examination and were positioned supine with the right arm in maximal abduction. The M probe was used by default, and the XL probe was used when the automatic probe-selection tool indicated it or when the skin-to-liver-capsule distance exceeded 25 mm. An examination was accepted as reliable when at least 10 valid measurements were obtained, and the ratio of the interquartile range to the median LSM was 0.30 or less. The median of the valid measurements was used for analysis.[18] The probe used in each individual examination was not retrievable from the archived reports, so the proportion of examinations performed with the M probe and with the XL probe could not be determined.

Of the 92 patients in the staging cohort, a reliable CAP value was obtained in 91 and a reliable LSM value in 90. One examination yielded neither a reliable LSM nor a reliable CAP, and one yielded a reliable CAP without a reliable LSM, in both instances because the interquartile range to median ratio criterion was not met. These patients were excluded from the corresponding analyses, which explains the differing denominators. One waist circumference value was recorded as 12 cm, which is anatomically impossible, and was set to missing rather than corrected, so waist circumference was available in 91 patients.

Outcomes

The primary outcomes were significant hepatic steatosis and elevated liver stiffness. CAP grades were defined using the published thresholds of the individual patient data meta-analysis of Karlas et al.,[19] namely S0 for CAP below 248 dB/m, S1 for 248–267 dB/m, S2 for 268–279 dB/m and S3 for 280 dB/m or higher. Significant steatosis was defined as CAP 268 dB/m or higher, corresponding to grade S2 or S3. Elevated liver stiffness was defined as LSM 7.0 kPa or higher. This threshold lies within the range of cutoffs reported for significant fibrosis in CHB in a meta-analysis of 18 studies and 2,772 patients, in which the estimated cutoff was 7.9 kPa with a reported range of 6.1–11.8 kPa, and it is consistent with current guidance that a value below 7 kPa makes significant fibrosis unlikely.[18,20] Because no liver biopsy was performed, no METAVIR stage was assigned, and the endpoint is reported throughout as elevated liver stiffness rather than as histological fibrosis. Sensitivity analyses were performed at LSM thresholds of 7.2 kPa and 8.0 kPa and at CAP thresholds of 248 dB/m and 280 dB/m.

Statistical Analysis

Continuous variables are summarized as mean with standard deviation or as median with interquartile range and were compared with the t-test or the Mann–Whitney U test. Categorical variables were compared with the Chi-square test or the Fisher exact test. Associations of the indices with continuous CAP and LSM were quantified by the Spearman rank correlation coefficient. Differences across CAP grades were assessed by the Kruskal–Wallis test, and an ordered trend across grades was tested by the Spearman rank correlation between the ordinal grade and the index.

Discrimination for the binary outcomes was summarized by the areas under the curve (AUC) with 95% confidence intervals (CIs) by the DeLong method and additionally by 1000 non-parametric bootstrap resamples. Correlated AUCs were compared by the DeLong test. Cutoffs were derived by the Youden index. Because cutoffs derived and evaluated in the same dataset yield optimistic estimates, the sensitivity and specificity at each Youden cutoff were internally validated by the enhanced bootstrap procedure of Harrell with 1,000 resamples, in which the cutoff was re-derived in each resample and applied to the original data, and the mean difference was subtracted from the apparent value to give an optimism-corrected estimate. External validation was not feasible in a cohort of this size.

The structure of every multivariable logistic regression model was fixed before the models were fitted, and no data-driven variable selection was performed at any stage. Each model contained the marker of interest together with age and sex, which were fixed as core confounders. With 44 steatosis events and 48 elevated liver stiffness events, models were restricted to a maximum of four covariates so that at least 10 events per variable were retained. Age and sex were retained in every model without exception. Four additional models each added a single further covariate to the age- and sex-adjusted model, namely FIB-4, CMI, CAP or diabetes mellitus, in order to test whether the waist circumference signal was independent of the conventional fibrosis scores, of the degree of steatosis and of diabetes. CMI and waist circumference were also entered together with age and sex in a single model for the steatosis outcome. Model discrimination was internally validated by the same bootstrap procedure and the calibration slope was estimated in the same resamples. Two-sided p-values below 0.05 were considered significant. Analyses were performed in Python 3.12 (Python Software Foundation, Beaverton, Oregon, USA) with the SciPy, statsmodels and scikit-learn libraries. Reporting follows the STROBE recommendations for observational studies.

Results

Inactive Carriers versus HBV-negative Controls

The 21 inactive carriers and the 27 HBV-negative controls were comparable in age (median 52 vs. 47 years, p=0.27), sex (p=0.82) and BMI (27.9 vs. 26.3 kg/m^2, p=0.21). No metabolic index differed significantly between the groups. CMI was 1.09 versus 1.28 (p=0.80), MCMI was 124.0 versus 148.2 (p=0.62), the exploratory TG-to-estimated-glucose ratio was 1.94 versus 2.36 (p=0.53), APRI was 0.19 versus 0.17 (p=0.45) and FIB-4 was 0.87 versus 0.68 (p=0.47) (Table 1). These groups were small, and the study was not designed or powered as an equivalence study, so this result indicates only the absence of a statistically significant difference and does not demonstrate that the cardiometabolic profiles of inactive carriers and HBV-negative controls are comparable.

CHB Cohort

The treated CHB cohort (n=92) had a mean age of 55.9 (standard deviation 11.0) years and 45 patients (49%) were male. Antiviral therapy comprised tenofovir disoproxil fumarate in 44 patients, entecavir in 36 and tenofovir alafenamide in 12, with a median treatment duration of 7 years (interquartile range [IQR] 3–11). Diabetes mellitus was

Table 1. Characteristics and metabolic indices of inactive HBV carriers and HBV-negative controls

Variable	Inactive HBV carriers (n=21)	HBV-negative controls (n=27)	p
Age, years	52 (39–59)	47 (37.5–52.5)	0.270
Male sex, n (%)	7 (33)	11 (41)	0.822
BMI, kg/m^2	27.89 (26.56–31.59)	26.30 (24.78–29.14)	0.205
Waist circumference, cm	100.00 (96.00–103.00)	96.00 (87.50–105.00)	0.473
TG, mg/dL	111 (83–155)	123 (95–161)	0.747
HDL-C, mg/dL	50 (45–62)	50 (40.50–55.50)	0.618
TG/HDL-C ratio	1.86 (1.65–3.41)	2.43 (1.51–3.70)	0.575
HbA1c, %	5.40 (5.30–5.95)	5.40 (5.25–5.60)	0.736
ALT, U/L	22 (18–27)	20 (14–24)	0.201
AST, U/L	22 (18–23)	19 (17.50–21)	0.312
Platelet count, ×10^9/L	259 (205–321)	260 (210.50–309.50)	0.967
CAP, dB/m	263 (243–292)	282 (246.50–307.50)	0.383
LSM, kPa	6.30 (5.50–7.40)	5.70 (4.05–6.75)	0.187
CMI	1.09 (0.97–2.13)	1.28 (0.86–2.11)	0.803
MCMI (exploratory)	124.03 (95.30–222.75)	148.21 (94.43–241.32)	0.624
TG-to-estimated-glucose ratio (exploratory)	1.94 (1.57–2.75)	2.36 (1.65–2.79)	0.532
APRI	0.19 (0.15–0.25)	0.17 (0.14–0.23)	0.454
FIB-4	0.87 (0.49–0.99)	0.68 (0.61–0.91)	0.467

Values are median (interquartile range) unless stated otherwise. p-values are from the Mann–Whitney U test for continuous variables and from the Chi-square test for sex. The two glucose-dependent measures are exploratory and were derived from an HbA1c-based estimated average glucose because fasting plasma glucose was not available. The TG-to-estimated-glucose ratio is triglycerides divided by half the estimated average glucose and is not the conventional logarithmic TyG index. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body-mass index; CAP: Controlled attenuation parameter; CMI: Cardiometabolic index; HBV: Hepatitis B virus; HDL-C: High-density lipoprotein cholesterol; LSM: Liver stiffness measurement; MCMI: Modified cardiometabolic index; TG: Triglycerides; APRI: Aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis-4 index.

present in 15 patients (16%), hypertension in 23 (25%) and hyperlipidemia in 12 (13%). Median ALT was 20 U/L (IQR 17–26), median AST 22 U/L (IQR 20–24) and median platelet count 225×10^9/L (IQR 192–264). Median CAP was 267 dB/m (IQR 234–288) and median LSM 7.1 kPa (IQR 6.1–8.4). CAP grades were S0 in 32 patients, S1 in 15, S2 in 11 and S3 in 33. Significant steatosis was present in 44 of 91 patients (48%) and elevated liver stiffness in 48 of 90 patients (53%) (Table 2).

Metabolic Indices and Hepatic Steatosis

CMI correlated positively with CAP (rho=0.37, p<0.001) and increased across CAP grades, from a median of 1.11 in grade S0 to 2.02 in grade S3 (Kruskal-Wallis p=0.009, ordered trend p=0.001; Fig. 1a, b). CMI was higher in patients with significant steatosis than in those without (1.85 vs. 1.13, p=0.002), as were MCMI (217.3 vs. 129.7, p=0.003), waist circumference (105 vs. 98 cm, p=0.001) and BMI (29.7 vs. 27.9 kg/m2, p=0.011). The AUC of CMI for significant steatosis was 0.70 (95% CI, 0.59–0.81; bootstrap 95% CI, 0.58–0.80) with a Youden cutoff of 1.51 (apparent sensitivity 0.67 and specificity 0.70, optimism-corrected sensitivity 0.64 and specificity 0.67). This AUC did not differ from that of waist circumference (0.70, DeLong p=0.96), BMI (0.65, p=0.58) or MCMI (0.68, p=0.53) (Fig. 2a and Table 3). In a model adjusted for age and sex, each one-unit increase in CMI was associated with a 71% higher odds of significant steatosis (odds ratio 1.71; 95% CI, 1.07–2.73; p=0.025). When CMI and waist circumference were entered together in a model that also contained age and sex, only waist circumference remained significant (odds ratio 2.08/10 cm; 95% CI, 1.21–3.56; p=0.008) while CMI did not (odds ratio 1.32; 95% CI, 0.83–2.10; p=0.245), which indicates that the CMI signal for steatosis is carried largely by its anthropometric component (Table 4).

Metabolic Measures and Elevated Liver Stiffness

Waist circumference correlated with LSM (rho=0.52, p<0.001; Fig. 1c) and was higher in patients with elevated liver stiffness (median 106 vs. 97 cm, p<0.001). Waist circumference showed the highest discrimination for elevated liver stiffness (AUC 0.75; 95% CI, 0.65–0.85; bootstrap 95% CI, 0.64–0.85), followed by the waist-to-height ratio (0.73), BMI (0.66), CMI (0.58), FIB-4 (0.57; 95% CI, 0.45–0.70) and APRI (0.56; 95% CI, 0.44–0.68) (Fig. 2b and Table 3). On formal DeLong testing, the AUC of waist circumference was higher than that of FIB-4 (p=0.023), APRI (p=0.022), CMI (p=0.006) and BMI (p=0.036), while FIB-4 and APRI did not differ from each other (p=0.74). At the Youden cutoff of 101 cm, the apparent sensitivity and specificity of waist circumference were 0.69 and 0.71, and the optimism-corrected values were 0.65 and 0.67.

Table 2. Clinical, laboratory and elastographic characteristics of the treated chronic hepatitis B cohort (n=92)

Characteristic	Value	Characteristic	Value
Age, years, mean±SD	55.9±11.0	HDL-C, mg/dL, median (IQR)	48 (42–56.50)
Male sex, n (%)	45 (49)	TG/HDL-C ratio, median (IQR)	2.38 (1.60–3.34)
BMI, kg/m^2, mean±SD	28.5±4.3	LDL-C, mg/dL, median (IQR)	112 (91–131)
Waist circumference, cm, mean±SD	101.4±11.3 (n=91)	HbA1c, %, median (IQR)	5.50 (5.10–5.95)
Waist-to-height ratio, median (IQR)	0.61 (0.56–0.65)	CMI, median (IQR)	1.47 (1.00–2.16)
Antiviral agent, TDF/ETV/TAF, n	44/36/12	MCMI (exploratory), median (IQR)	160.48 (105.10–269.77)
Treatment duration, years, median (IQR)	7 (3–11)	APRI, median (IQR)	0.23 (0.19–0.30)
Diabetes mellitus, n (%)	15 (16)	FIB-4, median (IQR)	1.18 (0.79–1.46)
Hypertension, n (%)	23 (25)	CAP, dB/m, mean±SD	265.7 ± 41.1
Hyperlipidemia, n (%)	12 (13)	CAP grade S0/S1/S2/S3, n	32 / 15 / 11 / 33
ALT, U/L, median (IQR)	20 (17–26)	LSM, kPa, median (IQR)	7.10 (6.12–8.40)
AST, U/L, median (IQR)	22 (20–24)	Significant steatosis (CAP≥268 dB/m), n/N (%)	44/91 (48)
Platelet count, ×10^9/L, median (IQR)	225 (191.75–264.25)	Elevated liver stiffness (LSM ≥7.0 kPa), n/N (%)	48/90 (53)
TG, mg/dL, median (IQR)	109 (88.15–152)		

Waist circumference was available in 91 patients because one recorded value was anatomically impossible and was set to missing. A reliable CAP value was obtained in 91 patients and a reliable LSM value in 90. HBV DNA level and HBeAg status were not systematically recorded for this cohort and are therefore not reported. CAP grades follow Karlas et al.[19] ETV: Entecavir; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body-mass index; CAP: Controlled attenuation parameter; CMI: Cardiometabolic index; HBV: Hepatitis B virus; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; LSM: Liver stiffness measurement; MCMI: Modified cardiometabolic index; TG: Triglycerides; APRI: Aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis-4 index; SD: Standard deviation; IQR: Interquartile range; HbA1c: Glycated hemoglobin.

In a model adjusted for age and sex, waist circumference remained associated with elevated liver stiffness (odds ratio 2.94/10 cm; 95% CI, 1.65–5.24; p<0.001). In four further models that retained age and sex and added one covariate at a time, the association was essentially unchanged when FIB-4 (odds ratio 3.08; 95% CI, 1.70–5.61), CMI (odds ratio 3.17; 95% CI, 1.70–5.91), CAP (odds ratio 2.73; 95% CI, 1.46–5.09) or diabetes mellitus (odds ratio 2.95; 95% CI, 1.65–5.25) was included, and in none of these models was the added covariate independently associated with the outcome (Table 4). The optimism-corrected AUC of the age- and sex-adjusted model was 0.73 with a calibration slope of 0.87. Results were consistent in sensitivity analyses at LSM thresholds of 7.2 kPa (waist circumference AUC 0.79, DeLong p=0.014 vs. FIB-4 and p=0.010 vs. APRI) and 8.0 kPa (AUC 0.80, p=0.017 and p=0.007).

Co-occurrence of Steatosis and Elevated Liver Stiffness

Significant steatosis and elevated liver stiffness occurred together more often than expected by chance. Among the 90 patients with both a valid CAP and a valid LSM measurement, 29 of the 43 patients with significant steatosis had elevated liver stiffness, compared with

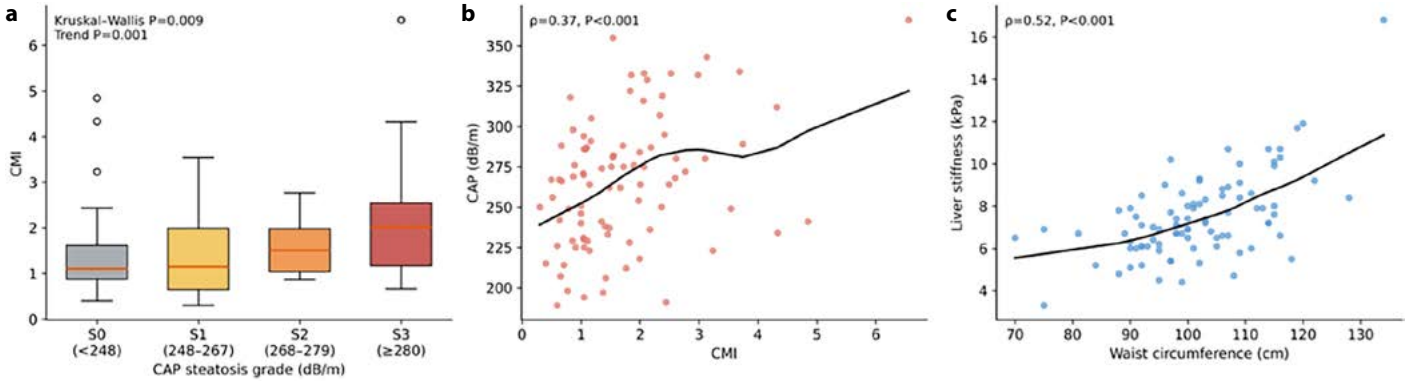


Figure 1. Cardiometabolic index (CMI) and anthropometry in relation to hepatic steatosis and liver stiffness in the chronic hepatitis B cohort. **(a)** CMI across controlled attenuation parameter (CAP) steatosis grades defined according to Karlas et al.[19] (S0 below 248 dB/m, S1 248–267 dB/m, S2 268–279 dB/m, S3 280 dB/m or higher). p-values are from the Kruskal-Wallis test and from the Spearman rank correlation between the ordinal grade and CMI (ordered trend). **(b)** CMI versus CAP. **(c)** Waist circumference versus liver stiffness measurement. **(b, c)** The correlation coefficient is the Spearman rank correlation, and the superimposed curve is a locally weighted scatterplot smoother (LOWESS, span 0.75) shown for visualization only. It is not a fitted regression model, and it is not used in any inference.

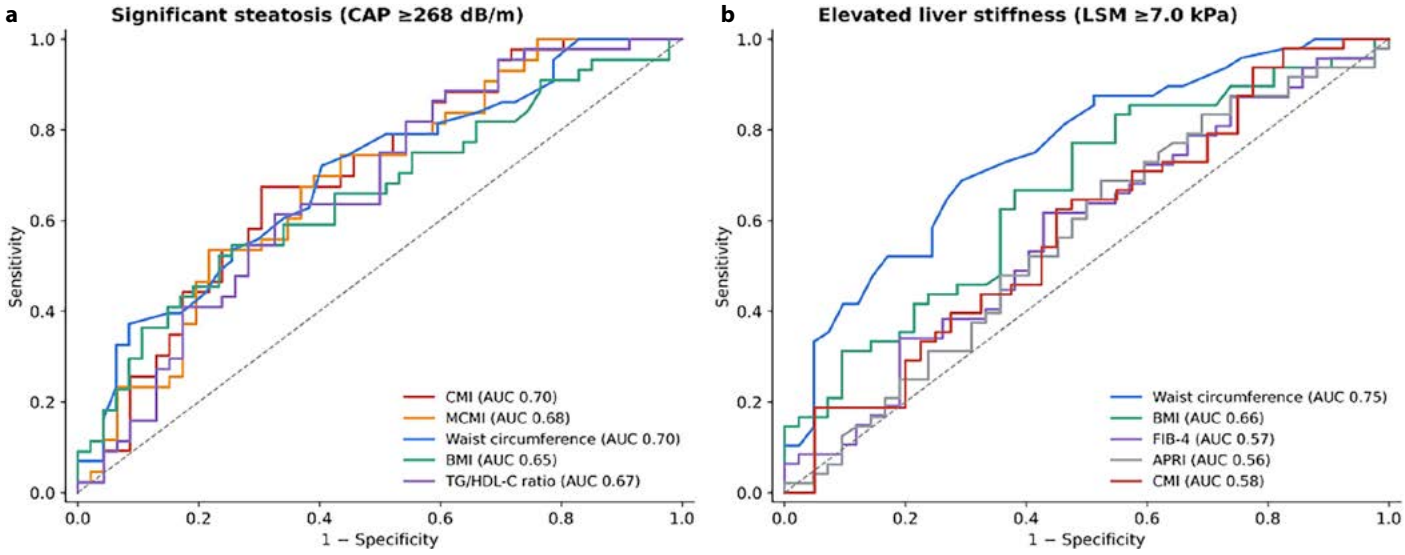


Figure 2. Receiver-operating-characteristic curves in the chronic hepatitis B cohort. **(a)** Significant hepatic steatosis, defined as controlled attenuation parameter 268 dB/m or higher. **(b)** Elevated liver stiffness, defined as a liver stiffness measurement of 7.0 kPa or higher. Areas under the curve with 95% confidence intervals, Youden cutoffs and optimism-corrected sensitivity and specificity are reported in Table 3.

19 of the 47 patients without significant steatosis (odds ratio 3.05, Fisher p=0.012, Chi-square p=0.019). One patient with significant steatosis had no valid LSM measurement and is therefore not included in this comparison. CAP and LSM were weakly correlated as continuous variables (rho=0.23, p=0.033). The two features therefore overlap substantially in the same patients, and the markers examined here are best regarded as complementary summaries of a shared metabolic burden rather than as indicators of separate processes.

Table 3. Discrimination of metabolic, anthropometric and conventional measures for significant hepatic steatosis and elevated liver stiffness

Marker	AUC (95% CI, DeLong)	Bootstrap 95% CI	Youden cutoff	Apparent Se/Sp	Optimism-corrected Se / Sp
Significant steatosis (CAP ≥268 dB/m); 44 events, 91 patients					
CMI	0.70 (0.59–0.81)	0.58–0.80	1.51	0.67/0.70	0.64/0.67
MCMI (exploratory)	0.68 (0.57–0.80)	0.57–0.79	191.24	0.53/0.78	0.49/0.75
Waist circumference	0.70 (0.59–0.81)	0.58–0.80	100.00	0.72/0.60	0.68/0.56
Waist-to-height ratio	0.67 (0.56–0.78)	0.56–0.78	0.62	0.58/0.77	0.55/0.74
BMI	0.65 (0.54–0.77)	0.54–0.77	29.39	0.55/0.74	0.50/0.71
TG/HDL-C ratio	0.67 (0.55–0.78)	0.55–0.77	2.54	0.61/0.67	0.57/0.63
Elevated liver stiffness (LSM ≥7.0 kPa); 48 events, 90 patients					
Waist circumference	0.75 (0.65–0.85)	0.64–0.85	101.00	0.69/0.71	0.65/0.67
Waist-to-height ratio	0.73 (0.63–0.84)	0.62–0.83	0.58	0.85/0.54	0.82/0.50
BMI	0.66 (0.55–0.77)	0.55–0.77	27.08	0.77/0.52	0.73/0.49
FIB-4	0.57 (0.45–0.70)	0.45–0.69	1.16	0.62/0.57	0.57/0.53
APRI	0.56 (0.44–0.68)	0.44–0.68	0.21	0.69/0.48	0.64/0.43
CMI	0.58 (0.46–0.70)	0.46–0.70	1.41	0.62/0.55	0.58/0.50
MCMI (exploratory)	0.58 (0.46–0.70)	0.45–0.70	152.14	0.62/0.57	0.59/0.53

DeLong 95% CIs are shown alongside percentile CIs from 1,000 non-parametric bootstrap resamples. Cutoffs were derived by the Youden index. Optimism-corrected sensitivity (Se) and specificity (Sp) were obtained by the enhanced bootstrap procedure with 1,000 resamples, in which the cutoff was re-derived in each resample and applied to the original data. By the DeLong test, for significant steatosis, CMI did not differ from waist circumference (p=0.96), BMI (p=0.58) or MCMI (p=0.53). For elevated liver stiffness, waist circumference exceeded FIB-4 (p=0.023), APRI (p=0.022), CMI (p=0.006) and BMI (p=0.036), whereas FIB-4 and APRI did not differ from each other (p=0.74). AUC: Area under the receiver-operating characteristic curve; BMI: Body-mass index; CAP: Controlled attenuation parameter; CI: Confidence interval; CMI: Cardiometabolic index; HDL-C: High-density lipoprotein cholesterol; LSM: Liver stiffness measurement; MCMI: Modified cardiometabolic index; TG: Triglycerides; APRI: Aspartate aminotransferase-to-platelet ratio index; FIB-4: Fibrosis-4 index; Se: Sensitivity; Sp: Specificity

Table 4. Multivariable logistic regression models for significant hepatic steatosis and elevated liver stiffness

Model and covariate	OR (95% CI)	p
Model 1. Significant steatosis; CMI (n=88, events=43, 3 covariates, EPV 14.3)		
CMI, per 1 unit	1.71 (1.07–2.73)	0.025
Age, per 1 year	1.01 (0.97–1.05)	0.774
Male sex	1.20 (0.50–2.87)	0.686
Model AUC apparent 0.69, optimism-corrected 0.64, calibration slope 0.74		
Model 2. Significant steatosis; waist circumference (n=89, events=43, 3 covariates, EPV 14.3)		
Waist circumference, per 10 cm	2.35 (1.40–3.94)	0.001
Age, per 1 year	0.98 (0.94–1.03)	0.392
Male sex	1.24 (0.50–3.06)	0.641
Model AUC apparent 0.72, optimism-corrected 0.69, calibration slope 0.87		
Model 3. Significant steatosis; CMI and waist circumference together (n=88, events=43, 4 covariates, EPV 10.8)		
CMI, per 1 unit	1.32 (0.83–2.10)	0.245
Waist circumference, per 10 cm	2.08 (1.21–3.56)	0.008
Age, per 1 year	0.98 (0.94–1.03)	0.444
Male sex	1.19 (0.48–2.96)	0.714
Model AUC apparent 0.73, optimism-corrected 0.69, calibration slope 0.80		
Model 4. Elevated liver stiffness; waist circumference (n=88, events=47, 3 covariates, EPV 15.7)		
Waist circumference, per 10 cm	2.94 (1.65–5.24)	<0.001
Age, per 1 year	0.99 (0.94–1.03)	0.547
Male sex	0.99 (0.39–2.55)	0.985
Model AUC apparent 0.76, optimism-corrected 0.73, calibration slope 0.87		
Model 5. Elevated liver stiffness; waist circumference plus FIB-4 (n=88, events=47, 4 covariates, EPV 11.8)		
Waist circumference, per 10 cm	3.08 (1.70–5.61)	<0.001
Age, per 1 year	0.97 (0.91–1.03)	0.272
Male sex	0.96 (0.37–2.48)	0.930
FIB-4, per 1 unit	1.86 (0.53–6.52)	0.332
Model AUC apparent 0.76, optimism-corrected 0.72, calibration slope 0.81		
Model 6. Elevated liver stiffness; waist circumference plus CMI (n=87, events=47, 4 covariates, EPV 11.8)		
Waist circumference, per 10 cm	3.17 (1.70–5.91)	<0.001
Age, per 1 year	0.98 (0.94–1.03)	0.498
Male sex	0.96 (0.37–2.48)	0.931
CMI, per 1 unit	0.83 (0.52–1.30)	0.408
Model AUC apparent 0.76, optimism-corrected 0.72, calibration slope 0.82		
Model 7. Elevated liver stiffness; waist circumference plus CAP (n=88, events=47, 4 covariates, EPV 11.8)		
Waist circumference, per 10 cm	2.73 (1.46–5.09)	0.002
Age, per 1 year	0.99 (0.94–1.03)	0.613
Male sex	1.01 (0.39–2.60)	0.989
CAP, per 1 dB/m	1.00 (0.99–1.02)	0.556
Model AUC apparent 0.75, optimism-corrected 0.71, calibration slope 0.82		

Table 4 (cont.). Multivariable logistic regression models for significant hepatic steatosis and elevated liver stiffness

Model and covariate	OR (95% CI)	p
Model 8. Elevated liver stiffness; waist circumference plus diabetes mellitus (n=88, events=47, 4 covariates, EPV 11.8)		
Waist circumference, per 10 cm	2.95 (1.65–5.25)	<0.001
Age, per 1 year	0.99 (0.94–1.03)	0.569
Male sex	0.99 (0.38–2.54)	0.981
Diabetes mellitus	0.91 (0.27–2.99)	0.873
Model AUC apparent 0.76, optimism-corrected 0.71, calibration slope 0.80		

No data-driven variable selection was performed. The structure of every model was fixed before fitting, and every model contained age and sex as fixed core confounders in addition to the marker of interest. Models 5 to 8 each add one further covariate to the age- and sex-adjusted model of Model 4 and are therefore parallel rather than sequential, so the odds ratios for waist circumference in Models 5 to 8 should not be read as a chain of successive adjustments. Every model was restricted to a maximum of four covariates so that at least 10 events per variable were retained. Model discrimination and the calibration slope were internally validated by 1,000 bootstrap resamples. CAP: Controlled attenuation parameter; OR: Odds ratio; CI: Confidence interval; CMI: Cardiometabolic index; EPV: Events per variable; AUC: Area under the receiver-operating-characteristic curve; FIB-4: Fibrosis-4 index.

Discussion

In this two-part study of CHB, CMI showed no significant difference between inactive carriage and HBV-negative controls but was associated with hepatic steatosis in patients receiving long-term nucleos(t)ide analogue therapy, whereas waist circumference was the strongest single correlate of elevated liver stiffness and exceeded APRI and FIB-4 on formal statistical comparison. Significant steatosis and elevated liver stiffness frequently coexisted in the same patient.

These findings extend to the CHB setting a body of work establishing CMI as a marker of metabolic steatosis. In MASLD cohorts, a higher CMI tracks the degree of hepatic fat and predicts fibrosis and mortality, and a recent meta-analysis of 10 studies and 51,037 participants reported a pooled AUC of 0.81 for the detection of MASLD.[11–13] Our data show that the association between CMI and steatosis persists in treated CHB, but that its magnitude is more modest (AUC 0.70) and that it is not superior to waist circumference alone. This is biologically coherent because CMI is a product of the TG-to-HDL ratio and the waist-to-height ratio, so in a population in which central adiposity dominates the metabolic signal, the composite adds little beyond its anthropometric component. The mutually adjusted model supports this interpretation, since waist circumference retained an independent association with steatosis while CMI did not.

The association between waist circumference and elevated liver stiffness is consistent with the view that, once viral replication is controlled, residual liver injury in CHB is increasingly metabolically driven.[5,6,21] It must, however, be interpreted with caution. Obesity and increased subcutaneous fat thickness are the principal causes of unreliable and failed VCTE examinations and can bias the measurement itself, and although the XL probe substantially reduces failure, it yields systematically lower stiffness values than the M probe, so probe-dependent effects can operate in either direction.[18,22–24] Part of the relationship we observed may therefore reflect measurement-related effects of body habitus on VCTE rather than a direct biological relationship with fibrosis. Several observations argue against this being the whole explanation. Standard reliability criteria were applied, and only two examinations were excluded; the association was unchanged after adjustment for CAP, and it persisted at higher LSM thresholds at which measurement noise would be expected to matter less. The possibility nevertheless cannot be excluded without a histological reference standard, and it is the main reason we describe the endpoint as elevated liver stiffness rather than as fibrosis.

Our results also require a more careful statement of how steatosis interacts with non-invasive tests than is often made. Shen et al.[7] showed that the effect of moderate to severe steatosis on LSM in CHB was confined to patients without significant fibrosis, and Con et al.[8] showed reduced accuracy of APRI and FIB-4 in patients with concurrent MASLD without isolating steatosis as the cause. Consistent with this, CAP was not independently associated with elevated liver stiffness in our adjusted model. The weak performance of APRI and FIB-4 in our cohort (AUC 0.56 and 0.57) is best explained by the characteristics of the population rather than by steatosis alone, since aminotransferases and platelet counts were largely within the normal range after years of effective antiviral therapy, which leaves these scores with little dynamic range.

The practical implication is modest but useful. In a treated CHB population in which the platelet-based scores perform poorly, a tape measure identified patients with elevated liver stiffness at least as well as, and in this sample better than, the scores in routine use. Waist circumference costs nothing, requires no laboratory test and is already recommended for the cardiometabolic characterization of steatotic liver disease.[4,25] It should be regarded as a triage aid that helps decide who needs elastography, not as a substitute for it, and it fits the wider effort to build practical non-invasive pathways for chronic liver disease.[26]

Strengths and Limitations

Strengths include a uniformly treated and well-characterized CHB cohort, simultaneous assessment of steatosis and stiffness by VCTE with externally referenced thresholds applied uniformly to every valid measurement, formal head-to-head comparison against es-

tablished scores, and internal validation of cutoff performance by bootstrap resampling. Several limitations temper the conclusions. First, the design is cross-sectional and single-center, which precludes causal or prognostic inference. Second, no liver biopsy was performed, so all outcomes are elastography-defined and are subject to the limitations of VCTE discussed above. Third, HBV DNA level and hepatitis B e-antigen (HBeAg) status were not systematically available for the staging cohort, so residual virological activity could not be modeled. The cohort is therefore described by its treatment status, namely long-term nucleos(t)ide analogue therapy for a median of 7 years, and not by documented viral suppression, and we have avoided the term virally suppressed throughout for that reason. Fourth, fasting glucose was unavailable, so the glucose-dependent indices relied on an HbA1c-derived estimate and are reported as exploratory only. Fifth, the sample size limits the precision of the AUC comparisons and of the regression estimates, and although internal validation was performed, external validation in an independent cohort is required. Finally, residual confounding by treatment duration, prior disease activity and unmeasured metabolic factors cannot be excluded.

Conclusion

In CHB treated with long-term nucleos(t)ide analogue therapy, CMI was associated with CAP-defined hepatic steatosis, whereas waist circumference showed the highest discrimination for elevated liver stiffness and exceeded FIB-4 and APRI on formal statistical comparison. Steatosis and elevated liver stiffness often occurred in the same patient. These findings support the inclusion of inexpensive metabolic and anthropometric measures in the non-invasive evaluation of treated CHB and warrant validation in larger, biopsy-anchored, prospective cohorts.

Ethics Committee Approval: The study protocol was approved by the Ankara Provincial Health Directorate Non-Interventional Clinical Research Ethics Committee (dated April 10, 2025, and numbered 04-10-2025), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors did not have any conflicts of interest to declare.

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ORIGINAL RESEARCH

Cardiometabolic index fails to discriminate the histological status of metabolic dysfunction-associated steatotic liver disease patients: A report from biopsy-proven Turkish metabolic dysfunction-associated steatotic liver disease cohort

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Highlights & Insights

- **Scientific Gap:** Previous studies have linked the cardiometabolic index (CMI) with MASLD and liver fibrosis using imaging-based definitions; however, its relationship with biopsy-proven histological severity has not been established.
- **Key Finding:** In a large biopsy-proven MASLD cohort, CMI was not associated with steatosis, activity, or clinically relevant fibrosis stages and showed poor discriminatory performance for significant and advanced fibrosis.
- **Clinical Impact:** CMI appears to reflect cardiometabolic dysfunction rather than histological liver injury and should not be used as a standalone marker for fibrosis risk stratification in patients with MASLD.

ABSTRACT

Background and Aim: Metabolic dysfunction-associated steatotic liver disease (MASLD) is a major global health challenge, and cardiovascular mortality has been shown to be significantly associated with the cardiometabolic index (CMI). However, data linking CMI with histological severity in MASLD are lacking. In this study, we aimed to investigate the association between CMI and histological parameters and to evaluate its discriminatory performance for clinically relevant fibrosis stages in a biopsy-proven MASLD cohort.

Materials and Methods: A total of 617 biopsy-proven MASLD patients from the Turkish MASLD Biobank were included in the analysis. Histological assessments were performed according to the steatosis, activity, fibrosis (SAF) fatty liver inhibition of progression algorithm. The CMI was calculated as follows: Triglyceride (TG) to high-density lipoprotein (HDL) multiplied by waist-to-height ratio.

Results: The median age was 48 (18–71) years, and 329 participants were male (53.3%). Neither CMI nor the TG/HDL ratio showed a significant monotonic trend across SAF fibrosis, activity, or steatosis grades (all $p>0.05$). Across clinically relevant fibrosis thresholds, neither marker differed significantly, except for a lower TG/HDL ratio in patients with cirrhosis (Holm-adjusted $p=0.036$). The AUROCs of CMI were 0.530 (95% CI: 0.483–0.577) for significant fibrosis and 0.475 (95% CI: 0.418–0.532) for advanced fibrosis, whereas fibrosis-4 index demonstrated better discrimination, with corresponding AUROCs of 0.688 (95% CI: 0.645–0.731) and 0.755 (95% CI: 0.708–0.803). In an exploratory analysis of cirrhosis (n=26), lower TG/HDL values showed inverse discrimination for cirrhosis, with an AUROC of 0.651 (95% CI: 0.544–0.757).

Conclusion: CMI was not significantly associated with histological fibrosis severity and showed poor discriminatory performance across clinically relevant fibrosis thresholds. These findings do not support the use of CMI as a non-invasive marker of histological fibrosis severity in MASLD.

Keywords: Cardiometabolic Index, fibrosis, metabolic dysfunction-associated steatotic liver disease.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the most prevalent chronic liver disease globally, affecting approximately 30% of the global population. The Middle East and North Africa (MENA) region has significantly higher prevalence rates (36.5%) when compared to other global regions.[1] The progressive burden of this disease is particularly high in Türkiye, which ranks among the highest-prevalence countries within the MENA region. A multicenter Turkish study involving 909 patients reported a MASLD prevalence reaching almost 50%.[2] Fibrosis stage is the strongest independent histological predictor of liver-related morbidity and mortality in MASLD.[3] Data from a biopsy-proven cohort at a Turkish center demonstrated a high prevalence of metabolic dysfunction-associated steatohepatitis (MASH), affecting up to 90.4% of biopsied patients, while significant fibrosis (≥F2) and metabolic syndrome were present in 35% and 63% of patients, respectively.[4] The substantial metabolic and histological burden of MASLD in Türkiye underscores the need for reliable, non-invasive tools for risk stratification and highlights the country as an important setting for their development and validation.

Liver biopsy remains the reference standard for assessing the histological severity of MASLD.[5,6] However, its use at a population scale remains limited due to its cost, invasive nature, associated procedural risks, sampling error, and susceptibility to inter-observer variability.[7] These constraints have allowed for the development of non-invasive biomarkers as surrogates for biopsy-proven histological endpoints. While established serum-based scores such as the fibrosis-4 index (FIB-4) and the NAFLD fibrosis score can be used as clinical decision aids to exclude advanced fibrosis,[8–10] they perform poorly in ruling in advanced fibrosis.[11] The limitations of existing non-invasive surrogates have prompted the search for simple markers that integrate various dimensions of cardiometabolic dysfunction simultaneously.

The cardiometabolic index (CMI) is one such composite marker, calculated as the product of the triglyceride-to-HDL cholesterol ratio (TG/HDL) and the waist-to-height ratio (WHtR): CMI=(TG [mmol/L] / HDL [mmol/L]) × (waist circumference [cm] / height [cm]). The TG/HDL ratio is used as a surrogate for insulin resistance due to its ability to reflect the downstream metabolic consequences of insulin resistance on lipid metabolism. The WHtR is a sensitive anthropometric index of central/visceral adiposity that outperforms body mass index (BMI) in capturing metabolic risk.[12,13] Visceral adiposity, captured by WHtR, also positively correlates with the severity of hepatic steatosis.[14] Notably, four of the five MASLD-defining CMRFs (elevated BMI/waist circumference, hypertriglyceridemia, low HDL, and hyperglycemia) are directly represented within CMI's components.[15] Hence, CMI provides a simple, reproducible composite signal of cardiometabolic dysregulation in patients with MASLD, with a potential to be used as a non-invasive screening and stratification tool for MASLD.

Cross-sectional studies using ultrasound and transient elastography-based definitions of MASLD have consistently found that higher CMI values are independently associated with hepatic steatosis and, in some analyses, liver fibrosis.[13,16] A systematic review and meta-analysis reported higher CMI levels in patients with MASLD, supporting its potential utility for identifying MASLD.[17] A study utilizing NHANES III data further reported that CMI was positively correlated with liver fibrosis in MASLD patients and associated with an increased risk of all-cause and other-cause mortality.[13]

However, in the existing CMI-MASLD literature, all studies have defined MASLD using imaging modalities either abdominal ultrasonography or FibroScan-derived controlled attenuation parameter and liver stiffness measurement, rather than liver biopsy. Whether CMI is associated with clinically important histological endpoints and fibrosis stage on liver biopsy remains unstudied and constitutes an important knowledge gap. In this study, we aimed to evaluate the association of CMI with different histological parameters of MASLD and its discriminatory performance for clinically relevant fibrosis stages in a biopsy-proven cohort derived from the Turkish MASLD Biobank.

Materials and Methods

Patients

A total of 617 adult (≥18 years) patients with biopsy-proven MASLD from the Turkish MASLD Biobank were included in this study. The biobank represents the demographic, biochemical, and histological data from Turkish MASLD patients. Initially, 693 patients were included in the dataset. Of these, 76 were excluded due to missing data required for the calculation of CMI. For other variables with occasional missing values, analyses were performed using the available data, and patients with missing values for a specific variable were excluded only from the respective analysis. Laboratory measurements, including TG and HDL cholesterol levels, were obtained after an overnight fast. The dataset excluded individuals with viral hepatitis, autoimmune/genetic/metabolic liver diseases, drug-induced injuries, or a high alcohol intake (>20 g/day in women, >30 g/day in men). All anthropometric and laboratory measurements were obtained within 6 months of the liver biopsy. CMI was calculated as follows: (TG [mmol/L] / HDL-C [mmol/L]) × (waist circumference [cm] / height [cm]). FIB-4 was calculated as age (years) × AST (U/L) / [platelet count (10^9/L) × √ALT (U/L)].

Liver Biopsy

Liver biopsy specimen assessments were performed according to the steatosis, activity, fibrosis (SAF) scoring algorithm developed by the Fatty Liver Inhibition of Progression (FLIP) consortium. Steatosis was graded from 0 to 3 based on the percentage of hepatocytes showing macrovesicular steatosis. Activity score (range 0–4) represents the sum of hepatocyte ballooning (0–2) and lobular inflammation (0–2). Fibrosis was staged from F0 (no fibrosis) to F4 (cirrhosis). Significant fibrosis was defined as F≥2 and advanced fibrosis as F≥3. MASH was diagnosed when the activity score was ≥2 with at least grade 1 ballooning in the presence of steatosis.[6]

Statistical Analysis

Due to the non-parametric distribution of the CMI values, the Mann–Whitney U test was used to compare CMI and TG/HDL ratio between different histological endpoints (presence of fibrosis, significant fibrosis [≥F2], advanced fibrosis [≥F3], cirrhosis [F4]). As SAF fibrosis, activity, and steatosis scores represent ordinal variables, the Jonckheere–Terpstra test for ordered alternatives was used to assess whether CMI and the TG/HDL ratio exhibited monotonic trends across increasing fibrosis (F0–F4), activity (A0–A4), and steatosis (S1–S3) grades. For the four binary fibrosis-threshold comparisons (F0 vs. F≥1, F0–F1 vs. F≥2, F0–F2 vs. F≥3, and F0–F3 vs. F4), P values were adjusted for multiple comparisons using the Holm method separately for CMI and the TG/HDL ratio.

Spearman's rank correlation coefficient (ρ) was used to assess the correlation between CMI and TG/HDL ratio with various histological parameters (SAF fibrosis, SAF activity, and SAF steatosis). To evaluate the diagnostic performance of the CMI and TG/HDL ratio, receiver operating characteristic (ROC) curve analysis was performed, and the area under the ROC curve (AUROC) was calculated. ROC curve analysis was performed to evaluate the discriminatory performance of CMI, the TG/HDL ratio, and FIB-4 for significant (F≥2) and advanced fibrosis (F≥3). To enable direct descriptive comparison of AUROCs, analyses were restricted to patients with complete data for all markers included in the respective analysis. A binary logistic regression analysis was performed to evaluate the independent association of CMI with fibrosis after adjustment for potential confounding factors. Age, sex, hypertension, and diabetes were included as clinically relevant covariates given their potential association with CMI. Dyslipidemia and body mass index were not included in the model to minimize collinearity with CMI and its components. Statistical significance was defined as $p < 0.05$ (two-tailed). Statistical analyses were performed using IBM SPSS Statistics, version 29.0 for Windows (IBM Corp., Armonk, NY, USA).

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki. Due to the retrospective nature of the study, the requirement for informed consent was waived. The study protocol was approved by the local ethics committee (04.02.2026; Protocol No. 2026/10). The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Results

General characteristics of the study patients are presented in Table 1. The median age of the cohort was 48 years (18–71). The median BMI was 31.3 kg/m^2 with a median waist circumference of 104 cm. Liver enzymes were mildly to moderately elevated, with a median aspartate aminotransferase of 41 U/L and alanine aminotransferase of 65 U/L. The prevalence of type 2 diabetes mellitus (T2DM) was 44.4% and hypertension was 37.1%, representing a high metabolic burden. Significant fibrosis (≥F2) was present in 40.5%, advanced fibrosis (≥F3) in 20.7%, while patients with cirrhosis (4.2%) constituted a small proportion of the cohort. A significant portion of the patients were diagnosed with MASH (n=553, 89.6%) (Table 2). We examined whether CMI and the TG/HDL ratio showed monotonic trends across increasing SAF fibrosis, activity, and steatosis grades using the Jonckheere–Terpstra test (Table 3). Neither CMI nor the TG/HDL ratio showed a significant monotonic trend across increasing fibrosis stages (p=0.781 and p=0.527, respectively). Similarly, no significant monotonic trends were observed across activity grades (p=0.791 and p=0.851, respectively) or steatosis grades (p=0.376 and p=0.465, respectively).

When fibrosis was analyzed according to clinically relevant thresholds (F≥1, F≥2, F≥3, and F4), neither CMI nor the TG/HDL ratio differed significantly across the respective fibrosis categories, with the exception of the TG/HDL ratio in patients with cirrhosis. The TG/HDL ratio was significantly lower in patients with cirrhosis than in those without cirrhosis, and this difference remained significant after Holm correction (adjusted p=0.036) (Table 4). No other significant differences were observed for CMI or the TG/HDL ratio across the evaluated fibrosis thresholds.

Table 1. General characteristics (n=617)

Parameters	Values
Age, years	48 [18–71]
Sex, male (n, %)	329 (53.3%)
BMI, kg/m^2	31.3 [21–56.0]
Height, cm	165 [135–193]
Weight, kg	86 [48–158]
Waist circumference, cm	104 [70–147]
Waist-to-height ratio	0.6 [0.5–1.0]
AST, U/L	41 [11–168]
ALT, U/L	65 [12–252]
Alkaline phosphatase, U/L	86 [11–278]
GGT, U/L	47 [8–251]
Platelets, x10^3/µl	237 [77–543]
Total bilirubin, mg/dL	0.7 [0.1–3.2]
Total cholesterol, mmol/L	5.3±1.2
Triglycerides, mmol/L	1.8 [0.4–8.1]
HDL, mmol/L	1.1 [0.5–2.5]
LDL, mmol/L	3.4 [0.7–10.3]
Type 2 diabetes mellitus, n (%)	274 (44.4%)
Hypertension, n (%)	229 (37.1%)
FIB-4	1.1 [0.01–6.3]
CMI	1.0 [0.2–6.5]
TG/HDL	1.6 [0.2–10.1]

BMI: Body-mass index; AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma glutamyl transferase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; FIB-4: Fibrosis-4 index; CMI: Cardiometabolic index. Data are presented as median [minimum–maximum], mean±standard deviation, or as counts and percentages, as appropriate.

Table 2. Histological parameters of the study patients (n=617)

Parameters	Values
Steatosis (S1/S2/S3), n (%)	135 (21.9%) / 236 (38.2%) / 246 (39.9%)
Activity (A0/A1/A2/A3/A4), n (%)	9 (1.5%)/48 (7.8%)/145 (23.5%) / 200 (32.4%) / 215 (34.8%)
Fibrosis (F0/F1/F2/F3/F4), n (%)	169 (27.4%)/198 (32.1%)/122 (19.8%)/102 (16.5%) / 26 (4.2%)
MASH, n (%)	553 (89.6%)
Significant fibrosis (F≥2), n (%)	250 (40.5%)
Advanced fibrosis (F≥3), n (%)	128 (20.7%)
Cirrhosis, n (%)	26 (4.2%)

MASH: Metabolic dysfunction-associated steatohepatitis.

Table 3. Distribution of CMI and TG/HDL ratio across SAF histological grades

Histological category	CMI, median (interquartile range)	Standardized J-T statistic	p	TG/HDL ratio, median (interquartile range)	Standardized J-T statistic	p
SAF fibrosis		**0.278**	**0.781**		**-0.632**	**0.527**
F0 (n=169)	0.98 (0.59–1.66)			1.55 (0.98–2.74)		
F1 (n=198)	0.91 (0.59–1.50)			1.45 (0.95–2.29)		
F2 (n=122)	1.14 (0.76–1.65)			1.72 (1.17–2.56)		
F3 (n=102)	1.01 (0.68–1.51)			1.61 (1.02–2.31)		
F4 (n=26)	0.77 (0.52–1.24)			1.08 (0.75–1.79)		
SAF activity		**0.265**	**0.791**		**-0.188**	**0.851**
A0 (n=9)	0.52 (0.46–1.98)			0.82 (0.71–1.63)		
A1 (n=48)	1.15 (0.59–1.68)			1.87 (1.09–2.59)		
A2 (n=145)	0.96 (0.68–1.69)			1.51 (1.09–2.72)		
A3 (n=200)	0.91 (0.62–1.42)			1.47 (0.96–2.22)		
A4 (n=215)	1.02 (0.64–1.57)			1.61 (0.96–2.53)		
SAF steatosis		**0.886**	**0.376**		**0.731**	**0.465**
S1 (n=135)	0.93 (0.56–1.53)			1.49 (0.83–2.56)		
S2 (n=236)	1.00 (0.63–1.56)			1.58 (1.07–2.42)		
S3 (n=246)	0.97 (0.65–1.58)			1.61 (1.00–2.45)		

Data are presented as median (interquartile range). Monotonic trends in CMI and TG/HDL ratio across increasing SAF fibrosis, activity, and steatosis grades were evaluated using the Jonckheere–Terpstra test for ordered alternatives. Standardized Jonckheere–Terpstra (J-T) statistics and two-sided p-values are reported. CMI: Cardiometabolic index; HDL: High-density lipoprotein cholesterol; SAF: Steatosis-activity-fibrosis; TG: Triglyceride.

Spearman correlation analysis showed no significant associations between CMI and SAF fibrosis, activity, or steatosis, as shown in Table 5. Similarly, TG/HDL ratio was not significantly correlated with any SAF component. Binary logistic regression analyses were performed to assess the independent association of CMI with significant and advanced fibrosis. After adjustment for age, sex, T2DM, and hypertension, CMI remained not significantly associated with either significant or advanced fibrosis. The results of the multivariable logistic regression analyses are presented in Table 6.

ROC curve analysis showed no meaningful discriminatory ability of either CMI or the TG/HDL ratio for significant or advanced fibrosis. For significant fibrosis, the AUROCs were 0.530 (95% CI: 0.483–0.577) for CMI and 0.511 (95% CI: 0.464–0.558) for the TG/HDL ratio. For advanced fibrosis, the corresponding AUROCs were 0.475 (95% CI: 0.418–0.532) and 0.458 (95% CI: 0.401–0.515), respectively. In contrast, FIB-4 demonstrated better discriminatory performance, with AUROCs of 0.688 (95% CI: 0.645–0.731) for significant fibrosis and 0.755 (95% CI: 0.708–0.803) for advanced fibrosis. FIB-4 data were unavailable in 23 patients. Accordingly, ROC analyses comparing CMI, the TG/HDL ratio, and FIB-4 were performed in the 594 patients with complete data for all three markers, ensuring that all AUROCs were derived from the same study population (Fig. 1).

In the exploratory cirrhosis analysis, both the TG/HDL ratio and CMI showed discrimination in the inverse direction. When lower values

Table 4. Comparison of CMI and TG/HDL ratio across fibrosis stages

Histological category	CMI, median (IQR)	p	Holm-adjusted p	TG/HDL, median (IQR)	p	Holm-adjusted p
Any fibrosis						
F0 (n=169)	0.98 (0.59–1.66)			1.55 (0.98–2.74)		
F≥1 (n=448)	0.96 (0.63–1.51)	0.769	1.000	1.55 (1.00–2.30)	0.344	0.688
Significant fibrosis						
F0–F1 (n=367)	0.93 (0.59–1.59)			1.50 (0.95–2.56)		
F≥2 (n=250)	1.04 (0.68–1.54)	0.121	0.363	1.62 (1.01–2.34)	0.460	0.688
Advanced fibrosis						
F0–F2 (n=489)	0.97 (0.62–1.60)			1.55 (1.01–2.56)		
F≥3 (n=128)	0.96 (0.65–1.42)	0.520	1.000	1.56 (0.94–2.17)	0.209	0.627
Cirrhosis						
F0–F3 (n=591)	0.98 (0.63–1.58)			1.56 (1.02–2.53)		
F4 (n=26)	0.77 (0.52–1.24)	0.051	0.204	1.08 (0.75–1.79)	0.009	0.036

Data are presented as median (interquartile range). p-values were derived from the Mann–Whitney U test. p-values were adjusted for multiple comparisons within each family of tests using the Holm method. CMI: Cardiometabolic index; IQR: Interquartile range; TG/HDL: Triglyceride-to-high-density lipoprotein cholesterol ratio.

Table 5. Spearman correlations between CMI, TG/HDL ratio, and SAF histological scores

Variables	Spearman's ρ	p
CMI versus SAF scores		
SAF Fibrosis	+0.010	0.801
SAF Activity	+0.010	0.800
SAF Steatosis	+0.036	0.373
TG/HDL versus SAF scores		
SAF Fibrosis	-0.026	0.524
SAF Activity	-0.009	0.833
SAF Steatosis	+0.029	0.469

ρ: Spearman's rank correlation coefficient. CMI: Cardiometabolic index; SAF: Steatosis-activity-fibrosis; TG/HDL: Triglyceride-to-high-density lipoprotein cholesterol ratio.

were considered indicative of cirrhosis, the AUROC was 0.651 (95% CI: 0.544–0.757) for the TG/HDL ratio and 0.613 (95% CI: 0.505–0.721) for CMI. The inverse discrimination of the TG/HDL ratio was consistent with its significantly lower values in patients with cirrhosis (Holm-adjusted p=0.036). Given the small number of patients with cirrhosis (n=26), these cirrhosis-specific findings should be considered exploratory (Fig. 2).

Discussion

In this cohort of 617 Turkish patients with MASLD, we evaluated the association of CMI and its TG/HDL ratio component with histological disease severity and their discriminatory performance for fibrosis. Neither CMI nor the TG/HDL ratio showed a significant monotonic trend across increasing SAF fibrosis stages, activity, or steatosis grades. Furthermore, CMI was not independently associated with significant or advanced fibrosis, and both markers demonstrated poor discriminatory performance for clinically relevant fibrosis

Table 6. Multivariable logistic regression analysis of factors associated with significant and advanced fibrosis

Variables	Significant fibrosis				Advanced fibrosis			
	B	SE	OR	p	B	SE	OR	p
Age	0.037	0.010	1.037	<0.001	0.045	0.012	1.046	<0.001
Sex	-0.057	0.186	0.944	0.757	0.038	0.223	1.039	0.863
T2DM	0.887	0.181	2.427	<0.001	1.119	0.228	3.062	<0.001
Hypertension	-0.205	0.194	0.814	0.290	-0.265	0.227	0.767	0.243
CMI	0.053	0.105	1.054	0.613	-0.128	0.143	0.880	0.369

Multivariable binary logistic regression models were adjusted for age, sex, T2DM, hypertension, and CMI. CMI: Cardiometabolic index; T2DM: Type 2 diabetes mellitus; OR: Odds ratio; SE: Standard error.

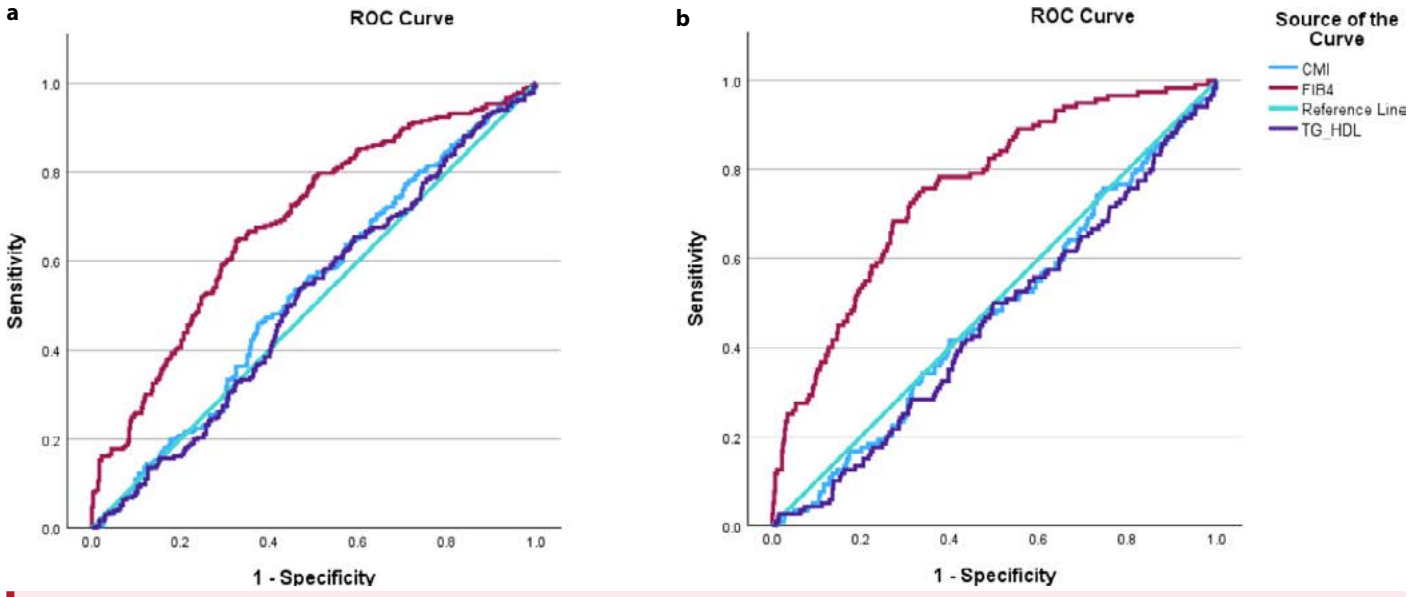


Figure 1. Receiver operating characteristic curves for the discrimination of histological fibrosis severity. **(a)** cardiometabolic index (CMI), triglyceride/high-density lipoprotein (TG/HDL) ratio, and fibrosis-4 index (FIB-4) for significant fibrosis; **(b)** CMI, TG/HDL ratio, and FIB-4 for advanced fibrosis. Receiver operating characteristic (ROC) curve analyses comparing CMI, the TG/HDL ratio, and FIB-4 were restricted to the 594 patients with complete data available for all three markers, ensuring that all AUROCs were derived from the same study population.

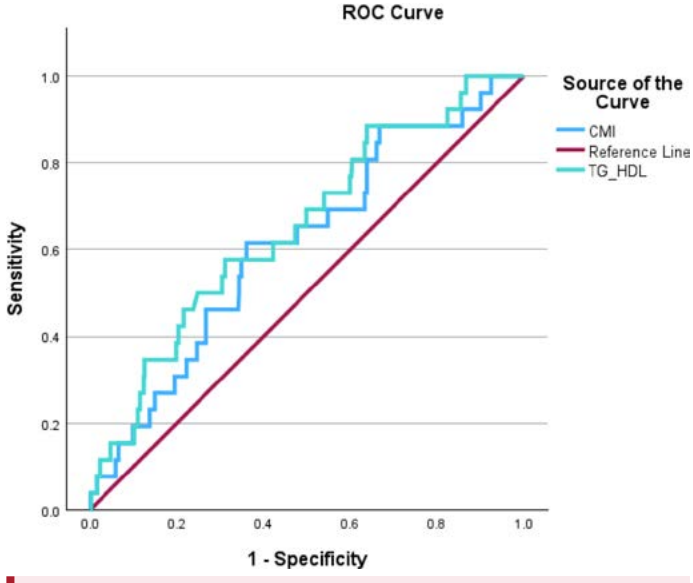


Figure 2. Receiver operating characteristic curves for the discrimination of cirrhosis using cardiometabolic index and the triglyceride/high density lipoprotein ratio. Both markers showed an inverse direction of discrimination, with lower values associated with cirrhosis (n=617).

thresholds. Although the TG/HDL ratio was significantly lower in patients with cirrhosis, this isolated finding did not translate into an overall association with increasing fibrosis severity. Importantly, FIB-4 demonstrated substantially better discrimination for advanced fibrosis than either CMI or the TG/HDL ratio. The ability of an established fibrosis-specific score to discriminate advanced fibrosis within the same cohort provides an important positive comparator for our findings. This suggests that the poor performance of CMI was unlikely to be explained simply by an inability to discriminate fibrosis within this study population but rather reflects the limited utility of CMI as a marker of histological fibrosis severity.

Previous studies evaluating CMI in MASLD have relied predominantly on imaging-based modalities such as abdominal ultrasound or transient elastography. Cross-sectional studies conducted in Asian and NHANES populations demonstrated associations between CMI and hepatic steatosis or elastography-based fibrosis measurements.[12,15,18] However, imaging-based steatosis or fibrosis does not equate to histological severity, particularly when reflecting inflammatory activity and fibrosis stage. To our knowledge, this is the first study to evaluate CMI against liver biopsy, which remains the reference standard for histological assessment in MASLD. A major strength of our study is the inclusion of a large, well-characterized biopsy-proven cohort. Our findings further support the concept that metabolic indices, although useful for characterizing metabolic dysfunction, may not reliably reflect the severity or progression of histological liver injury.

An exploratory finding was the lower TG/HDL ratio observed in patients with cirrhosis. Consistent with this finding, when lower TG/HDL values were considered indicative of cirrhosis, the inverse AUROC was 0.651 (95% CI: 0.544–0.757). This finding should not be interpreted as evidence that the TG/HDL ratio is a validated marker of cirrhosis, particularly given the small number of patients with cirrhosis (n=26) and the resulting uncertainty of the estimate. Moreover, the lower TG/HDL ratio in advanced liver disease may reflect alterations in lipid metabolism associated with hepatic dysfunction rather than a direct relationship between cardiometabolic risk and fibrosis severity. Therefore, this observation should be considered hypothesis-generating and requires confirmation in larger independent cohorts.

Several biological and methodological factors may account for the poor performance of CMI. First, CMI captures metabolic dysfunction but does not directly measure the molecular pathways which drive hepatocellular injury and fibrogenesis. Progression from steatosis to MASH involves lipotoxicity, oxidative stress, mitochondrial dysfunction, and activation of various inflammatory signaling pathways including NF-κB and JNK.[19] Fibrosis progression is mediated by hepatic stellate-cell activation, TGF-β signaling, and extracellular matrix deposition. These mechanisms cannot be accurately captured by anthropometric or lipid-based indices. Moreover, the components of CMI are influenced by multiple confounders, including age, sex, ethnicity, diet, medications, and comorbid conditions. From a health systems perspective, reliance on simple biomarkers for fibrosis staging may lead to both under- and over-classification, potentially delaying appropriate care. While these indices may be helpful in identifying individuals at risk for metabolic syndrome or imaging-defined steatosis, they cannot replace other validated fibrosis-specific non-invasive tools to direct treatment decisions.

The poor discriminatory performance of CMI for histological severity highlights the need for biomarkers that more directly reflect hepatocellular injury and fibrogenesis. Markers such as the PRO-C3-based score (ADAPT) and ELF panel components have shown great promise in identifying MASLD and advanced fibrosis.[20,21] Advanced imaging modalities such as MR elastography also demonstrate stronger correlations with histology.[22] Future studies integrating metabolic, inflammatory, fibrotic, and genetic markers using machine learning approaches may improve risk stratification. Longitudinal studies evaluating prediction of hard clinical outcomes and assessment of prognostic performance are also required.

The results of this study should be interpreted in the context of its strengths and limitations. To our knowledge, this is the first study to evaluate the performance of CMI in a biopsy-proven MASLD cohort, with liver histology providing a robust reference standard. However, as the study population consisted of patients selected for liver biopsy, selection bias cannot be excluded. In addition, anthropometric and laboratory measurements were obtained within 6 months of liver biopsy. Given the retrospective design, changes in metabolic status, lifestyle, or treatment during this interval cannot be completely excluded. Furthermore, the characteristics of this highly selected cohort may limit the generalizability of our findings to the broader MASLD population and the general population. Another limitation is the lack of detailed information on concomitant medications, particularly lipid-lowering and antidiabetic therapies. As these medications may influence metabolic parameters, including TG and HDL cholesterol levels, their potential impact on CMI and the TG/HDL ratio could not be accounted for in the present analyses. Importantly, these treatment effects may not represent random variability, as treatment intensity may be related to the underlying cardiometabolic burden and could therefore have contributed to the weak or inverse associations observed between CMI-related parameters and fibrosis severity. As this was a retrospective database-based study, potential inaccuracies related to data entry cannot be completely excluded, despite careful data review and validation before the analysis. Finally, the cirrhosis subgroup was relatively small (n=26), resulting in uncertainty around the corresponding estimates; therefore, the cirrhosis-specific findings should be considered exploratory and require validation in larger independent cohorts.

Conclusion

This study demonstrated that CMI did not discriminate biopsy-proven histological severity in patients with MASLD. Neither CMI nor the TG/HDL ratio showed a significant monotonic trend across fibrosis, activity, or steatosis grades, and CMI was not independently associated with significant or advanced fibrosis. In contrast, FIB-4 showed better discriminatory performance for significant and advanced fibrosis within the same cohort, supporting the interpretation that the poor performance of CMI reflects its limited utility as a marker of histological fibrosis severity rather than an inability to discriminate fibrosis in the study population. The lower TG/HDL ratio observed in patients with cirrhosis may reflect metabolic alterations associated with advanced liver disease and should be considered exploratory. Taken together, our findings do not support the use of CMI as a non-invasive marker for the assessment of fibrosis severity.

Ethics Committee Approval: The study protocol was approved by the Recep Tayyip Erdogan University ethics committee (04.02.2026; Protocol No. 2026/10), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived.

Conflict of Interest: The authors did not have any conflicts of interest to declare.

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ORIGINAL RESEARCH

Hepatitis B surface antigen seroclearance after nucleos(t)ide analogue discontinuation in non-cirrhotic patients with chronic hepatitis B

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Highlights & Insights

- **Scientific Gap:** HBsAg seroclearance is rare during long-term nucleos(t)ide analogue therapy in HBeAg-negative chronic hepatitis B, and data on outcomes after treatment discontinuation are scarce and heterogeneous.
- **Key Finding:** HBsAg seroclearance occurred in 11.0% of patients after nucleos(t)ide analogue discontinuation and in none of those who continued treatment; 75% of these patients developed anti-HBs. Clinical relapse occurred in 39.7%, mostly within the first 3 months.
- **Clinical Impact:** Nucleos(t)ide analogue discontinuation may increase the likelihood of functional cure in carefully selected non-cirrhotic, HBeAg-negative patients, provided that close post-treatment monitoring is ensured.

ABSTRACT

Background and Aim: This study aimed to evaluate the clinical outcomes following the discontinuation of nucleos(t)ide analogue (NA) treatment in hepatitis B e antigen (HBeAg)-negative patients with chronic hepatitis B (CHB).

Materials and Methods: This single-center retrospective cohort study included 146 non-cirrhotic patients with CHB who achieved long-term viral suppression under NA treatment. Seventy-three patients discontinued NA treatment, while a historical age- and sex-matched control group consisted of 73 patients who continued NA treatment.

Results: Hepatitis B surface antigen (HBsAg) seroclearance occurred in eight patients (11%) in the treatment-discontinuation group, while none was observed in the treatment-continued group ($p = 0.004$). The cumulative probability of HBsAg loss was 16.9% at month 120 after NA discontinuation. Firth-penalized Cox regression analysis identified younger age (<50 years) at treatment discontinuation ($p=0.023$) and elevated baseline serum AST levels ($p=0.018$) as independent predictors of HBsAg seroclearance. Seventy-five percent of these patients experienced HBsAg seroconversion to hepatitis B surface antibody (anti-HBs). After NA discontinuation, 67% of the patients (49/73) in the treatment-discontinuation group experienced virological relapse. Of these, 29 developed clinical relapse and reinitiated antiviral treatment, while the remaining 20 patients continued follow-up without antiviral therapy. Most clinical relapses (72%) occurred within the first 3 months after treatment discontinuation. Virological relapse did not occur in the other 24 patients. Overall, 44 patients in the treatment-discontinuation group (60%) did not require retreatment during follow-up.

Conclusion: Discontinuation of long-term NA treatment in selected HBeAg-negative patients was associated with HBsAg seroclearance and may contribute to a functional cure. Close post-discontinuation surveillance remains essential for early detection and management of clinical relapse.

Keywords: Antiviral therapy discontinuation, HBsAg Seroclearance, Hepatitis B virus.

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Introduction

Chronic hepatitis B virus (HBV) infection continues to pose a significant public health concern globally, affecting approximately 250 million individuals.[1,2] HBV accounts for most adult cases of cirrhosis and hepatocellular carcinoma (HCC) in Türkiye.[3–5] A 2009 epidemiological study found that the prevalence of hepatitis B surface antigen (HBsAg) was approximately 4%, with more than 2 million adults testing positive for HBsAg in Türkiye.[6]

Nucleos(t)ide analog (NA) antiviral therapy provides effective long-term viral suppression and mitigates disease progression in patients with chronic hepatitis B (CHB). The primary goal of antiviral treatment for HBV is to eliminate HBsAg and achieve seroconversion to hepatitis B surface antibody (anti-HBs). Unfortunately, HBsAg seroclearance rarely occurs after long-term NA treatment with current antiviral therapies.[2,7] HBsAg loss was observed in approximately 10% of patients with hepatitis B e antigen (HBeAg)-positive and around 1% of HBeAg-negative patients after 8 years of tenofovir disoproxil fumarate (TDF) treatment.[8,9] Consequently, many patients with HBeAg-negative require indefinite therapy, which presents challenges related to adherence, cumulative drug exposure, and potentially side effects, antiviral resistance, and long-term healthcare costs.[2,7,10] Emerging evidence from randomized trials and real-world studies has reignited interest in discontinuing NA therapy to stimulate host immune responses that may lead to HBsAg seroclearance.[11–13]

According to previous studies, NA treatment may be discontinued in selected patients with CHB.[7,12–14] In some cases, discontinuation of NA treatment can lead to a functional cure by triggering immune control.[12–16] However, the data are heterogeneous and scarce. Additionally, previous studies do not clearly define the characteristics of the selected patients. In this single-center study, we examined the clinical outcomes of NA discontinuation in a rigorously selected cohort of non-cirrhotic, HBeAg-negative patients with CHB.

Materials and Methods

Study Design and Patient Population

This is a retrospective, single-center observational cohort study conducted at the Liver Diseases Outpatient Clinic. Chronic HBV infection was diagnosed and treated based on the European Association for the Study of the Liver guideline.[7] A total of 852 patients with CHB who were followed at our center between January 2014 and December 2024 were screened for eligibility. The study protocol was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (approval number: 2025/393, date: 22/05/2025) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Patient Selection, Study Groups, and Monitoring Protocol

All patients in the screened cohort were evaluated using the same eligibility and exclusion criteria before being classified by treatment status. Eligible patients were adults with non-cirrhotic, HBeAg-negative CHB who had received licensed oral NA for at least 5 years, maintained virological suppression, defined as undetectable serum HBV DNA, for at least 3 years before the index date, and had normal serum ALT levels. Patients with cirrhosis, a history of hepatic decompensation, liver stiffness greater than 10 kPa, hepatocellular carcinoma, viral coinfection, another concomitant liver disease, or insufficient clinical follow-up were excluded. The discontinuation of NA treatment was conducted in accordance with local regulations. Of the 477 eligible patients, 73 had discontinued NA treatment, and 404 had continued treatment. Propensity scores based on age and sex were used for 1:1 matching without replacement. Each patient in the discontinuation group was matched to one patient in the continuation group with a maximum absolute propensity score difference of 0.01. The final matched cohort included 146 patients: 73 in the NA-discontinuation group and 73 in the NA-continuation group. The index date was defined as the NA discontinuation date for the discontinuation group and the corresponding cohort-entry date for the matched continuation group. The patient-selection process is presented in Figure 1.

Laboratory Measurements

Laboratory parameters, including serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), bilirubin, and complete blood cell counts, were measured at baseline and during follow-up using standard automated methods in our institution's central laboratory. Baseline laboratory values were those obtained immediately before initiation of NA treatment. Histological activity and fibrosis stage were based on the pretreatment liver biopsy. Quantitative HBsAg at NA discontinuation was measured using the Elecsys HBsAg II Quant assay (Roche Diagnostics, Mannheim, Germany). Serum HBV DNA levels were assessed using the Cobas TaqMan assay (Roche Diagnostics, Branchburg, NJ, USA) with a lower limit of detection of 20 IU/mL.

Definitions and Study Endpoints

The primary endpoints of the study were to investigate sustained HBsAg seroclearance and to identify factors associated with seroclearance. HBsAg seroclearance was defined as the loss of detectable HBsAg for at least six months, with or without seroconversion to anti-HBs following discontinuation of NA treatment. The secondary endpoints included virological, biochemical, and clinical relapse through the last follow-up. Virological relapse was defined as a serum HBV DNA level >2,000 IU/mL at any time after NA discontinuation, whereas biochemical relapse was defined as an increase in serum ALT to >2× the upper limit of normal. Clinical relapse was defined as the concomitant occurrence of virological and biochemical relapse. TDF, entecavir (ETV), or tenofovir alafenamide (TAF) was immediately recommended at the physician's discretion in cases of clinical relapse.

Follow-up

Patients were regularly seen in an outpatient clinic. Laboratory tests were performed during this period. Serum ALT and HBV DNA levels

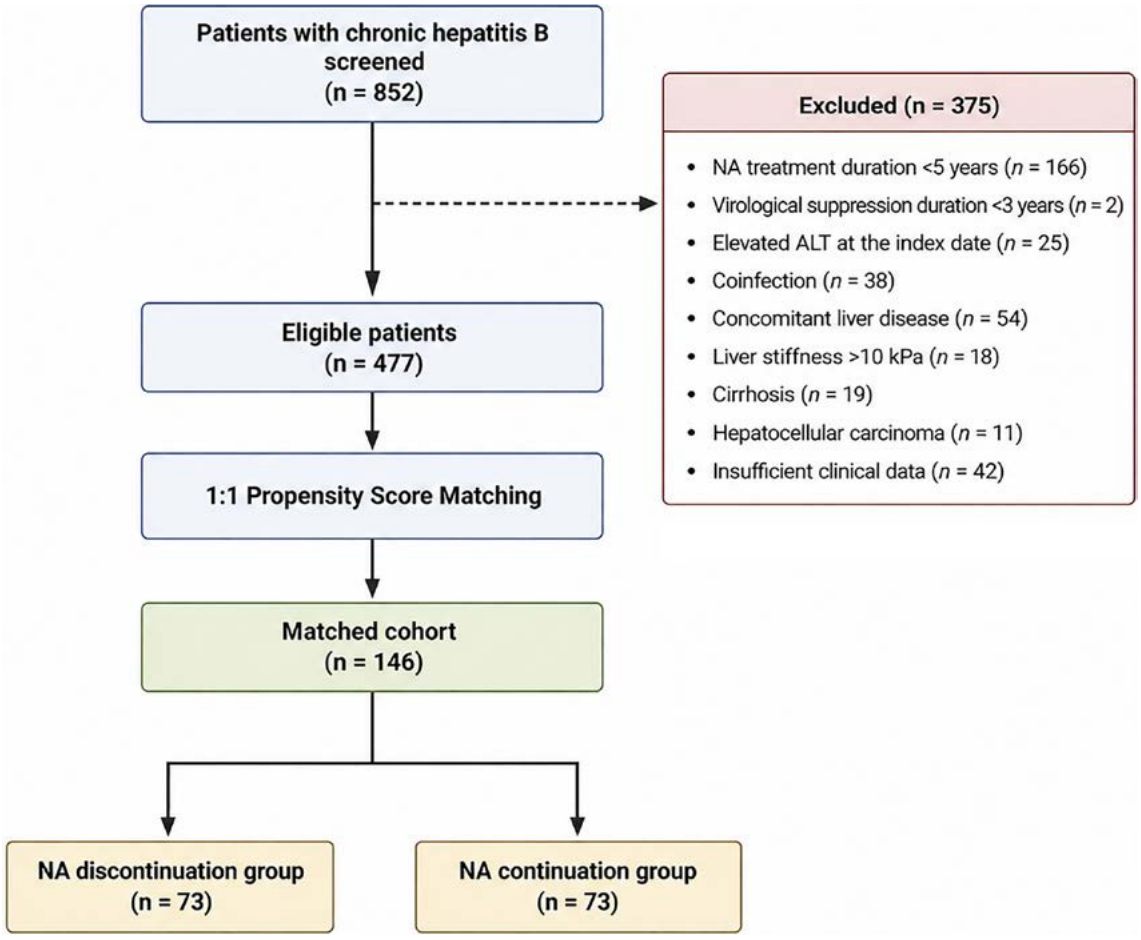


Figure 1. Flowchart illustrating patient selection and propensity score matching.

were serially monitored on the 3rd, 7th, 14th, 28th, 56th days in the discontinuation group, and every three months in both groups.

Statistical Analysis

To minimize confounding factors introduced by the retrospective, and nonrandomized design, 1:1 propensity score matching was performed by age and gender. The propensity score without replacement was calculated with a binary logistic regression for each patient. For the matching process, the tolerance for the score in matching cases and controls was set at 0.01. A control is eligible to match a case if the absolute value of the difference in the propensity scores is less than or equal to 0.01. Descriptive statistics are summarized as counts and percentages 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, Fisher's Exact tests or Fisher-Freeman-Halton Exact Test, where appropriate. The Mann-Whitney U test was used to compare two groups regarding ordinal or non-normally distributed continuous variables. The survival estimations were performed using the Kaplan-Meier algorithm, and the comparison between groups was evaluated with the Log-rank test. Variables with a p-value <0.25 in the univariable Firth penalized Cox proportional hazards regression were considered candidates for the multivariable Firth penalized Cox model. Variables of established clinical importance were also included, irrespective of their univariable significance, using a purposeful selection approach. The final model was constructed using variables with a p-value less than 0.05, which were considered statistically significant. The hazard ratio (HR) and the associated 95% confidence interval (CI) were calculated. Statistical analyses were performed using IBM SPSS Statistics version 30.0 (IBM Corp., Armonk, NY, USA). A two-tailed P-value less than 0.05 was considered statistically significant.

Results

A total of 146 non-cirrhotic patients with HBeAg-negative CHB were included in the analysis: 73 patients in the NA discontinuation group and 73 in the NA continuation group. The median age of the patients was 52.5 years, and the majority of patients were male (56%). There were no significant differences in baseline characteristics among patients, except that the histological activity index (HAI) was higher in the NA discontinuation group (p<0.001), (Table 1). The median duration of NA therapy before discontinuation was 93 months (IQR: 72–120). The median follow-up duration after NA discontinuation was 44 months (IQR: 25-89).

Table 1. Characteristics of the matched study cohort

Characteristic	Overall (n=146)	NA discontinuation (n=73)	NA continuation (n=73)	p
Age at the index date (years)	52.5 (44–59)	53 (44–59)	52 (45–59)	0.943
Sex, male/female (%)	56/44	56/44	56/44	1.000
Disease duration at the index date (months)	205.0 (160–229)	205.0 (176–225)	205.0 (138–232)	0.707
Serum HBV DNA (log10 IU/mL)	5.38 (4.28–6.74)	5.37 (4.0–6.7)	5.38 (4.7–6.8)	0.405
Serum ALT (U/L)	56 (24–113)	48 (23–117)	57.5 (27–112)	0.592
Serum AST (U/L)	35 (23–62)	33 (22–81)	35 (25–53)	0.948
Serum GGT (U/L)	23 (16–35)	22 (15–35)	24 (16–34)	0.576
Total bilirubin (mg/dL)	0.75 (0.53–1.0)	0.7 (0.5–1.1)	0.8 (0.6–1.0)	0.892
Albumin (g/dL)	4.3 (4.1–4.5)	4.3 (4.1–4.5)	4.3 (4.1–4.5)	0.821
Platelet count ($\times10^3$/μL)	220 (183–269)	218 (184–277)	221 (183–264)	0.601
INR	1.0 (0.96–1.0)	1.0 (0.97–1.0)	1.0 (1.0–1.1)	0.506
HAI on liver biopsy	7 (5.5–9.0)	8 (6.0–9.0)	6.0 (5–8)	<0.001
Fibrosis score	1 (1–2)	1 (1–2)	2 (1–2)	0.122
NA treatment at the index date, n	27 ETV 105 TDF 14 other	12 ETV 50 TDF 11 other	15 ETV 55 TDF 3 other	0.0764

Data are presented as median (25^{th}–75^{th} percentiles), percentage, or count, as appropriate. Laboratory and histological variables are pretreatment values obtained before NA initiation; age and disease duration were assessed at the index date. The index date was the date of NA discontinuation for the discontinuation group and the matched cohort-entry date for the continuation group. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHB: Chronic hepatitis B; ETV: Entecavir; GGT: Gamma-glutamyl transferase; HAI: Histological activity index; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; INR: International normalized ratio; NA: Nucleos(t)ide analogue; TDF: Tenofovir disoproxil fumarate. Other NAs included lamivudine and telbivudine.

HBsAg seroclearance was observed in eight patients in the NA discontinuation group, compared to none in the treatment continuation group (p=0.004). HBsAg seroclearance occurred progressively over time. The cumulative probability of HBsAg seroclearance, estimated using the Kaplan–Meier method, reached 16.9% at 120 months (Fig. 2). The median time to HBsAg seroclearance after NA discontinuation was 4.5 months (range, 1 to 81 months). There were no significant differences in baseline characteristics between patients with and without HBsAg seroclearance (Table 2). Firth-penalized Cox regression analysis revealed that only younger age (<50 years) at treatment discontinuation (hazard ratio [HR], 5.72; 95% confidence interval [CI], 1.26–35.01; p=0.023) and elevated baseline AST levels (HR, 6.29; 95% CI, 1.36–39.96; p=0.018) were independently associated with HBsAg seroclearance in patients with CHB (Table 3). Six (75%) patients experienced HBsAg seroconversion to anti-HBs.

After NA discontinuation, 67% of patients (49/73) in the treatment-discontinuation group experienced virological relapse. Virological relapse was first detected in 19 patients during the first month, 15 during the second month, 5 during the third month, 2 during the fourth month, 4 during the fifth month, and 4 during the sixth month. Virological relapse did not occur in the remaining 24 patients. Of these patients with virological relapse, 29 developed clinical relapses. Most clinical relapses (72%) occurred within the first 3 months after treatment discontinuation. The median time from NA discontinuation to relapse was 2 months (range, 1–60 months). Of these patients, nine had ALT levels >3×ULN, seven had levels >5×ULN, and six had levels >10×ULN. None of these patients had a serum bilirubin level >2 mg/dL. All 29 patients with clinical relapse were successfully retreated with NAs and achieved virological and biochemical responses within a median of 10.5 weeks after retreatment. Overall, 44 patients in the treatment-discontinuation group (60%) did not require retreatment during follow-up. No patient in this group developed cirrhosis or HCC or required hospitalization. There was no significant difference in patient characteristics between patients with and without clinical relapse (Table 4).

Quantitative HBsAg measurements at the time of NA discontinuation were available for 60 patients. No clinical relapse was observed in patients with HBsAg levels <100 IU/mL (0/5), whereas relapse occurred in 52.2% (12/23) of patients with HBsAg levels between 100 and <1000 IU/mL and in 46.9% (15/32) of those with HBsAg levels ≥1000 IU/mL (p=0.228) (Table 5).

Discussion

In the present study, we evaluated the long-term clinical outcomes of CHB following the discontinuation of NA treatment in patients with HBeAg-negative chronic hepatitis B. These patients had been treated with NA for at least five years and had achieved HBV suppression for at least the last three years preceding discontinuation. In this study, the cumulative HBsAg seroclearance rate among pa-

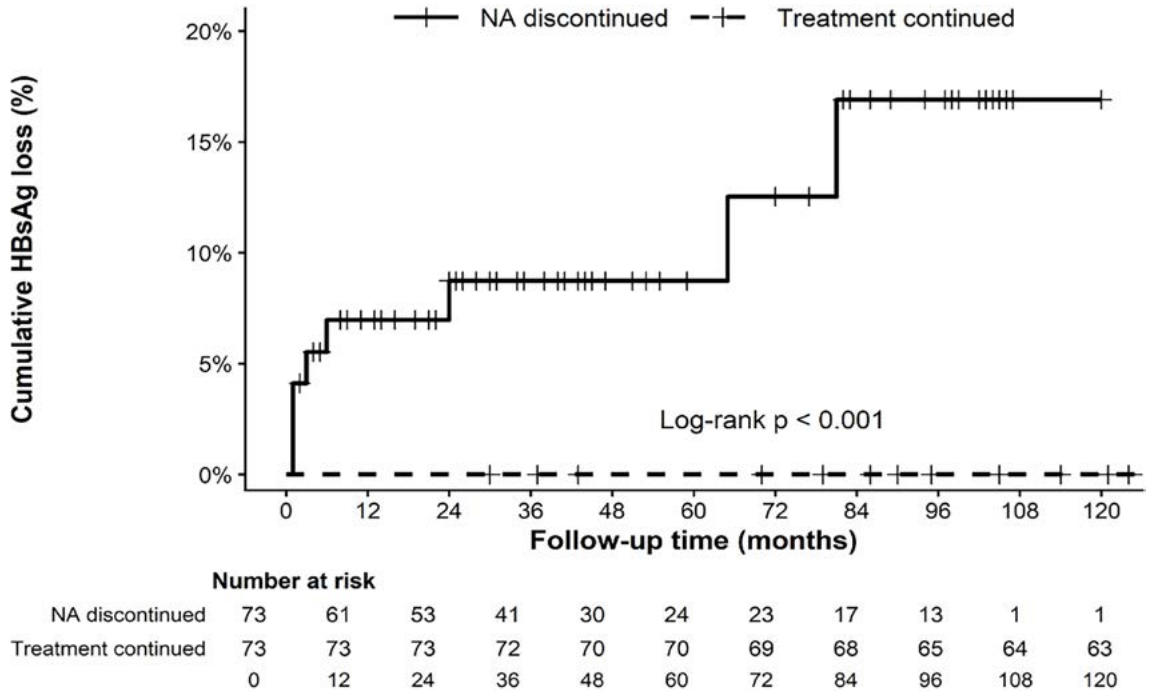


Figure 2. Kaplan–Meier curves illustrating the cumulative probability of HBsAg seroclearance in the nucleos(t)ide analogue discontinuation and continuation groups.

tients who discontinued NA treatment was 16.9% at month 120, with three-quarters of those who achieved HBsAg seroclearance also seroconverting to anti-HBs. However, none of the patients who continued NA treatment had HBsAg seroclearance. This finding confirms that previous studies have shown higher HBsAg seroclearance rates following NA cessation.[12,17–19] It also indicates that discontin-

Table 2. Characteristics of patients with and without HBsAg seroclearance in the NA discontinuation group

Characteristic	HBsAg seroclearance (n=8)	No HBsAg seroclearance (n=65)	p
Age at the index date (years)	48 (46–55)	53 (44–59)	0.572
Sex, male/female	7/1	34/31	0.072
Disease duration at the index date (months)	197.5 (168.5–212)	205 (176–228)	0.270
Serum HBV DNA (log10 IU/mL)	4.94 (3.67–6.20)	5.40 (4.00–6.80)	0.310
Serum HBV DNA >20,000 IU/mL (%)	57.1	69.0	0.672
Serum ALT (U/L)	94 (25–258)	37.5 (23–109)	0.270
Serum AST (U/L)	55 (29–124)	30 (22–74)	0.203
Serum GGT (U/L)	28 (20–56)	22 (14–32)	0.167
Total bilirubin (mg/dL)	0.70 (0.40–1.20)	0.80 (0.50–1.10)	0.773
Albumin (g/dL)	4.20 (3.90–4.30)	4.40 (4.20–4.60)	0.069
Platelet count ($\times 10^3$/μL)	188 (136–269)	221 (188–277)	0.186
INR	1.00 (1.00–1.10)	1.00 (0.96–1.03)	0.152
HAI on liver biopsy	8.50 (8–9)	8.00 (6–9)	0.351
Fibrosis score	1.00 (0–2.00)	1.00 (1.00–2.00)	0.700
Significant fibrosis (stage ≥2) (%)	20	36.5	0.647

Percentages for significant fibrosis (stage ≥2) were calculated among patients with available pretreatment liver biopsy data on fibrosis stage. Data are presented as median (25^{th}–75^{th} percentiles) or percentage, as appropriate. Laboratory and histological variables are pretreatment values obtained before NA initiation; age and disease duration were assessed at the index date, defined as the date of NA discontinuation. Percentages were calculated among patients with available data; denominators may vary because of missing values. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHB: Chronic hepatitis B; GGT: Gamma-glutamyl transferase; HAI: Histological activity index; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; INR: International normalized ratio; NA: Nucleos(t)ide analogue.

Table 3. Firth-penalized Cox regression analysis of HBsAg seroclearance after NA discontinuation in patients with CHB

Variable	Univariable HR (95% CI)	p	Multivariable HR (95% CI)	p
Age at NA discontinuation, <50	2.53 (0.67–10.97)	0.170	5.72 (1.26–35.01)	0.023
Sex, male vs female	3.94 (0.86–37.39)	0.081		
ALT ≥40	3.23 (0.73–19.07)	0.125		
AST ≥40	4.12 (0.96–23.53)	0.056	6.29 (1.36–39.96)	0.018
GGT ≥50	3.14 (0.56–13.32)	0.173		
HBV DNA, <20,000	1.40 (0.31–5.87)	0.647		
Liver fibrosis stage, <2	1.18 (0.26–6.80)	0.832		
HBsAg level at NA discontinuation, <1,000 IU/mL	2.60 (0.57–15.16)	0.220		

Reference ranges: ALT and AST, 0–40 U/L; GGT, 10–50 U/L. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHB: Chronic hepatitis B; CI: Confidence interval; GGT: Gamma-glutamyl transferase; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HR: Hazard ratio; NA: Nucleos(t)ide analogue.

Table 4. Characteristics of patients with and without clinical relapse after NA discontinuation

Characteristic	Clinical relapse (n=29)	No clinical relapse (n=44)	p
Age ≥50 years at NA discontinuation (%)	62.1	54.5	0.525
Male sex (%)	58.6	54.5	0.731
Pretreatment serum HBV DNA >20,000 IU/mL (%)	67.9	67.6	0.980
Pretreatment serum ALT ≥40 U/L (%)	48.3	52.5	0.729
Pretreatment serum AST ≥40 U/L (%)	41.4	42.5	0.926
Pretreatment serum GGT ≥50 U/L (%)	13.8	15.0	1.000
Significant fibrosis on pretreatment liver biopsy (stage ≥2) (%)	37.5	33.3	0.784
HBsAg seroclearance, n (%)	0 (0)	8 (18.2)	0.019

Percentages for significant fibrosis (stage ≥2) were calculated among patients with available pretreatment liver biopsy data on fibrosis stage. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CHB: Chronic hepatitis B; GGT: Gamma-glutamyl transferase; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; NA: Nucleos(t)ide analogue.

uing long-term NA treatment can successfully lead to a functional cure in HBeAg-negative patients with CHB.

HBsAg seroclearance can occur spontaneously in individuals with chronic HBV infections over time. HBsAg seroclearance is associated with sustained immune control of HBV and better clinical outcomes.[7,10,11] Several factors, including age, gender, serum HBsAg and HBV DNA levels, HBeAg status, disease stage, the presence of hepatic steatosis, type and duration of NA therapy, and HBsAg levels at the time of NA discontinuation, affected HBsAg seroclearance.[7,10,11] We recently reported that hepatic steatosis, as documented by liver biopsy, contributes to HBsAg seroclearance in patients with chronic HBV infection.[20] Serum AST level appeared to be a more robust immunologic indicator than serum ALT level and possibly reflects greater immune-mediated hepatocellular activity relevant to functional cure.[21] In the present study, younger age and elevated pretreatment serum AST levels were significantly associated with achieving a functional cure, and this association increased over time. Additionally, nearly all patients who achieved a functional cure had low serum HBsAg levels at the time of discontinuation of NA treatment.

The immune control network of HBV infection is a complex interplay between HBV and host immunity. There is a consensus regarding the

Table 5. Clinical relapse rates according to quantitative HBsAg level at NA discontinuation

Outcome	Quantitative HBsAg Titer (IU/ml)			
	<100 IU/mL (n=5)	100 to <1,000 IU/mL (n=23)	≥1,000 IU/mL (n=32)	p
Clinical relapse rate, % (n/N)	0.0 (0/5)	52.2 (12/23)	46.9 (15/32)	0.228

The analysis included 60 patients with available quantitative HBsAg measurements at NA discontinuation. HbsAg: Hepatitis B surface antigen; NA: Nucleos(t)ide analogue.

relationship between adaptive immune responses and HBV-specific T-cell responses. Multispecific and robust HBV-specific T cells play a significant role in managing HBV infection by directly killing HBV-infected hepatocytes and through non-cytolytic degradation of HBV markers, such as cccDNA, during a self-limiting acute HBV infection.[21–23] However, HBV-specific T cell responses are often hardly detectable and non-functional in patients with CHB due to chronic antigenic overstimulation of these T cells.[21] This phenomenon is referred to as T-cell exhaustion. NA treatment can help recover T cell responses.[18,21,24,25] The extent of virological or biochemical relapse after discon-

tinuation of NA treatment is a key factor in triggering the immune system and achieving a functional cure.[18,21,24,25]

Virological relapse induces the production of inflammatory and antiviral cytokines, chemokines, and growth factors.[18,21,24,25] This altered cytokine milieu, along with an increased amount of HBV antigens, may act as activators of the immune response against HBV. A maximum peak level of serum HBV DNA during virological relapse and an increase in serum ALT levels are associated with subsequent HBsAg seroclearance.[18] Furthermore, after discontinuation of NA treatment, virological relapse may induce multifunctional T-cell responses in patients with CHB. Clinical relapse has therefore been proposed as a potential trigger for immune control.[18]

HBV-specific T cell responses were heterogeneous among patients with CHB. In addition to a functional cure, most patients who discontinued NA treatment achieved sustained remission after stopping treatment.[7,8] These patients had negative or low HBV DNA levels (<2000 IU/mL) and normal serum ALT levels during the follow-up period, similar to those with chronic HBV infection.

The timing of retreatment with NA in patients with clinical relapse is unclear. After the discontinuation of NA treatment, serum HBV DNA levels increased immediately. Most clinical relapse cases occurred within the first three months following treatment discontinuation, consistent with previous reports.[8,12] A virological relapse should be considered a precursor to a biochemical relapse. Notably, only half of these spikes were accompanied by serum aminotransferase elevations exceeding twice the upper limit of normal. These findings support structured monitoring after NA discontinuation, particularly during the first 24 weeks, when the risk of reactivation is highest. In the subsequent assessments conducted during the first six months after discontinuing treatment, we observed 49 virological relapses. Importantly, clinical relapses in these 29 patients were reliably controlled with NAs and responded favorably to retreatment. No serious adverse events were observed following NA retreatment.

This study involved a well-defined and homogeneous CHB patient population, with long-term follow-up and comparison to an age- and sex-matched control group. There are a few limitations that should be acknowledged. This study employed a retrospective single-center design, which may limit the generalizability of our findings. Propensity-score matching was based solely on age and sex. Additionally, quantitative HBsAg levels measured using the Roche Elecsys HBsAg II kit were not routinely available in clinical practice, hindering a more detailed analysis of virological dynamics.

Conclusion

In conclusion, the discontinuation of long-term NA treatment for non-cirrhotic, HBeAg-negative CHB patients represents a promising strategy toward achieving a functional cure. Younger age and elevated baseline serum aminotransferase levels appear to be strong indicators of a potential functional cure. Ensuring close post-discontinuation surveillance remains essential to promptly manage clinical relapses.

Ethics Committee Approval: The study protocol was approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (dated May 22, 2025, and numbered 2025/393), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors did not have any conflicts of interest to declare.

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ORIGINAL RESEARCH

Anthropometric measurements, nutritional status, and diet quality of cirrhosis patients: Comparison of two etiologies

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Highlights & Insights

- **Scientific Gap:** Data comparing nutritional status, anthropometric measures, and diet quality across different cirrhosis etiologies are limited.
- **Key Finding:** Diet quality did not differ by etiology, while higher NRS-2002 scores were associated with greater cirrhosis severity.
- **Clinical Impact:** Nutritional risk screening and etiology-specific assessment may support individualized nutritional management in patients with cirrhosis.

ABSTRACT

Background and Aim: This study aimed to compare anthropometric measurements, nutritional status, and diet quality between two etiologic groups of patients with cirrhosis.

Materials and Methods: This study was conducted with 60 patients (30 women–30 men) with non-alcoholic fatty liver disease (NAFLD) and hepatitis B-C who were followed up in a university hospital in Ankara between February and May 2024. A questionnaire was administered to determine sociodemographic characteristics and disease-related information. Child-Turcotte-Pugh (CTP) and nutritional risk screening (NRS-2002) scores were calculated. Height, body weight, middle arm circumference, triceps skinfold thickness, and handgrip strength were measured. Nutritional status was evaluated using a 3-day food record, and diet quality index-international (DQI-I) was used to assess diet quality.

Results: The mean age of the participants was 58.6±7.27 years. After Bonferroni correction, body mass index was significantly higher among women with NAFLD than among women with hepatitis B/C ($p=0.004$), whereas left handgrip strength was significantly higher among men with hepatitis B/C than among men with NAFLD ($p=0.003$). After Bonferroni correction, the total DQI-I score did not differ significantly between the NAFLD and hepatitis B/C groups. A positive correlation was found between CTP and NRS-2002 scores ($r=0.607$, $p<0.001$). Regression analysis showed that DQI-I score was not a significant predictor of CTP score, whereas NRS-2002 score was a significant positive predictor in both disease subgroups and the overall study population.

Conclusion: Diet quality assessed by DQI-I was not significantly different between patients with NAFLD and hepatitis B/C cirrhosis after Bonferroni correction. Nutritional status and body composition parameters should be evaluated considering the etiology of cirrhosis.

Keywords: Cirrhosis, nutritional status, quality of diet.

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Introduction

Cirrhosis is one of the important causes of morbidity and mortality all over the world and is the final stage of chronic liver diseases, in which normal liver cells are damaged and replaced by connective tissue.[1] Liver cirrhosis is a progressive disease that occurs as a result of the deterioration and change of the morphological structure of the liver, commonly with hepatocellular necrosis, increase in connective tissue, hepatic regeneration, nodular formation, and increased fibrous tissue.[2]

The etiology of cirrhosis varies geographically; alcoholism, hepatitis C virus (HCV) infection, and non-alcoholic fatty liver disease (NAFLD) are the most common causes in western countries, while in the Asia-Pacific region, hepatitis B virus (HBV) infection is the primary cause of liver cirrhosis. Some cases are idiopathic or cryptogenic.[3] However, the past decade has seen major changes in the etiology and burden of liver disease. Increasing HBV vaccination coverage and better availability of antivirals effective against HBV have led to reduced mortality rates from HBV-associated cirrhosis.[4]

15–30% of cirrhotic patients are hypermetabolic and have a resting energy expenditure (REE) above 120%, which negatively affects nutritional status.[5] Disease-induced inflammation appears to be a contributing factor to hypermetabolism and malnutrition, as well as increased beta-adrenergic activity.[6,7] Also in liver cirrhosis, food consumption is difficult due to ascites and anorexia, so energy requirements vary among patients with cirrhosis. Individuals with cirrhosis often have increased energy and protein requirements due to metabolic disorders that include hypercatabolism and increased proteolysis.[8] Deficiency of fat-soluble vitamins is common in liver cirrhosis, especially in patients with cholestasis due to inadequate supply of bile acid. Other reasons for the development of fat-soluble vitamin deficiencies include decreased adequate oral intake, malabsorption, and decreased synthesis of carrier and transfer proteins such as retinol-binding protein.[9] In patients with liver cirrhosis, especially zinc, magnesium, and Vitamin A levels being within normal limits have a positive effect on the sense of taste and, therefore, can indirectly improve nutritional status by increasing food intake.[10,11]

This study aimed to compare anthropometric measurements, nutritional status, and diet quality of cirrhosis patients with different two etiologies.

Material and Methods

Participants and Procedure

This study included 60 inpatients and outpatients with NAFLD or HBV/HCV-related chronic liver disease who were treated or followed at the Department of Gastroenterology of a university hospital in Ankara between February and May 2024. Assuming an effect size of Cohen's d = 0.78, equal allocation between groups (1:1), a two-sided significance level (α) of 0.05, and a statistical power of 84%, the required total sample size was calculated as 60 participants (30 per group) using G*Power for a two-tailed independent-samples t-test. The study groups consisted of 28 patients with NAFLD and 32 patients with chronic hepatitis B or C. Hepatitis B and C patients were combined into a single group because both conditions belong to the chronic viral hepatitis spectrum and share similar pathophysiological mechanisms, including hepatic inflammation and fibrosis. NAFLD-related cirrhosis was diagnosed based on clinical evaluation supported by imaging findings (ultrasonography and/or elastography) and laboratory data, in the absence of other causes of chronic liver disease. Alcohol-related liver disease was excluded based on detailed patient history and reported alcohol consumption below established threshold levels. Information regarding antiviral treatment status in HBV/HCV patients (treatment-naive or receiving therapy) was recorded and considered in the analysis. Patients aged 24–64 years with a diagnosis of cirrhosis of at least 1 year were included in the study. Patients with other etiologies of cirrhosis (e.g., alcohol-related liver disease), individuals older than 64 years, and pregnant or breastfeeding women were excluded from the study. Anthropometric measurements were obtained using standard procedures. The study was conducted in accordance with the Declaration of Helsinki and approved by the Baskent University Institutional Review Board and Ethics Committee (Project No: 22/519; Date: January 18, 2023). Written informed consents were obtained from patients who participated in this study.

Disease Severity

Patients' Child-Turcotte-Pugh (CTP) score was calculated by a gastroenterologist to determine the severity of cirrhosis. CTP score was calculated using prothrombin time, albumin, bilirubin, and clinical findings of ascites and encephalopathy. CTP score was stratified as class A (5–6), B (7–9), and C (10–15).[12] The biochemical parameters to be used in calculating the disease severity of individuals were taken digitally from the patient records belonging to the patients' protocol numbers.

Anthropometric Measurements

Patients' body weight (kg) and height (cm) were measured and body mass index (BMI) was calculated. Triceps skinfold thickness (TSF) (mm), middle arm circumference (MUAC), and handgrip strength were measured. The MUAC was measured at the center point of the connecting line between the shoulder and the upper end of the ulna. TSF was measured to the nearest 0.1 mm using Holtain Skinfold Calipers. Patients' TSF and MUAC measurement values were used in appropriate formulas and middle arm muscle circumference (MAMC), midarm muscle area and mid-arm fat area (MAFA) values were calculated.[13]

HGS data were obtained with a Jamar Plus + Digital Hand Dynamometer (Sammons Preston, Bolingbrook, Illinois, USA) calibrated by the manufacturer, with a resolution of 0.1 kgf. Measurements were carried out with the subject seated, shoulders adducted and neutrally rotated, elbow flexed at 90°, forearm in neutral, and wrist between 0 and 30° of dorsiflexion.[14] Each participant performed three measurements with 1-min pauses in between, then the mean of the three measurements was calculated.

Nutritional Status and Nutritional Risk Screening (NRS)

In the study, a survey form was applied to determine the sociodemographic characteristics, nutrition, and disease status of the patients. The nutritional status of the patients was determined by a 3-day food consumption record. BeBiS nutrition information system (BeBiS 7.0, Ebispro for Windows, Stuttgart, Germany, Turkish Version) was used to determine the energy and macro and micronutrient intakes.

NRS-2002 was used as a malnutrition screening tool. It is a screening test consisting of two steps. The first stage is the initial screening. At this stage, participants are asked whether their BMI value is below 20.5 kg/m^2, whether there has been any weight loss in the last 3 months, whether there was a decrease in food intake in the week before the scan, and whether they have a serious illness. If the answer to any of these questions is yes, the second stage is started. The second step screening of NRS-2002 is the final screening and scoring is done at this stage. The final screening consists of two parts: "Nutritional status" and "disease severity." In the first part of the final screening, nutrition is evaluated and BMI, percentage of recent weight loss, and the ratio of food intake in the week before the scan to food intake in normal times are questioned. In the second part of the final screening, the severity of the disease is questioned. In the NRS-2002 evaluation, scores given to the nutritional status and disease severity sections are collected. One is added to the scores of patients aged 70 and over and the total score is created in this way. In this study, this score was not added because individuals over the age of 64 were not included in the study. Patients with a total score ≥3 are at risk of malnutrition; patients with a total score <3 were considered to have no risk of malnutrition.[15,16] The NRS-2002 score was calculated by a dietitian.

Diet Quality

It is a summary measure of dietary quality representing four categories of the diet, including variety, adequacy, moderation, and overall balance. The overall DQI-I score constitutes the sum of the scores for each of these four categories and ranges from 0 to 100 (where 0=The poorest and 100=The highest dietary quality). Dietary variety (score 0–20) captures diversity in food choices and protein sources. Dietary adequacy (score 0–40) captures the adequate intake of food groups and nutrients (vegetables, fruit, grains, fibers, proteins, Fe, Ca, and Vitamin C). Dietary moderation (score 0–30) is scored on the basis of intake of total fat, saturated fat, cholesterol, Na, and empty calorie foods. Finally, overall balance (score 0–10) captures the proportion of energy from carbohydrates, protein and fat, as well as the fatty acid composition, according to accepted general guidelines for the proportion of energy from carbohydrate, protein, fat, and fat composition.[17]

Statistical Analysis

Descriptive statistics were presented according to data type. Categorical variables were expressed as number (n) and percentage (%), while continuous variables were expressed as mean ± standard deviation (SD). The normality of continuous variables was assessed using the Shapiro–Wilk test. For comparisons between two groups, the independent-samples t-test was used for normally distributed continuous variables, whereas the Mann–Whitney U-test was used for non-normally distributed continuous variables. The relationships between categorical variables were analyzed using the Pearson Chi-square test or Fisher's exact test when expected cell counts were <5. Correlations between continuous variables were evaluated using Spearman's correlation analysis due to non-normal distribution. Univariate regression analyses were performed to investigate the association between CTP scores and diet quality and NRS-2002. Statistical analyses were conducted using IBM Statistical Package for the Social Sciences Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). $p<0.05$ was considered statistically significant.

Results

A total of 60 adults, including 30 women (50.0%) and 30 men (50.0%), who were treated or followed at the Department of Gastroenterology participated in the study. The mean age of the individuals was 58.6±7.27 years. It was determined that 73.3% of the women and 80.0% of the men who participated in the research were married (Table 1).

Among the patients with viral hepatitis-related cirrhosis, 29 patients had HBV infection, whereas three patients had HCV infection (unshown data). The mean and SD values of individuals' cirrhosis diagnosis time were found to be 4.8±4.43 years in the NAFLD group, while it was 10.3±12.07 years for individuals in the hepatitis B-C group. Diabetes was present in 24 patients (40.0%). No statistically significant differences were observed in cirrhosis-related symptoms according to disease etiology (all $p>0.05$). Antiviral medication use was observed exclusively in the HBV/HCV group (21/32, 65.6%), whereas none of the patients in the NAFLD group received antiviral therapy (0/28, 0.0%; $p<0.001$) (Table 2). Of the 21 patients who received antiviral therapy, 20 had HBV-related cirrhosis and one had HCV-related cirrhosis (data not shown).

The mean and SD of anthropometric measurements of individuals according to gender and etiology are shown in Table 3. After multiple comparison correction, no statistically significant differences were observed in most anthropometric parameters between groups. After Bonferroni correction, BMI was significantly higher among women with NAFLD than among women with hepatitis B/C ($p=0.004$), whereas left handgrip strength was significantly higher among men with hepatitis B/C than among men with NAFLD ($p=0.003$).

Energy, macronutrient and micronutrient intake mean and SD values according to gender and etiology are given in Table 4. After multiple comparison correction, no statistically significant differences were found between patients with NAFLD and viral hepatitis-related cirrhosis in terms of energy intake, macronutrient distribution, and micronutrient intake.

Before Bonferroni correction, the NAFLD group appeared to have significantly lower scores for variety, overall food group variety, vegetable group, and total DQI-I score compared with the hepatitis B/C group. However, after applying a Bonferroni-adjusted significance

Table 1. Socio-demographic characteristics

Demographics	Women (n=30)		Men (n=30)		Total (n=60)		p
	n	%	n	%	N	%	
Age (year) (Mean±SD)	59.0±5.94		58.2±8.48		58.6±7.27		0.958
Age (year)							0.261
20–29	–	–	1	3.3	1	1.7	
30–39	–	–	–	–	–	–	
40–49	4	13.3	1	3.3	5	8.3	
50–59	9	30.0	13	43.3	22	36.7	
60–64	17	56.7	15	50.0	32	53.3	
Educational status							<0.001
Primary school	23	76.7	8	26.7	31	51.7	
Middle school	4	13.3	6	20.0	10	16.7	
High school	1	3.3	11	36.7	12	20.0	
University	2	6.7	5	16.7	7	11.7	
Marital status							0.542
Married	22	73.3	24	80.0	46	76.7	
Single	8	26.7	6	20.0	14	23.3	

SD: Standard deviation.

threshold of p<0.0023 for 22 comparisons, none of these differences remained statistically significant (Table 5).

The correlation between CTP score, NRS-2002, and DQI-I values is given in Table 6. It was found that there was a positive correlation between CTP and NRS-2002 (r=0.607, p<0.001). There was a negative correlation between CTP and DQI-I (r=-0.328, p=0.010).

Separate simple linear regression analyses were performed to examine the associations of DQI-I and NRS-2002 scores with CTP score (Table 7). DQI-I score was not significantly associated with CTP score in the NAFLD group, the hepatitis B/C group, or the overall study population (all p>0.05). In contrast, higher NRS-2002 scores were significantly associated with higher CTP scores across all analyses. In the NAFLD group, NRS-2002 score explained 23.1% of the variance in CTP score (R^2=0.231, B=0.944, p=0.010). In the hepatitis B/C group, it explained 46.3% of the variance (R^2=0.463, B=1.724, p<0.001), and in the overall study population, it explained 34.0% of the variance in CTP score (R^2=0.340, B=1.325, p<0.001) (Table 7).

Discussion

Liver cirrhosis is the common pathological consequence of liver damage resulting from a wide variety of chronic liver diseases. Nutritional deficiencies in these patients are associated with increased complications and mortality rates. This exploratory cross-sectional single-center study was conducted to compare the anthropometric measurements, nutritional status, disease severity, and diet quality of 60 patients with cirrhosis of different etiologies.

Clinical conditions and pathophysiological mechanisms contributing to malnutrition in cirrhosis are complex and interrelated. Therefore, especially as liver disease progresses, malnutrition is an important condition to manage effectively.[18] In cirrhotic patients, body weight is not used as an accurate measure of malnutrition due to ascites and edema caused by extracellular fluid accumulation. Before Bonferroni correction, several anthropometric parameters, including body weight, BMI, MAMC, and MAFA, differed according to gender and etiology. However, after Bonferroni correction, only BMI in women and left handgrip strength in men remained statistically significant. It should also be acknowledged that the observed differences in anthropometric and nutritional parameters may be substantially influenced by the significant differences in BMI between the etiological groups, rather than reflecting etiology-specific effects alone.

TSF measurement is useful to estimate subcutaneous adipose tissue and MAMC measurement is useful to estimate skeletal muscle mass in patients with ascites and edema.[19,20] Given the limited health resources of public hospitals in low- and middle-income countries, the MUAC value is an accessible, rapid, and inexpensive measurement and can be easily performed at the bedside in cirrhotic patients with edema and ascites.[21] Uncorrected analyses showed some differences in selected anthropometric measurements; however, these differences did not retain their significance after Bonferroni correction. These findings should be interpreted cautiously given the exploratory design and limited sample size.

The mean handgrip strength value was 17.6±3.1 kg in the group of healthy controls, 16.9±5.2 kg in hepatitis patients and 11.6±4.8 kg in cirrhosis patients, and this value was statistically significantly lower

Table 2. Disease information

Disease information	NAFLD (n=28)		Hepatitis B-C (n=32)		Total (n=60)		p
	n	%	n	%	n	%	
Diagnosis time (years)							0.151[a]
0-5	21	75.0	16	50.0	37	61.6	
6-10	2	7.1	5	15.6	7	11.7	
>10	5	17.9	11	34.4	16	26.7	
Mean±SD	4.8±4.43		10.3±12.07		7.7±9.65		0.082[d]
Chronic disease status							0.129[b]
Yes	21	75.0	18	56.3	39	65.0	
No	7	25.0	14	43.7	21	35.0	
Presence of chronic disease[§]							
Hypertension	11	39.3	7	21.9	18	30.0	0.142[b]
Diabetes mellitus	14	50.0	10	31.3	24	40.0	0.139[b]
Cardiovascular diseases	5	17.9	3	9.4	8	13.3	0.454[a]
Others (Gastrointestinal system diseases, anemia, bone diseases)	7	25.0	3	9.4	10	16.7	0.165[a]
Symptoms[§]							
Weakness, fatigue, lassitude	23	82.1	27	84.4	50	83.3	1.000[b]
Anorexia	10	35.7	10	31.3	20	33.3	0.787[b]
Nausea, vomiting	12	42.9	11	34.4	23	38.3	0.598[b]
Muscle cramps	25	89.3	27	84.4	52	86.7	0.722[a]
Itching	18	64.3	17	53.1	35	58.3	0.493[b]
Fever	4	14.3	8	25.0	12	20.0	0.349[a]
Dyspnea and tachypnea	17	60.7	14	43.7	31	51.7	0.208[b]
Body weight loss	14	50.0	15	46.9	29	48.3	1.000[b]
Medication type[§]							
Antihypertensive medications	10	35.7	8	25.0	18	30.0	0.366
Oral antidiabetic medications and insulin	13	46.4	10	31.3	23	38.3	0.228
Cardiovascular medications	5	17.9	6	18.8	11	18.3	0.929
Diuretics	16	57.1	22	68.7	38	63.3	0.352
Gastrointestinal medications	13	46.4	13	40.6	26	43.3	0.651
Antiviral medications	–	–	21	65.6	21	35.0	<0.001*
Neurological medications	4	14.3	4	12.5	8	13.3	0.839
Antibacterial medications	–	–	5	15.6	5	8.3	0.029*
Antibiotics	1	3.6	4	12.5	5	8.3	0.212
Other medications (thyroid medications, bone-related medications, iron supplements)	3	10.7	–	–	3	5.0	0.240
CTP class							
A (5-6 points)	11	39.3	14	43.8	25	41.7	
B (7-9 points)	12	42.9	9	28.1	21	35.0	0.433[b]
C (10-15 points)	5	17.9	9	28.1	14	23.3	
CTP Mean±SD	7.3±2.01		7.8±2.38		7.6±2.28		0.594[c]
NRS-2002 Mean±SD	1.68±1.02		1.66±0.94		1.67±0.97		0.979[c]

SD: Standard deviation; NAFLD: Non-alcoholic fatty liver disease; CTP: Child-Turcotte-Pugh; NRS-2002: Nutritional Risk Score-2002; §: More than one option selected; a: Fisher's exact test; b: Pearson Chi-square test; c: Independent samples t test; *: P<0.05.

Table 3. Anthropometric measurements according to gender and etiology

Anthropometric measurements	Women (n=30)		Men (n=30)		pBonf$_1$	pBonf$_2$
	NAFLD (n=17) Mean±SD	Hepatitis B-C (n=13) Mean±SD	NAFLD (n=11) Mean±SD	Hepatitis B-C (n=19) Mean±SD		
Height (cm)	154.8±5.40	158.3±7.50	172.9±6.52	174.1±6.38	0.156^c	0.627^c
Body weight (kg)	76.7±12.07	65.6±15.51	88.8±17.27	78.1±11.09	0.035^c	0.046^c
BMI (kg/m^2)	32.1±5.60	26.0±4.86	29.7±5.51	25.8±3.85	**0.004**^{c*}	0.031^c
MUAC (cm)	31.2±5.17	25.8±7.02	28.4±3.77	27.7±4.41	0.022^c	0.643^c
MAMC (cm)	25.2±4.78	21.1±5.16	23.6±3.24	24.0±4.62	0.036^c	0.026^d
MAMA (cm^2)	44.8±20.90	31.1±17.92	35.1±12.83	37.7±19.60	0.069^c	0.072^d
MAFA (cm^2)	18.2±6.08	12.9±8.01	14.1±5.02	10.8±4.31	0.047^c	0.025^d
TSF (mm)	19.3±5.73	15.0±7.01	15.4±5.17	11.5±5.99	0.073^c	0.085^c
Right handgrip strength (kgf)	13.6±3.81	16.0±4.81	24.5±9.24	31.2±6.00	0.384^c	0.023^c
Left handgrip strength (kgf)	11.8±4.42	15.8±3.98	21.4±7.88	29.4±5.50	0.061^c	0.003^{c*}
Right-left handgrip strength (kgf)	12.7±3.94	15.9±4.23	22.9±8.47	30.3±5.48	0.155^c	0.007^c

NAFLD: Non-alcoholic fatty liver; BMI: Body mass index; MUAC: Middle arm circumference; MAMC: Middle arm muscle circumference; MAMA: Middle arm muscle area; MAFA: Mid-arm fat area; TSF: Triceps skinfold thickness; P values are unadjusted. To account for 11 comparisons, statistical significance was evaluated using a Bonferroni-corrected threshold of p<0.0045 (0.05/11), separately for women and men. p_1: Comparison between NAFLD and hepatitis B/C groups among women; p_2: Comparison between NAFLD and hepatitis B/C groups among men; c: independent-samples t-test; d: Mann–Whitney U test. *p<0.0045.

in cirrhosis patients than in other groups.[22] In the present study, left handgrip strength was significantly higher among men with hepatitis B/C cirrhosis than among men with NAFLD-related cirrhosis after Bonferroni correction. Although handgrip strength is an indirect indicator of muscle function and nutritional status, this finding should be interpreted cautiously given the exploratory design and limited sample size. Decreased muscle mass, which is expected in patients with cirrhosis, may be a valuable predictive factor for malnutrition.[23]

Malnutrition in cirrhosis patients develops with the interaction of many different factors such as metabolic changes in the body, inadequate food intake, hypermetabolism, increased energy requirements as a result of systemic inflammation, nutrient deficiencies, and anorexia. Malnutrition has a significant impact on disease progression and worsens the patient's prognosis.[18] In a study evaluating inadequate protein intake in cirrhotic patients awaiting liver transplantation, the mean protein intake was 1.0±0.36 g/kg/day and only 24% of patients met the recommended protein intake (1.2 g/kg/day protein). Low protein intake (<0.8 g/kg/day) was associated with worse severity of liver disease. Protein intake below 0.8 g/kg/day was found to be an independent predictor of malnutrition and transplant waiting list mortality.[24] In this study, dietary protein intake was below recommended levels in both etiological groups, highlighting the importance of nutritional counseling in all patients with cirrhosis regardless of underlying cause. Nutrition education should emphasize the importance of adequate protein intake and appropriate protein sources. In this study, the lack of significant differences in energy and nutrient intake between groups after multiple comparison correction suggests that some of the observed baseline differences may be statistically coincidental. Uncorrected analyses showed some differences in selected micronutrient intakes; however, these differences did not retain their significance after Bonferroni correction. Nevertheless, the large number of variables involved in nutritional assessments and the limited sample size may have restricted the detection of possible minor differences related to etiology.

NAFLD is a major global health problem linked to several cardiometabolic disorders, including adiposity, insulin resistance, dyslipidemia, metabolic syndrome, and type 2 DM. An inactive lifestyle, diet quality, and obesity are among the factors contributing to the pathophysiology of NAFLD.[25] In a study investigating diet quality, the mean DQI-I score value of participants in the NAFLD group was lower than those in the control group. As a result of the study, it was suggested that greater dietary adherence with a higher DQI-I score may be associated with a lower likelihood of NAFLD.[26] In another study, a 10-unit decrease in DQI-I score was associated with a 24% increase in the probability of having NAFLD (p=0.009). Analyses showed that intake of vegetables and legumes, fruits, and dried fruits as well as Vitamin C was inversely associated with the prevalence of NAFLD (p<0.05).[27] In this study, although the total DQI-I score was lower in the NAFLD group before correction, this difference did not remain statistically significant after Bonferroni adjustment. Furthermore, DQI-I score was not associated with CTP score in the univariate simple linear regression analysis, indicating that diet quality was not an independent determinant of disease severity in this study population.

In this study, higher nutritional risk (NRS-2002) was associated with worse clinical status, whereas overall diet quality assessed by DQI-I was not significantly associated with disease severity in the simple linear regression analysis. Because NRS-2002 incorporates BMI as one of its components, its interpretation in patients with cirrhosis should be made cautiously, particularly in the presence

Table 4. Energy, macronutrient and micronutrient intake mean and standard deviation values according to gender and etiology

	Women (n=30)		Men (n=30)		pBonf$_1$	pBonf$_2$
	NAFLD (n=17) Mean±SD	Hepatitis B-C (n=13) Mean±SD	NAFLD (n=11) Mean±SD	Hepatitis B-C (n=19) Mean±SD		
Energy (kcal/day)	1694.2±349.35	1552.7±368.29	1361.4±375.14	1543.4±265.88	0.292[c]	0.132[c]
Energy (kcal/kg/day)	20.0±6.80	22.1±6.54	18.3±8.06	21.8±3.24	0.234[c]	0.193[c]
Carbohydrate (g)	182.9±44.91	165.2±46.77	140.9±52.33	162.8±42.30	0.302[c]	0.221[c]
Carbohydrates (%)	44.4±6.29	43.5±4.99	41.8±6.06	43.4±7.49	0.684[c]	0.551[c]
Protein (g)	65.6±17.76	54.9±18.53	56.1±16.29	57.8±11.4	0.117[c]	0.740[c]
Protein (g/kg/day)	0.7±0.27	0.7±0.28	0.6±0.26	0.7±0.21	0.971[c]	0.262[c]
Protein (%)	15.5±2.06	14.1±2.30	17.2±2.65	15.4±2.87	0.172[d]	0.101[c]
Vegetable protein (g)	26.1±6.29	23.5±6.30	20.8±6.81	22.5±6.98	0.275[c]	0.514[c]
Animal protein (g)	39.5±12.41	31.3±14.17	35.2±11.88	35.2±9.59	0.103[c]	0.993[c]
Lipid (g)	75.6±18.64	72.8±16.58	61.5±14.88	71.4±18.67	0.665[c]	0.114[c]
Lipid (%)	39.8±6.39	42.3±5.09	41.2±5.68	41.2±6.92	0.246[c]	0.980[c]
SFA (%)	11.9±2.03	13.3±3.09	12.4±2.37	12.9±3.31	0.147[c]	0.672[c]
MUFA (%)	15.2±4.69	15.5±2.83	14.9±3.04	16.1±4.06	0.880[c]	0.402[c]
PUFA (%)	10.3±2.56	10.9±4.50	11.3±3.72	9.6±2.58	0.623[c]	0.139[c]
Omega-3 (%)	1.0±0.04	1.0±0.38	1.0±0.02	1.0±0.03	0.786[d]	0.786[d]
Omega-6 (%)	9.5±2.72	10.1±4.45	10.6±3.59	8.9±2.47	0.917[d]	0.127[c]
Cholesterol (mg)	242.1±113.02	257.3±99.13	206.1±63.24	240.2±66.13	0.703[c]	0.691[d]
Fiber (g)	20.9±6.52	20.5±8.65	19.1±5.64	20.0±6.50	0.882[c]	0.660[d]
Vitamin A (mcg)	1517.0±785.85	898.5±443.70	1618.0±858.14	1253.3±994.91	0.017[c]	0.028[d]
Vitamin E (mg)	19.6±6.98	17.2±6.70	18.4±6.96	16.3±4.42	0.352[c]	0.346[d]
Vitamin K (mcg)	395.3±199.59	279.8±145.12	458.6±180.89	357.0±188.40	0.090[c]	0.160
Vitamin C (mg)	111.9±51.66	111.9±55.81	118.9±59.16	112.6±48.22	0.997[c]	0.753[c]
Thiamine (mg)	0.7±0.24	0.7±0.26	0.6±0.23	0.7±0.18	0.638[c]	0.706[d]
Riboflavin (mg)	1.3±0.50	1.0±0.32	1.2±0.51	1.3±0.39	0.039[c]	0.593[c]
Pantothenic acid (mg)	4.2±1.43	4.1±2.41	3.7±1.31	3.9±0.87	0.426[d]	0.553[c]
Vitamin B6 (mg)	1.2±0.40	1.0±0.37	1.0±0.29	1.0±0.25	0.194[c]	0.901[c]
Folate (mcg)	272.1±79.43	265.0±100.78	236.3±53.77	279.4±77.81	0.831[c]	0.851[d]
Vitamin B12 (mcg)	4.1±1.90	3.4±2.63	3.6±1.15	3.9±3.22	0.180[d]	0.180[d]
Iron (mg)	10.0±3.13	9.0±3.15	9.3±2.33	9.4±2.19	0.415[c]	0.875[c]
Magnesium (mg)	229.3±70.64	206.0±73.55	208.9±54.87	210.5±62.40	0.387[c]	0.945[c]
Zinc (mg)	8.7±2.35	7.4±2.18	7.8±2.14	7.9±1.78	0.157[c]	0.863[c]
Phosphorus (mg)	1104.6±334.89	915.8±283.44	943.1±321.82	996.6±246.90	0.114[c]	0.613[c]
Potassium (mg)	2218.8±737.65	1890.3±695.02	2124.4±661.41	2018.2±504.91	0.226[c]	0.624[c]
Calcium (mg)	809.7±330.82	574.1±215.94	723.8±329.78	732.9±248.02	0.034[c]	0.933[c]

NAFLD: Non-alcoholic fatty liver disease; SFA: Saturated fatty acids; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids. Bonferroni-adjusted significance level: p<0.0017 (≈ 30 comparisons), p1: Significance test of women according to disease etiology; p2: Significance test of men according to disease etiology; c: Independent samples t test; d: Mann–Whitney U-test.

of ascites and edema, which may influence BMI despite underlying malnutrition. This suggests that disease-specific nutritional assessment tools, such as the Royal Free Hospital–Nutritional Prioritizing Tool or the Global Leadership Initiative on Malnutrition criteria, may provide a more appropriate and sensitive evaluation of nutritional status in this patient population.

Table 5. DQI-I score and DQI-I's categories score mean and standard deviation values according to etiology

	NAFLD (n=28) Mean±SD	Hepatitis B-C (n=32) Mean±SD	pBonf[c]
Variety	9.46±3.33	12.3±4.10	0.100
Overall food group variety	6.82±2.58	9.12±2.99	0.054
Protein-sources variety	2.64±1.33	3.21±1.56	1.000
Adequacy	16.07±7.74	19.21±11.29	1.000
Vegetable group	0.15±0.92	0.78±1.84	0.502
Fruit group	1.78±2.43	2.03±2.49	1.000
Grain group	0.89±1.95	1.87±2.45	1.000
Fibre	2.14±2.51	2.65±0.94	1.000
Protein	4.82±0.94	4.37±1.68	1.000
Iron	2.85±2.51	3.75±2.19	1.000
Calcium	0.17±0.94	0.62±1.68	1.000
Vitamin C	3.21±2.43	3.12±2.45	1.000
Moderation	10.50±4.04	12.00±3.88	1.000
Total fat	0.32±1.70	0.09±0.53	1.000
Saturated fat	0.32±0.94	0.56±1.41	1.000
Cholesterol	4.92±2.19	5.15±1.90	1.000
Sodium	2.03±1.83	2.34±1.97	1.000
Empty calorie foods	3.53±2.16	4.03±2.59	1.000
Overall balance	1.57±1.75	1.75±1.81	1.000
Macronutrient ratio	0.00±0.12	0.00±0.70	1.000
Fatty acid ratio	1.57±1.75	1.62±1.64	1.000
DQI-I (Mean±SD)	36.42±9.01	42.59±15.56	0.426

NAFLD: Non-alcoholic fatty liver disease; DQI-I: Diet quality index–international. pBonf: Bonferroni-adjusted p value; c: independent-samples t-test. Statistical significance was set at pBonf<0.05. *p<0.05.

A positive correlation was observed between CTP and NRS-2002 scores, indicating that nutritional risk increased with disease severity. Consistent with this finding, separate simple linear regression analyses showed that NRS-2002 score was significantly associated with CTP score, whereas DQI-I score was not significantly associated with CTP score. These findings suggest that NRS may better reflect the clinical consequences of cirrhosis than overall diet quality in this study population. Although a significant negative Spearman correlation was observed between DQI-I and CTP score in the overall cohort, DQI-I was not significantly associated with CTP score in the simple linear regression analysis. This discrepancy may reflect differences in the statistical assumptions of correlation and regression analyses; while a monotonic association was observed, DQI-I score did not show a statistically significant linear association with CTP score in the regression model. Therefore, routine nutritional risk assessment using validated screening tools remains an important component of clinical management, although disease-specific instruments may offer additional advantages in patients with cirrhosis.

Table 6. Correlation between CTP, NRS-2002 and DQI-I

	CTP	NRS-2002
CTP		
r	1	
p		
NRS-2002		
r	0.607[e*]	1
p	p<0.001	
DQI-I		
r	-0.328[e]	-0.138[e]
p	0.010*	0.293

CTP: Child-Turcotte-Pugh; NRS-2002: Nutritional risk score-2002; DQI-I: Diet quality index–international; e: Spearman's rho correlation coefficient.

The past decade has seen major changes in the etiology and burden of liver disease. Increased coverage of HBV vaccination and availability of effective antivirals against HBV have contributed to a reduction in global age-standardized mortality rates for HBV-related cirrhosis.[4] In contrast, obesity and diabetes have led to a rapid increase in the prevalence of NAFLD, and global age-standardized mortality rates for NAFLD-related cirrhosis have increased.[28] While the disease burden of HBV-HCV cirrhosis is decreasing, the burden of alcohol-related and

Table 7. Univariate simple linear regression models predicting CTP score from DQI-I and NRS-2002

Group	Predictor	n	B	SE	β	95% CI Lower	95% CI Upper	R^2	F	p
NAFLD	DQI-I	28	0.008	0.044	0.034	-0.083	0.098	0.001	0.029	0.865
NAFLD	NRS-2002	28	0.944	0.338	0.480	0.249	1.639	0.231	7.789	0.010
Hepatitis B-C	DQI-I	32	-0.035	0.029	-0.210	-0.095	0.026	0.044	1.383	0.249
Hepatitis B-C	NRS-2002	32	1.724	0.339	0.680	1.032	2.417	0.463	25.851	<0.001
Total	DQI-I	60	-0.020	0.023	-0.110	-0.066	0.027	0.012	0.711	0.403
Total	NRS-2002	60	1.325	0.243	0.583	0.840	1.811	0.340	29.826	<0.001

CTP: Child-Turcotte-Pugh; DQI-I: Diet quality index-international; NRS-2002: Nutritional risk screening 2002; B: Unstandardized regression coefficient; β: Standardized regression coefficient; SE: Standard error; CI: Confidence interval. Each predictor was entered into a separate simple linear regression model.

NAFLD-related cirrhosis is increasing rapidly. Therefore, the etiology of cirrhosis patients should be analyzed separately and dietary recommendations should be made accordingly; energy and nutrient intake should be carefully monitored in patients with NAFLD-related cirrhosis. This shift highlights the importance of considering etiological background in nutritional assessment; however, causal inferences cannot be drawn from the present study.

This study has some limitations. Due to the relatively small sample size and the exploratory nature of some analyses, multiple comparisons were performed, and the possibility of type I error (false-positive findings) cannot be completely excluded. Appropriate multiple comparison correction was applied where indicated; however, the findings should still be interpreted with caution. Subgroup analyses for hepatitis B and hepatitis C were not performed separately due to the limited sample size, although these two etiologies have distinct natural histories and immunological mechanisms. Therefore, combining these groups may limit the interpretation of etiology-specific findings. In addition, the potential influence of ascites or peripheral edema on body composition measurements represents another limitation of this study. Finally, subgroup analyses, particularly those stratified by sex, were based on relatively small sample sizes and may have been underpowered; thus, these findings require confirmation in larger studies. Since inpatients and outpatients were included in the study, there may be differences in access to food. Handgrip strength measurements may have been affected by missing data on hand dominance; this could lead to variability in grip strength values and should be considered when interpreting subgroup results. In addition, although not statistically significant, the difference in disease duration between groups may still act as a clinically relevant confounder, as prolonged disease course is associated with progressive decline in nutritional status and muscle mass. Since assessment of body fat is important for monitoring body composition, more comprehensive body composition methods should be used in future studies. The multiple anthropometric assessment approach used in this study (TSF, MUAC, MAMC, MAFA, and handgrip strength) offers a robust methodological framework that goes beyond commonly used methods in clinical nutrition research. The use of the internationally validated DQI-I score in assessing diet quality provides a unique contribution in terms of comparing cirrhosis patients according to etiology. On the other hand, the 3-day food intake record method offers a more reliable diet assessment compared to the single-day 24-h recall method. Evaluating cirrhosis according to etiology further enhances the novelty of this study.

Conclusion

This exploratory cross-sectional single-center study compared two different cirrhosis etiologies and identified differences in selected anthropometric measurements, whereas no significant difference in overall diet quality remained after Bonferroni correction. Given the increasing global burden of cirrhosis due to NAFLD, understanding the nutritional requirements of patients with different etiologies is becoming increasingly critical for dietetic management. These findings suggest that dietary assessments and individualized nutritional recommendations provided by dietitians may benefit from consideration of disease etiology. Although studies evaluating the relationship between cirrhosis etiology and diet quality are limited in the literature, the present findings should be interpreted with caution due to the study design and sample size. Further longitudinal, multicenter studies with adequate adjustment for confounders are needed to clarify the relationship between cirrhosis etiology and nutritional status.

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Baskent University Institutional Review Board and Ethics Committee (Project No: 22/519; Date: January 18, 2023).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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ORIGINAL RESEARCH

Leptospirosis presenting with cholestatic jaundice: Hepatic features and clinical outcomes

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Highlights & Insights

- **Scientific Gap:** Hepatic manifestations and predictors of severe leptospirosis remain insufficiently characterized, particularly in non-endemic regions.
- **Key Finding:** Among 30 patients, AKI occurred in 60%, pulmonary involvement in 33.3%, ICU admission in 56.7%, and mortality in 6.7%. Pulmonary involvement and higher creatinine were associated with ICU admission.
- **Clinical Impact:** Leptospirosis should be considered in patients with marked hyperbilirubinemia and systemic findings; early recognition of pulmonary and renal involvement may help identify patients requiring intensive care.

ABSTRACT

Background and Aim: Leptospirosis is a zoonotic infection with a wide spectrum of clinical manifestations. Hepatic involvement is common, particularly in severe forms, such as Weil's disease, and poses diagnostic and therapeutic challenges.

Materials and Methods: We retrospectively evaluated the general characteristics and outcomes of patients diagnosed with leptospirosis at Harran University, Department of Gastroenterology between May 2019 and September 2025.

Results: We included 30 patients (86.7% male) with a median age of 45 years (range: 18–78 years); the median total bilirubin at presentation was 9.1 mg/dL (range: 2.5–49.0 mg/dL). All patients showed features of moderate-to-severe liver injury. A total of 18 (60%) patients developed acute kidney injury, 10 (33.3%) had pulmonary involvement, myocarditis was identified in 3 (10%) patients, and 5 (16.7%) patients exhibited neurological manifestations. All patients received antibiotics (doxycycline, cephalosporins, and carbapenems). Corticosteroids were given to nine patients. Therapeutic plasma exchange was performed in 12 (40%) patients. Seventeen (56.7%) patients required intensive care unit (ICU) admission, and 3 (10%) required invasive mechanical ventilation. Median creatinine (2.1 vs. 1.2 mg/dL, p=0.004) was higher, pulmonary involvement was more common (52.9% vs. 7.7%, p=0.017), plasma exchange (58.8% vs. 15.4%, p=0.026) and corticosteroid use (52.9% vs. 0%, p = 0.003) were more common among patients admitted to the ICU than among those not admitted to the ICU. Two (6.7%) patients did not respond to therapy and died during follow-up.

Conclusion: Leptospirosis presenting with liver injury and pulmonary involvement is associated with a higher probability of ICU admission. Corticosteroids and/or plasma exchange can be used, but prospective studies are necessary to reveal their prognostic relevance in patients presenting with severe leptospirosis.

Keywords: Hepatic dysfunction, jaundice, leptospirosis, multiorgan failure.

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Introduction

Leptospirosis is a widespread tropical disease caused by serotypes of the *Leptospira interrogans* group.[1] Most cases present as subclinical infections, but leptospirosis can lead to severe acute disease, resulting in multiorgan (hepatic, pulmonary, and renal) failure and death.[2]

Weil's disease is the most severe form of leptospirosis and is characterized by hepatic dysfunction.[3] Jaundice is the predominant manifestation of hepatic dysfunction; however, its exact mechanism in leptospirosis remains unclear. Other serum liver biomarkers, such as transaminases and alkaline phosphatase, are moderately increased in patients with Weil's disease.[1]

The agent of the disease is transmitted through contact with infected animals, and more commonly from contaminated waters or soils.[2] *Leptospires* enter the body through skin abrasions or by penetrating mucous membranes and disseminating through the hematogenous pathway.[1,2] Therefore, leptospirosis is an occupational hazard for individuals who work closely with soil and water systems, such as farmers, military workers, sewage workers, and waste workers.[3] Leptospirosis has been sporadically reported in Türkiye. Şanlıurfa has one of the largest agricultural areas in Türkiye, and most residents earn their living by farming.

Leptospirosis can be overlooked in non-endemic areas, particularly when patients present with jaundice, which creates substantial diagnostic and therapeutic challenges. When multiorgan failure develops, timely coordination of care across specialties, including hepatology, nephrology, pulmonology, neurology, and intensive care, is essential to avoid delays in management. Here, we present the data of 30 patients with severe leptospirosis who were diagnosed and managed at a gastroenterology clinic in a tertiary center. Our results suggest that clinicians should be aware of gastrointestinal symptoms related to leptospirosis.

Materials and Methods

This retrospective cohort study analyzed the data of patients diagnosed with leptospirosis at the Harran University Hospital Department of Gastroenterology between May 2019 and September 2025. Harran University Hospital is a tertiary referral center and has had an established liver transplantation program for the past 7 years, serving a population of more than 2.5 million people and a region containing approximately 1.18 million hectares of agricultural land.

A standardized electronic data extraction form was used to collect information from patients' medical records. Patient demographics (age, sex, weight, and height), clinical characteristics (presenting symptoms and comorbidities), laboratory findings (complete blood count, kidney and liver biochemistry, coagulation tests, and inflammatory markers), diagnostic serological tests, imaging modalities (ultrasonography or computed tomography [CT]), length of hospital stay, and adverse outcomes were recorded. The Harran University Ethics Committee approved the study protocol (August 05, 2024; HRU/24.10.33) and waived the requirement for informed consent due to the retrospective nature of the study.

Lung involvement was diagnosed based on the presence of pulmonary infiltrates (on chest radiograph or CT scan) and the need for oxygen support (>5 L/min) to maintain oxygen saturation >90%.[4] The severity of the liver injury was categorized as: (1) Mild if serum enzyme elevations reached criteria for liver injury but bilirubin concentration was <2× upper limit of normal (ULN); (2) moderate if either bilirubin ≥2× ULN or symptomatic hepatitis; and (3) severe if bilirubin concentration ≥2× ULN and signs of liver failure (International Normalized Ratio [INR] ≥1.5, ascites and/or encephalopathy) or other organ failure considered to be due to liver injury.[5] Myocarditis was considered based on troponin elevation and new-onset electrocardiographic abnormalities or suggestive echocardiographic findings. Neurological involvement was defined as altered consciousness, status epilepticus, findings of meningitis, and exclusion of alternative diagnoses.[4] Acute kidney injury (AKI) was diagnosed according to Kidney Disease: Improving Global Outcomes classification.[6]

Leptospirosis was diagnosed based on the presence of classic epidemiological risk factors, laboratory findings (leukopenia or leukocytosis, thrombocytopenia, and renal insufficiency) and radiological features (diffuse or localized alveolar infiltrates, an interstitial pattern, multiple nodular densities or lobar pneumonia on chest X-ray or CT), and absence of typical causes of acute or chronic hepatitis. Serum samples were evaluated by polymerase chain reaction (PCR) and/or microscopic agglutination test (MAT) for microbiological diagnosis of the disease.[7]

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 24.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean±standard deviation or median (minimum–maximum), as appropriate. Categorical variables were expressed as frequencies and percentages. Comparisons between the groups were performed using the chi-square test or Fisher's exact test for categorical variables and the Mann–Whitney U-test for continuous variables, as appropriate. Statistical significance was set at $p<0.05$.

Results

We included 30 patients (86.7% male) with a median age of 45 years (range: 18–78) at the time of leptospirosis. A total of 16 patients (53.3%) were seropositive for MAT and/or PCR. General characteristics, clinical features, and outcomes of the study population are shown in Table 1. All participants were farmers or farm workers. Most cases occurred during summer and autumn (76.7%).

At presentation, fever (96.7%) was the most common symptom, followed by myalgia (86.7%), calf pain (73.3%), vomiting (66.7%), asthenia (56.7%), and anorexia (50%). Thrombocytopenia (<100×10^3/mm^3) was observed in 26 patients (86.7%), whereas severe thrombocytopenia (<50×10^3/mm^3) was present in 18 patients (60%). Leukopenia (<4000/mm^3) and leukocytosis (>12 000/mm^3) were observed in 2 (6.7%) and 13 (43.3%) patients, respectively (Table 1). All patients had clinical and laboratory features of liver involvement. The median total bilirubin level was 9.1 mg/dL (range: 2.5–49.0), and the median

Table 1. General characteristics and outcomes of the study population

Total patients	n=30
Age (years), median (range)	45 (18–78)
Male, n (%)	26 (86.7)
Farmer/farm worker, n (%)	30 (100)
Summer–Autumn, n (%)	23 (76.7)
Laboratory values	
WBC (×10³/µL)	11.5 (2.7–27)
Hemoglobin (g/dL)	12.5 (5.5–15.7)
Platelet (×10³/µL)	33.7 (7–192)
Creatinine (mg/dL)	1.69 (0.1–9.0)
Total bilirubin (mg/dL)	9.1 (2.5–49)
AST (U/L)	114 (48–270)
ALT (U/L)	89 (43–236)
CRP (mg/L)	13.4 (4.5–24.5)
LDH (U/L)	377 (186–661)
Thrombocytopenia (<100×10³/µL), n (%)	26 (86.7)
Severe thrombocytopenia (<50×10³/µL), n (%)	18 (60)
Leukopenia (<4000/mm³), n (%)	2 (6.7)
Leukocytosis (>12 000/mm³), n (%)	13 (43.3)
Clinical features, n (%)	
Pulmonary involvement	10 (33.3)
Acute kidney injury	18 (60)
Neurological involvement	5 (16.7)
Myocarditis	3 (10.0)
Hepatomegaly	13 (43.3)
Splenomegaly	6 (20)
Hepato-splenomegaly	6 (20)
Treatment, n (%)	
Doxycycline	6 (20)
Cephalosporins	20 (66.7)
Carbapenems	4 (13.3)
Plasma exchange	12 (40)
High-dose steroids	9 (30)
Outcomes	
Hospitalization (days), median (range)	7.5 (2–19)
ICU admission, n (%)	17 (56.7)
ICU stay (days), median (range)	4 (1–13)
Mechanical ventilation, n (%)	3 (10)
Mortality, n (%)	2 (6.7)

*: Laboratory values presented as median (min–max). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CRP: C-reactive protein; LDH: Lactate dehydrogenase; WBC: White blood cell; ICU: Intensive care unit.

Table 2. Characteristics and outcomes of the study population according to ICU admission status

Variables	ICU admission (n=17)	No ICU admission (n=13)	p
Male sex, n (%)	14 (82.4)	12 (92.3)	0.613
Age (years)*	46 (21–78)	44 (18–65)	0.992
WBC (×10³/µL)*	13.0 (6–20)	8.9 (3–27)	0.080
Hemoglobin (g/dL)*	11.9 (6–14)	13.0 (7–16)	0.110
Platelet (×10³/µL)*	35.0 (7–192)	32.4 (8–113)	0.861
Creatinine (mg/dL)*	2.1 (1–8)	1.2 (0.1–9.0)	0.004
Total bilirubin (mg/dL)*	10.0 (2.6–49)	7.3 (2.5–36)	0.097
AST (U/L)*	113 (49–270)	123 (48–224)	0.877
ALT (U/L)*	77 (50–164)	93 (43–236)	0.802
CRP (mg/L)*	14.0 (5–25)	12.6 (7–19)	0.599
LDH (U/L)*	426 (191–661)	345 (186–514)	0.113
INR*	1.05 (0.95–6.07)	1.16 (0.99–1.51)	0.232
Pulmonary involvement**	9 (52.9)	1 (7.7)	0.017
Acute kidney injury**	13 (76.5)	5 (38.5)	0.061
Neurological involvement**	5 (29.4)	0 (0)	0.052
Myocarditis**	3 (17.6)	0 (0)	0.238
Corticosteroid therapy**	9 (52.9)	0 (0)	0.003
Plasma exchange**	10 (58.8)	2 (15.4)	0.026
Mortality**	2 (11.8)	0 (0)	0.492

*: Continuous variables are presented as median (min–max); **: Variables are presented as proportions (%). AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein; LDH: Lactate dehydrogenase; INR: International normalized ratio; WBC: White blood cell; ICU: Intensive care unit.

INR was 1.13 (range: 0.95–6.07). Among the patients, 25 (83.3%) had features of moderate liver injury and 5 (16.7%) had severe liver injury.

AKI developed in 18 (60%) patients and 10 (33.3%) patients showed clinical and radiological findings of lung involvement. Three (10%) developed myocarditis, and 5 (16.7%) had clinical features of neurological involvement.

All patients were treated with antibiotics for leptospirosis. Six (20%) patients received doxycycline, 20 (66.7%) cephalosporins (ceftriaxone and cefepime), and 4 (13.3%) carbapenems. Prednisolone (40–60 mg/day) was given for 3–14 days to nine of 10 patients with pulmonary involvement. Plasma exchange (2–5 cycles) was performed in 12 (40%) patients, whose median total bilirubin level was 22.7 mg/dL (range: 9.4–48 mg/dL).

The median duration of hospitalization was 7.5 days (range: 2–19 days) in the study population. Due to disease severity, 17 (56.7%) patients required intensive care unit (ICU) admission (Table 2). Overall, median creatinine (2.1 vs. 1.2 mg/dL, p=0.004) was higher, pulmonary involvement was more common (52.9% vs. 7.7%, p=0.017), plasma

exchange (58.8% vs. 15.4%, p=0.026) and corticosteroid use (52.9% vs. 0%, p=0.003) were more common among patients admitted to the ICU than among those not admitted to the ICU. Three patients (10%) required invasive mechanical ventilation, and 2 patients (6.7%) required non-invasive mechanical ventilation and 10 (33.3%) received oxygen supplementation by nasal cannula or mask. One patient with a congenital solitary kidney developed severe AKI that progressed to end-stage renal disease requiring long-term maintenance dialysis. Two patients (6.7%) died during the index hospitalization.

Discussion

We performed a retrospective study of patients diagnosed with and treated for leptospirosis from one of the largest farming areas in Türkiye. Our data were derived from the gastroenterology clinic and included patients who mainly presented with jaundice and increased transaminase levels, which are laboratory manifestations of hepatic dysfunction. Importantly, our patients showed concomitant involvement of other organs, including the kidney, lungs, heart, or brain. Seventeen (56.7%) patients required ICU admission. Most patients recovered following prompt and appropriate treatment, but two patients did not respond to therapy and died.

Weil's disease is the most severe form of leptospirosis and is characterized by liver involvement and jaundice.[1,3] The presence of jaundice is clinically relevant as it implies a worse prognosis with a mortality rate of 19.1% in untreated cases.[8] Several studies have evaluated liver injury caused by pathogenic *Leptospira*. In two previous studies,[9,10] liver biopsy showed non-specific hepatocellular damage affecting the sinusoidal pole, endoplasmic reticulum, mitochondria, and bile secretory apparatus. The absence of extensive cell necrosis in the liver histology of patients with leptospirosis can partly explain the low serum transaminase levels during the disease course.[9] An experimental study showed that invasion of pathogenic *Leptospira* into the intercellular junctions of host hepatocytes leads to disruption of the junction.[11] Subsequently, bile leaks from the biliary capillaries into the blood circulation, and jaundice develops quickly. In another study,[12] *Leptospiral* antigens and their glycolipoproteins showed a direct cytotoxic effect on liver cell membranes in guinea pigs. These results can partly explain the causes of liver injury in pathogenic leptospirosis, but the exact mechanisms of jaundice in these patients remain unclear.[1] In our study population, mildly elevated aminotransferases and jaundice were the main characteristics in most patients. This finding can help differentiate leptospirosis from other causes of acute liver injury, such as viral hepatitis, autoimmune hepatitis, or ischemic hepatitis. Importantly, some patients in our cohort had cognitive impairment and prolonged INR, which are features of acute liver failure, and were referred to our center for the evaluation of liver transplantation.[13] These results underscore the importance of considering leptospirosis in the differential diagnosis of unexplained acute liver injury, especially in the presence of geographical risk factors.

In leptospirosis, alveolar hemorrhage is a common finding that may be secondary to capillary endothelial damage.[1] Lung injury has been reported in 20–70% of patients with leptospirosis and is a predictor of increased mortality.[14] In our study, the rate of abnormal chest radiographic findings was 33.3%. Interestingly, two patients with pulmonary involvement presented at the time of the COVID-19 pandemic, and the initial diagnosis was severe COVID-19. Repeated PCR examinations did not confirm COVID-19, and the diagnosis of leptospirosis was established based on MAT positivity. Similar cases have been reported previously.[15] In our study, patients with pulmonary involvement more commonly required ICU admission, mechanical ventilation, or oxygen supplementation. The overall mortality rate was similar between the groups. Our sample size was small for more robust analyses, but previous larger cohort studies showed that isolated pulmonary involvement was associated with higher mortality.[4,16]

Renal insufficiency is commonly observed in leptospirosis and is characterized by the typical clinical and pathological findings of tubulointerstitial nephritis.[17] Some studies have reported that renal insufficiency is an independent risk factor of mortality.[8,17,18] Unfortunately, our study population was too small to evaluate the prognostic relevance of AKI in patients with leptospirosis. Five of our patients required hemodialysis and only one required permanent hemodialysis. These results suggest that close follow-up of AKI patients is essential.

In our study, three cases were diagnosed with myocarditis based on electrocardiogram, troponin assays, and echocardiographic findings. These patients also had concomitant neurological involvement. Previous studies have shown that myocarditis and neurological leptospirosis are significantly associated with mortality.[4,18] Two patients who died in our cohort had concomitant myocarditis and findings of neurological involvement.

We reported a 6.7% case-fatality rate, which is lower than that reported in Türkiye.[19,20] Importantly, mortality rates vary widely according to the severity of leptospirosis at diagnosis.[4,8,18,21] Typically, patients with leptospirosis are treated with systemic antibiotics,[3] while other management strategies include hemodialysis and intravenous corticosteroids for patients who develop pulmonary hemorrhage syndrome.[4,16,17]

Therapeutic plasma exchange was performed in 12 patients, particularly those with marked hyperbilirubinemia and multiorgan failure. Serum bilirubin levels can induce toxic effects on renal tubules, resulting in deterioration of kidney function.[22] The rapid removal of bilirubin from the systemic circulation leads to clinical improvement in severe leptospirosis.[22,23] A previous study showed a higher survival rate among patients with leptospirosis-associated severe pulmonary hemorrhagic syndrome who underwent plasma exchange than among those who did not receive plasma exchange.[24] In our cohort, mortality was similar between patients who underwent plasma exchange and those who did not, although the interpretation was limited by the small sample size and low number of deaths. This specific management strategy may have contributed to the relatively low mortality rate observed in our study population.

Similar to previous studies, leptospirosis was more common among male patients, which is related to occupational and exposure bias. Most of our cases involved farm workers and farmers.[1,4,8]

In our study, microbiological confirmation by MAT and/or PCR was obtained in 16 (53.3%) patients. During the early phase of the disease, enzyme-linked immunosorbent assay (ELISA) is more sensitive than MAT, and immunoglobulin M positivity can be detected earlier.[7] PCR is also accurate for the early diagnosis of leptospirosis. ELISA testing was not performed in our cohort. Since ELISA and PCR tests are difficult to perform and are not routinely available in all laboratories, some of our patients were diagnosed based on clinical and laboratory findings. Since prompt treatment is lifesaving, leptospirosis can be diagnosed based on suitable clinical and laboratory findings, especially in endemic areas.

Our study has several limitations. First, this is a retrospective, single-center, and small cohort study. We included patients who were diagnosed and treated at the gastroenterology department and some cases with mild disease may have been missed. Approximately half of the cases were diagnosed based on clinical and laboratory findings without confirmatory microbiological testing. The types of antibiotics used, indications for corticosteroid therapy, and plasma exchange were not standardized and were determined on a case-by-case basis.

Conclusion

We suggest that leptospirosis should be included in the differential diagnosis of patients with marked hyperbilirubinemia and/or systemic features. Leptospirosis presenting with cholestasis and pulmonary involvement is associated with a higher probability of ICU admission. In such patients, the additional use of corticosteroids and plasma exchange may provide potential benefit.

Ethics Committee Approval: The study protocol was approved by the Harran University Ethics Committee (dated August 05, 2024, and numbered HRU/24.10.33), and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of the study.

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

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SYSTEMATIC REVIEW

Prevalence of metabolic dysfunction-associated steatotic liver disease among obese, overweight, and at-risk children and adolescents in Türkiye: A meta-analysis

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Points to Note

- **Synthesis of Current Evidence:** Pediatric MASLD prevalence among overweight/obese and at-risk children in Türkiye is high (44.6%), with a higher pooled prevalence in boys.
- **Major Controversies:** Substantial heterogeneity, reliance on ultrasonography, and inclusion of mainly high-risk populations limit generalizability to all children in Türkiye.
- **Future Directions:** Population-based epidemiological studies and improved pediatric screening strategies using reliable non-invasive methods are needed.

ABSTRACT

Background and Aim: Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly non-alcoholic fatty liver disease (NAFLD), is the most common chronic liver disease worldwide. Among children, the overall prevalence of MASLD is estimated at around 7%, and early manifestation is associated with a more severe prognosis. Despite this growing burden, no systematic analysis of pediatric MASLD prevalence in Türkiye has yet been conducted. Here, we aimed to estimate the pediatric MASLD prevalence among children with specific conditions in Türkiye.

Materials and Methods: A comprehensive literature search was conducted for studies published in English and/or Turkish between 2005 and 2023 using the databases MEDLINE, PubMed, EMBASE, and ULAKBIM. The search strategy included the following terms: "Türkiye AND NAFLD AND Pediatric" and "Türkiye AND NAFLD AND Prevalence AND Children AND Adolescent." The studies identified through this literature review were incorporated into the meta-analysis, which included either obese/overweight or at-risk children or adolescents with specific conditions such as increased transaminases.

Results: The pooled overall prevalence of MASLD was estimated as 44.6% (95% confidence interval [CI]: 39.5–49.7) among at-risk children and adolescents. Heterogeneity among studies was considerable, with an I2 value of 96%, indicating substantial variability. Subgroup analysis showed a pooled prevalence of 54.9% in boys (95% CI: 48.6–61.1) and 41.2% in girls (95% CI: 35.6–46.9). Regionally, the prevalence was 49.0% (95% CI: 41.2–57.1) in the Marmara and Aegean regions, and 42.2% (95% CI: 35.3–49.1) in the Black Sea, Mediterranean, and Central Anatolian regions.

Conclusion: The results of this study indicate a markedly high prevalence of MASLD among at-risk children and adolescents. These findings should serve as an alert for policymakers to adapt healthcare strategies aimed at preventing childhood obesity and MASLD.

Keywords: Adolescent, fibrosis, MASH, metabolic dysfunction-associated steatotic liver disease, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, pediatric.

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Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD), is the most prevalent chronic liver condition worldwide, affecting approximately 30% of the adult population.[1] MASLD is a significant public health concern not only among adults but also in children and adolescents – a trend that reflects the growing global obesity pandemic affecting younger populations as well.[2] Notably, not all children with obesity are expected to develop MASLD. It is estimated that approximately one-third of obese boys and one-quarter of obese girls are affected by the condition.[2] A meta-analysis estimated the overall prevalence of MASLD among children to be 7.6%, with rates exceeding 35% among those with obesity.[3] Childhood MASLD is associated with higher rates of comorbidities and a 40-fold increased risk of mortality in adulthood. These numbers are therefore highly concerning.[4] Moreover, a recent meta-analysis based on biopsy-confirmed cases reported pooled prevalence rates of 60% for metabolic dysfunction-associated steatohepatitis (MASH), 31% for significant fibrosis (FIB), and 12% for advanced fibrosis among pediatric MASLD patients, figures that approach the burden observed in adult populations.[5]

Despite the overall scarcity of data on pediatric MASLD, the evidence from Türkiye is particularly limited. To date, no systematic analysis has been conducted to determine the prevalence of MASLD among children and adolescents in the country. However, understanding this prevalence is essential for developing effective screening and treatment strategies aimed at preventing complications from an early age. Therefore, the aim of this meta-analysis was to estimate the prevalence of pediatric MASLD among either obese/overweight or at-risk children or adolescents with specific conditions, such as increased transaminases in Türkiye, and to examine its regional distribution.

Patients and Methods

Data Collection

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[6] A comprehensive literature search was performed for studies published in English and/or Turkish using the databases MEDLINE, PubMed, EMBASE, and ULAKBIM (Turkish medical index). The following search terms were used: "Türkiye AND NAFLD AND Pediatric" and "Türkiye AND NAFLD AND Prevalence AND Children AND Adolescent." All identified articles were reviewed, and the reference lists of included studies were examined to identify additional relevant publications. These additional sources were retrieved either manually or through subsequent electronic searches.

The meta-analysis covers studies published between 2005 and 2023. The primary inclusion criterion was the availability of a MASLD diagnosis. We used MASLD and NAFLD interchangeably, as the two terms have near-complete overlap and are globally accepted as synonymous.[7] To avoid duplication, we carefully screened for overlapping data by cross-checking study periods, sample sizes, study locations (e.g., centers or hospitals), and author names. We extracted the following data once the study was included: study author and year, study setting/region, type of diagnostic method, age (age-group), number tested (boy/girl), and number positive (boy/girl). Two authors (MT and CK) checked all studies used in the analysis. Eligible studies were observational studies, including cross-sectional, retrospective, and clinic- or hospital-based studies that enrolled children or adolescents and reported extractable data on MASLD/NAFLD prevalence. Studies were excluded if they were adult-only studies; reviews, editorials, letters, case reports, or conference abstracts without sufficient data; did not provide a clear MASLD/NAFLD diagnosis; did not report extractable numerator and denominator data; or represented duplicate reports or likely overlapping study populations. When multiple reports from the same center appeared to include overlapping populations, we retained the most complete or most relevant dataset based on study period, sample size, setting, and available outcome data. Interventional studies in which participants were selected due to treatment allocation rather than prevalence ascertainment, as well as studies with methods not comparable with the included observational studies, were also excluded.

The studies focused on children with specific conditions, including obesity or overweight, elevated transaminases, and polycystic ovary syndrome. Children and adolescents were considered overweight if their body mass index was between the 85th and 95th percentiles for their age and sex, and obese if it was at or above the 95th percentile.[8]

Statistical Analysis

Data were analysed using MetaXL version 5.3 software, an add-in for meta-analysis in Microsoft Excel for Windows (https://www.epigear.com/index_files/metaxl.html). A random-effects model using the DerSimonian–Laird method was applied to estimate the pooled prevalence and corresponding 95% confidence intervals (CIs), accounting for both within- and between-study variability. Where data permitted, pooled prevalence estimates were also stratified by region. For regional analysis, the following groupings were used: Region A (Marmara and Aegean) representing Western Türkiye; Region B (Black Sea, Central Anatolia, and Mediterranean) representing Central Türkiye; and Region C (Eastern and Southeastern Türkiye), based on geography, population size, and socioeconomic characteristics. Due to the limited number of studies available from Region C, pooled prevalence estimates were calculated only for Regions A and B. To account for the potential sources of heterogeneity in the data, we used two types of statistical models: A random-effects model and a quality effects model. The quality effects model allowed us to examine the effects of study quality on the prevalence estimate independently of other covariates, while the random-effects model accounted for both within-study and between-study heterogeneity and provided an estimate of the average effect size across studies. The quality effects model uses a quality score (Supplementary Table 1), which is essential as a safeguard score (risk of bias instrument). We scored each study that was used for the meta-analysis (Supplementary Table 2).

To explore whether prevalence estimates differed by publication period, we performed an exploratory descriptive stratification of studies included in the quality-effects analysis according to year of publication. Studies were grouped into four publication periods: 2005–2009, 2010–2014, 2015–2019, and 2020–2023. Quality-effect-weighted pooled prevalence estimates were calculated for each period. Because the number of studies was uneven across periods and the included populations were heterogeneous and primarily consisted of obese/overweight or otherwise high-risk pediatric cohorts, these analyses were considered descriptive and were not interpreted as formal temporal trend analyses.

Results

The results of the search strategy and the final selection of studies are summarized in the flow diagram (Fig. 1). The electronic database search identified 57 articles, with one additional study retrieved through manual screening, resulting in a total of 58 eligible studies. Among these, 38 studies reported MASLD prevalence stratified by sex[8–45] while others did not provide sex-specific data.[46–65] The age of participants across studies ranged from 2 months to 18 years.

A total of 9,600 participants were included across the 58 studies. Of these, 56 studies comprising 9,279 participants of both sexes contributed to the primary pooled prevalence analysis, yielding an overall MASLD prevalence of 44.6% (95% CI: 39.5–49.7) (Fig. 2). The remaining two studies included exclusively one sex: one study comprised 197 obese boys and the other comprised 124 girls with polycystic ovary syndrome. These two studies were excluded from the overall pooled prevalence estimate and contributed only to the sex-specific analyses. Of the 56 included studies, 52 focused on obese/overweight children, while the remaining studies were conducted in children with specific conditions, including elevated transaminases and polycystic ovary syndrome.[26,28,47,53,63,64] Ultrasonography was employed as the diagnostic method in 100% of the studies. In addition, transient elastography was used in one study, shear-wave elastography in another, and magnetic resonance imaging–proton density fat fraction was applied in one study as complementary diagnostic methods. A total of 14 studies were identified from the Marmara region, 10 from the Aegean region, 3 from the Black Sea region, 27 from Central Anatolia, 3 from the Mediterranean region, and 1 from the Southeastern Anatolian region. The heterogeneity among studies was substantial, with an I2 value of 96%, indicating significant variability.

The pooled prevalence results from the quality effects model were comparable; see the Supplementary material for the forest plots and study quality scores (Supplementary Figs. 1a and 2a; Supplementary Tables 3a and 4a).

Of the included studies, only 38 reported sex-specific outcomes. The pooled prevalence was 54.9% in boys (95% CI: 48.6–61.1) (Fig. 3a) and 41.2% in girls (95% CI: 35.6–46.9) (Fig. 3b). The pooled prevalence results from the quality effects model were comparable; see the Supplementary material for the forest plots and study quality scores (Supplementary Fig. 1b and c; Supplementary Tables 3b and c and 4b and c).

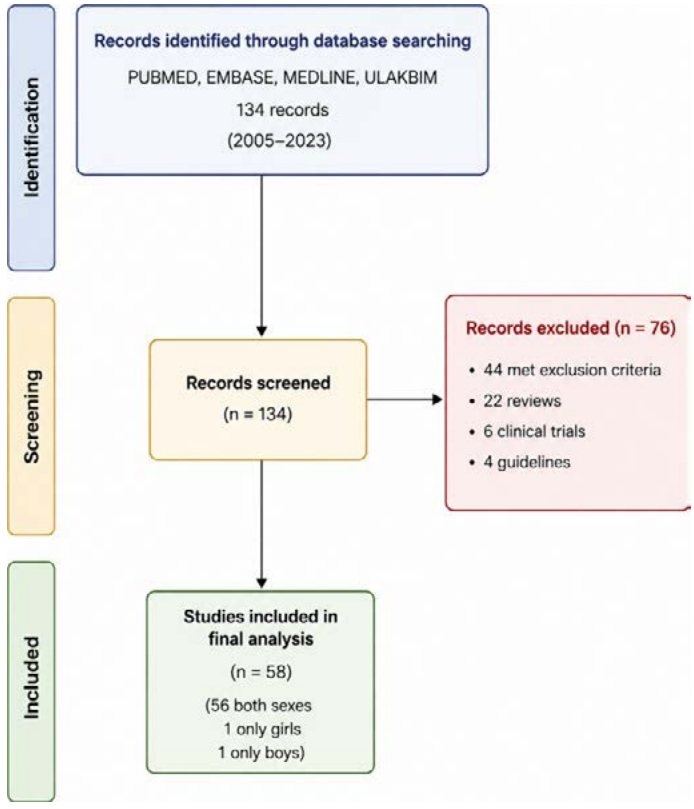


Figure 1. Literature search strategy.

Region-specific pooled prevalence was calculated for Regions A and B. The prevalence in Region A was 49.0% (95% CI: 41.2–57.1), and in Region B, 42.2% (95% CI: 35.3–49.1) (Fig. 4a and b). Due to an insufficient number of studies from Region C, a pooled prevalence estimate could not be calculated. However, a single study from this region reported a prevalence of 63.2%.[41]

In an exploratory stratification by publication period, three studies were published in 2005–2009, 24 studies in 2010–2014, 16 studies in 2015–2019, and 15 studies in 2020–2023. The corresponding quality-effect-weighted prevalence estimates were 31.2%, 43.2%, 41.4%, and 45.8%, respectively. The characteristics of the included studies according to study population and publication period are summarized in Table 1. These findings suggest broadly comparable prevalence estimates across the later publication periods, although the earliest period included only three studies.

Discussion

In this study, we reported for the first time the prevalence of MASLD among Turkish children and adolescents with obesity or specific conditions that make them at risk for MASLD. Our meta-analysis revealed a pooled prevalence of approximately 45% among predominantly overweight/obese and other at-risk children, with rates exceeding 50% in boys and with broadly comparable pooled estimates in Regions A and B. These findings underscore the alarming prevalence of MASLD in our country and its projected growing burden.

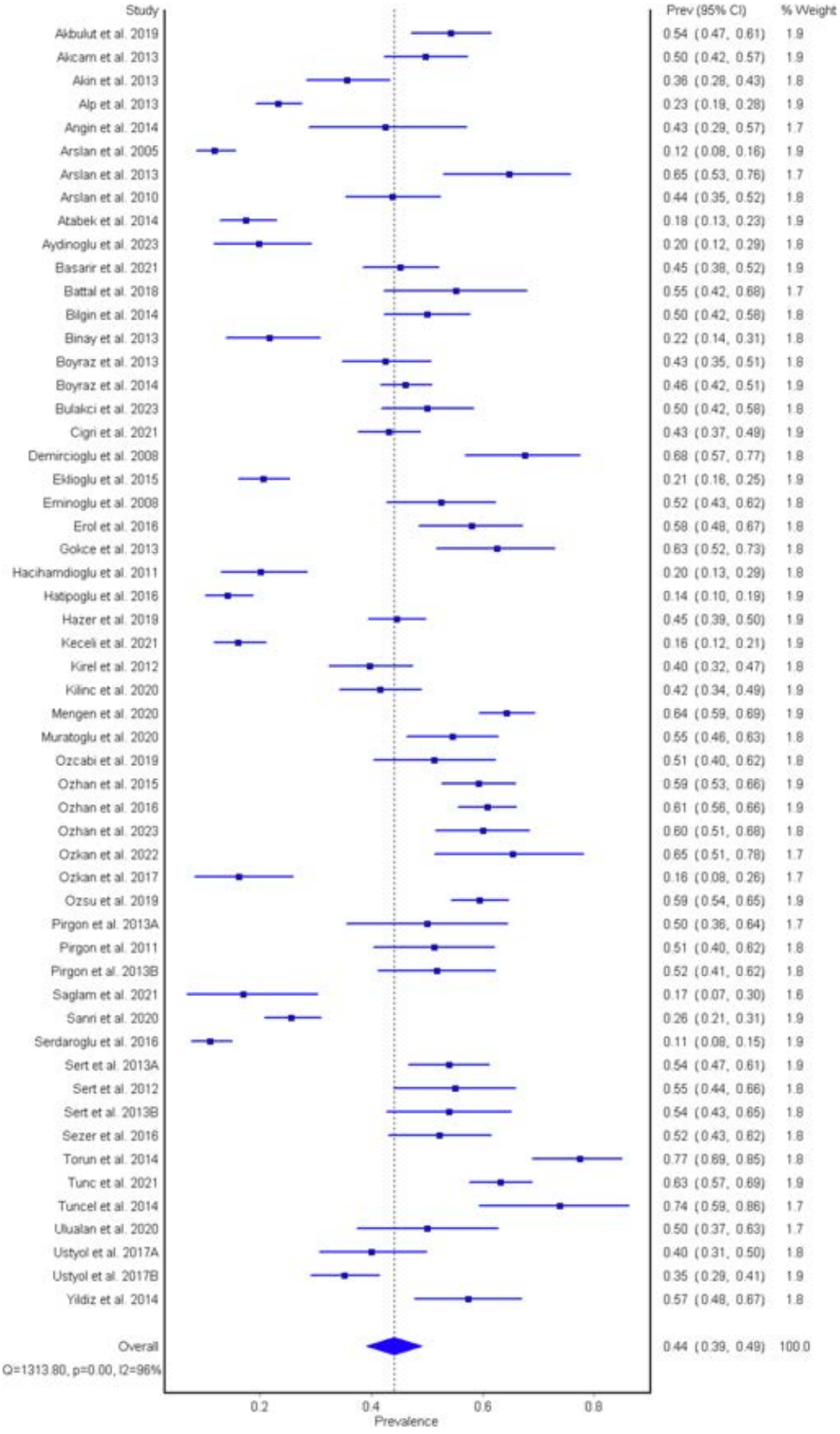
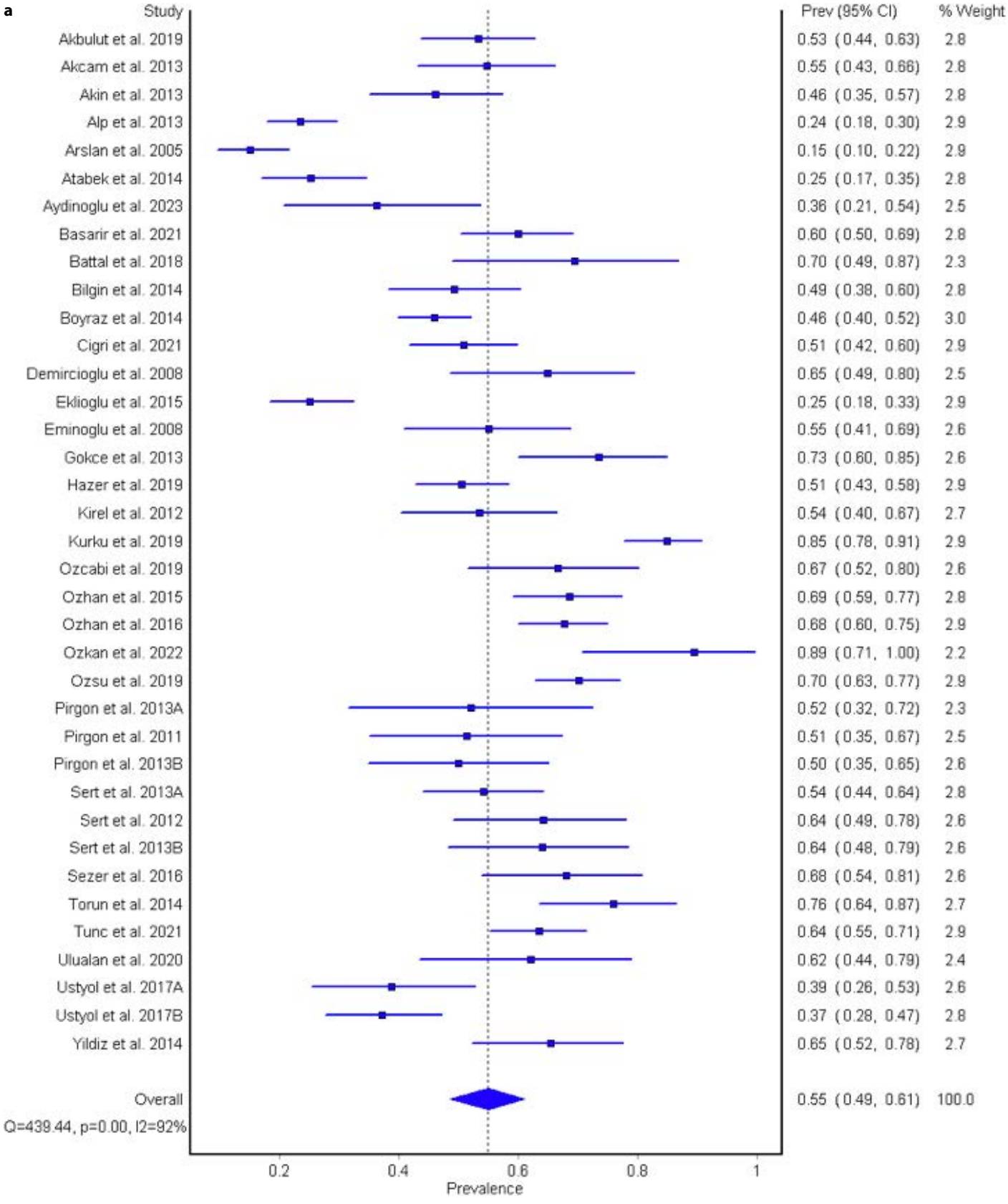


Figure 2. The pooled prevalence of pediatric metabolic dysfunction-associated steatotic liver disease across all studies.


a
Study
Prev (95% CI)
% Weight
Akbulut et al. 2019 0.53 (0.44, 0.63) 2.8
Akcam et al. 2013 0.55 (0.43, 0.66) 2.8
Akin et al. 2013 0.46 (0.35, 0.57) 2.8
Alp et al. 2013 0.24 (0.18, 0.30) 2.9
Arslan et al. 2005 0.15 (0.10, 0.22) 2.9
Atabek et al. 2014 0.25 (0.17, 0.35) 2.8
Aydinoglu et al. 2023 0.36 (0.21, 0.54) 2.5
Basarir et al. 2021 0.60 (0.50, 0.69) 2.8
Battal et al. 2018 0.70 (0.49, 0.87) 2.3
Bilgin et al. 2014 0.49 (0.38, 0.60) 2.8
Boyraz et al. 2014 0.46 (0.40, 0.52) 3.0
Cigri et al. 2021 0.51 (0.42, 0.60) 2.9
Demircioglu et al. 2008 0.65 (0.49, 0.80) 2.5
Eklioglu et al. 2015 0.25 (0.18, 0.33) 2.9
Eminoglu et al. 2008 0.55 (0.41, 0.69) 2.6
Gokce et al. 2013 0.73 (0.60, 0.85) 2.6
Hazer et al. 2019 0.51 (0.43, 0.58) 2.9
Kirel et al. 2012 0.54 (0.40, 0.67) 2.7
Kurku et al. 2019 0.85 (0.78, 0.91) 2.9
Ozcabi et al. 2019 0.67 (0.52, 0.80) 2.6
Ozhan et al. 2015 0.69 (0.59, 0.77) 2.8
Ozhan et al. 2016 0.68 (0.60, 0.75) 2.9
Ozkan et al. 2022 0.89 (0.71, 1.00) 2.2
Ozsu et al. 2019 0.70 (0.63, 0.77) 2.9
Pirgon et al. 2013A 0.52 (0.32, 0.72) 2.3
Pirgon et al. 2011 0.51 (0.35, 0.67) 2.5
Pirgon et al. 2013B 0.50 (0.35, 0.65) 2.6
Sert et al. 2013A 0.54 (0.44, 0.64) 2.8
Sert et al. 2012 0.64 (0.49, 0.78) 2.6
Sert et al. 2013B 0.64 (0.48, 0.79) 2.6
Sezer et al. 2016 0.68 (0.54, 0.81) 2.6
Torun et al. 2014 0.76 (0.64, 0.87) 2.7
Tunc et al. 2021 0.64 (0.55, 0.71) 2.9
Ulualan et al. 2020 0.62 (0.44, 0.79) 2.4
Ustyol et al. 2017A 0.39 (0.26, 0.53) 2.6
Ustyol et al. 2017B 0.37 (0.28, 0.47) 2.8
Yildiz et al. 2014 0.65 (0.52, 0.78) 2.7
Overall 0.55 (0.49, 0.61) 100.0
Q=439.44, p=0.00, I2=92%
0.2
0.4
0.6
0.8
1
Prevalence

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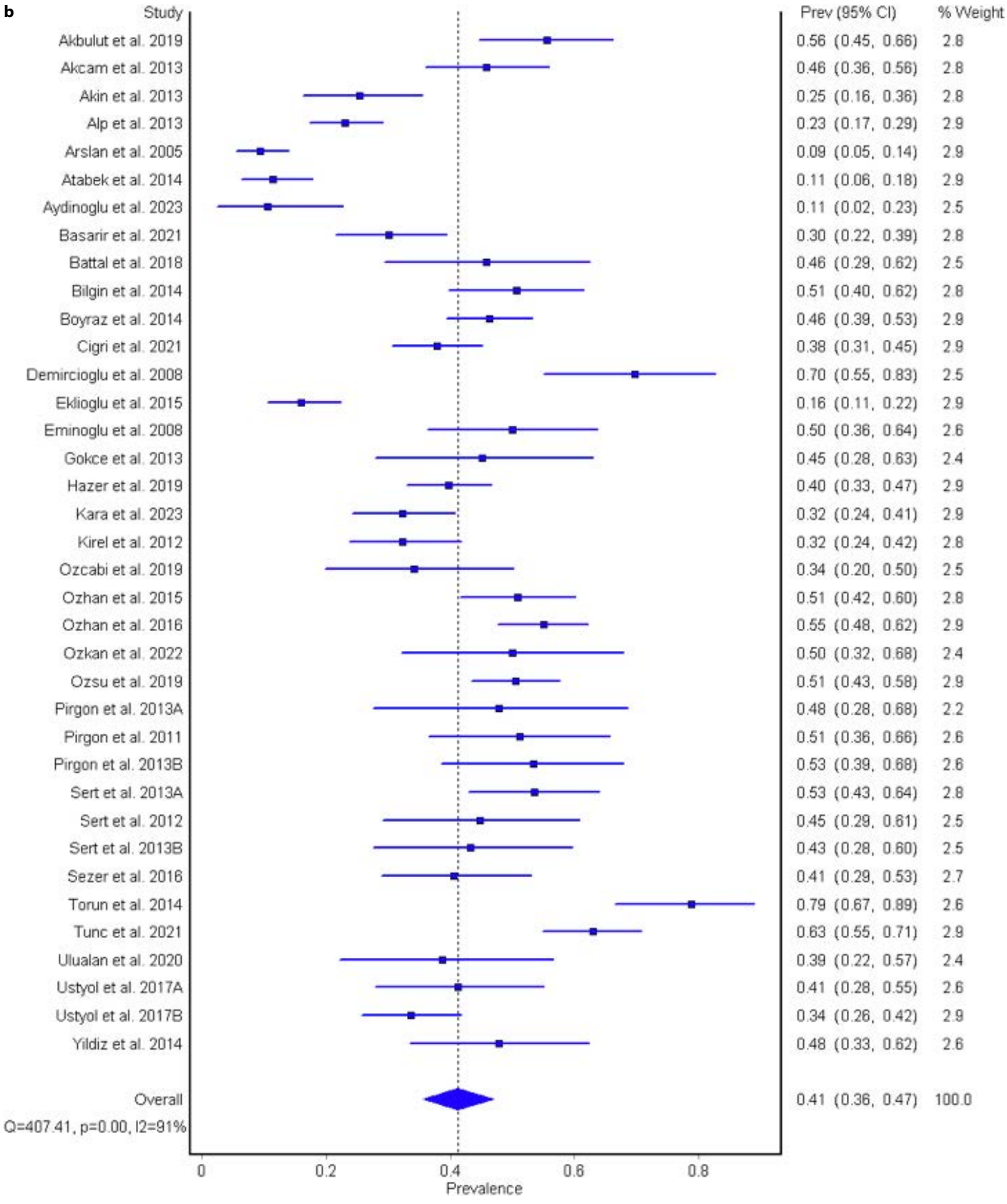
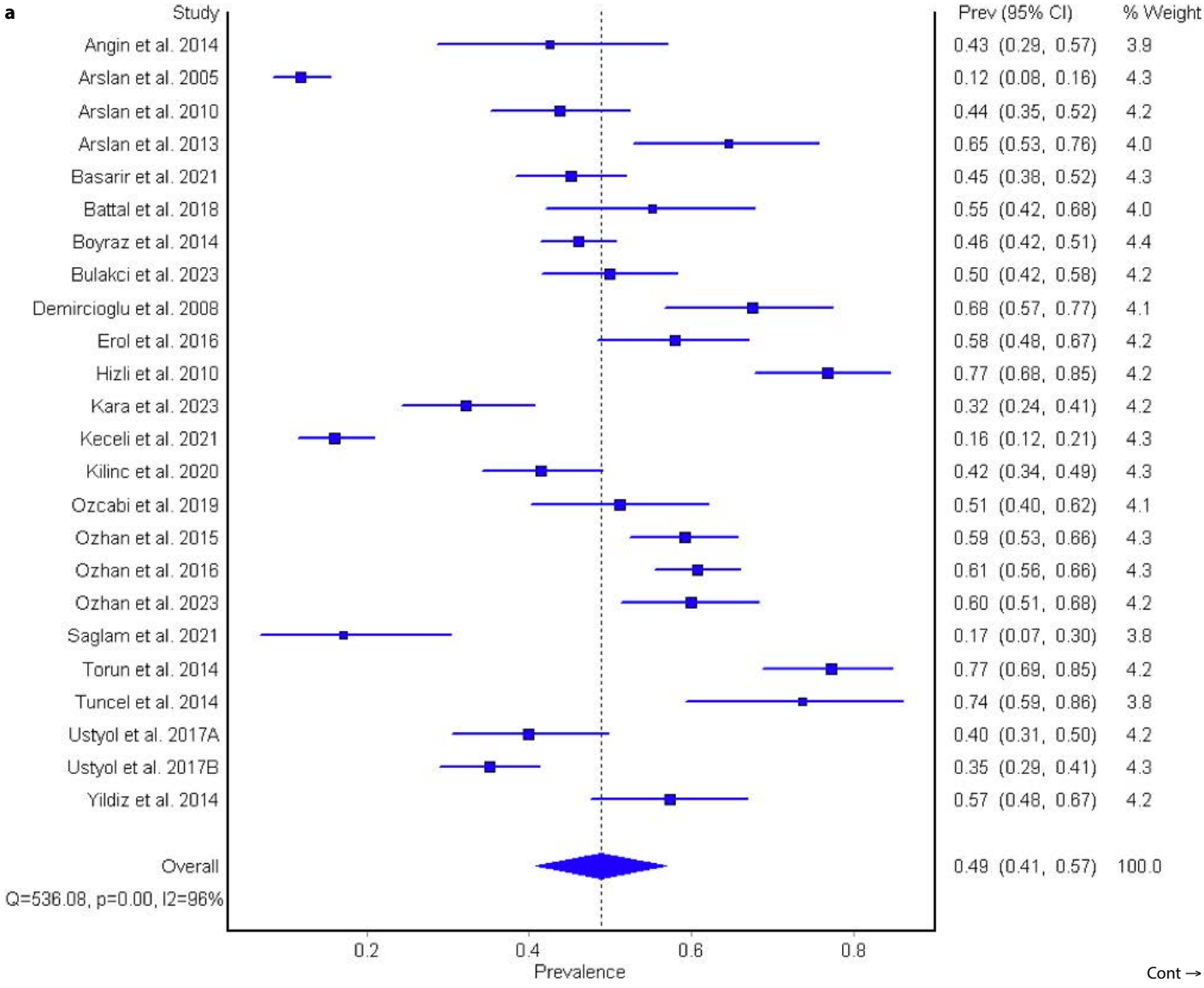


Figure 3. (a) Prevalence of pediatric metabolic dysfunction-associated steatotic liver disease (MASLD) among boys; **(b)** prevalence of pediatric MASLD among girls.



Worldwide, the prevalence of MASLD increased from 25.3% in 1990–2006 to 38.0% in 2016–2019.[1] Accumulating data from Türkiye, primarily derived from adult populations over the past decade, also consistently demonstrated a significantly high prevalence of MASLD. The most recent multicenter study, conducted mainly among patients presenting to tertiary care centers with dyspeptic complaints, reported a prevalence of 50%.[66] Another study conducted in the Central Anatolian region reported a MASLD prevalence of 60% based on ultrasonography. Remarkably, within this cohort, 40% of the participants were obese, and 36% were overweight.[67] However, the most striking prevalence rates were reported in studies conducted among apparently healthy young individuals. One study, carried out among medical students using transient elastography, which is a highly sensitive tool, demonstrated a prevalence of 23%.[68] A study conducted in a military hospital among apparently healthy young men, using ultrasonography, reported a prevalence of 10%.[69] The discrepancy between these two studies may be explained by differences in nutrition, physical activity, and the diagnostic methods used to assess hepatic steatosis.[68,69] In our study, we report an alarming prevalence of MASLD among children and adolescents, approaching the rates observed in the adult population. The higher prevalence compared with that in apparently healthy young individuals is primarily attributable to the predominance of children with obesity in our analysis. In obese patients, prevalence rates of at least 60% have been reported in Türkiye, increasing to as high as 85% with higher classes of obesity.[70] Among children with obesity, however, we found a lower prevalence of MASLD than that reported in adults. Notably, one study from 2006, which we excluded due to methodological differences, investigated the prevalence of NAFLD in children aged 2–10 years who had undergone autopsy. In that study, the prevalence was 10% among obese children and 5% among non-obese children, with an overall prevalence of 6%.[71] Given the increasing prevalence of obesity among children today, higher rates would be expected. Indeed, obesity affected <1% of the pediatric population in the 1970s, whereas today its prevalence exceeds 7% worldwide.[72]

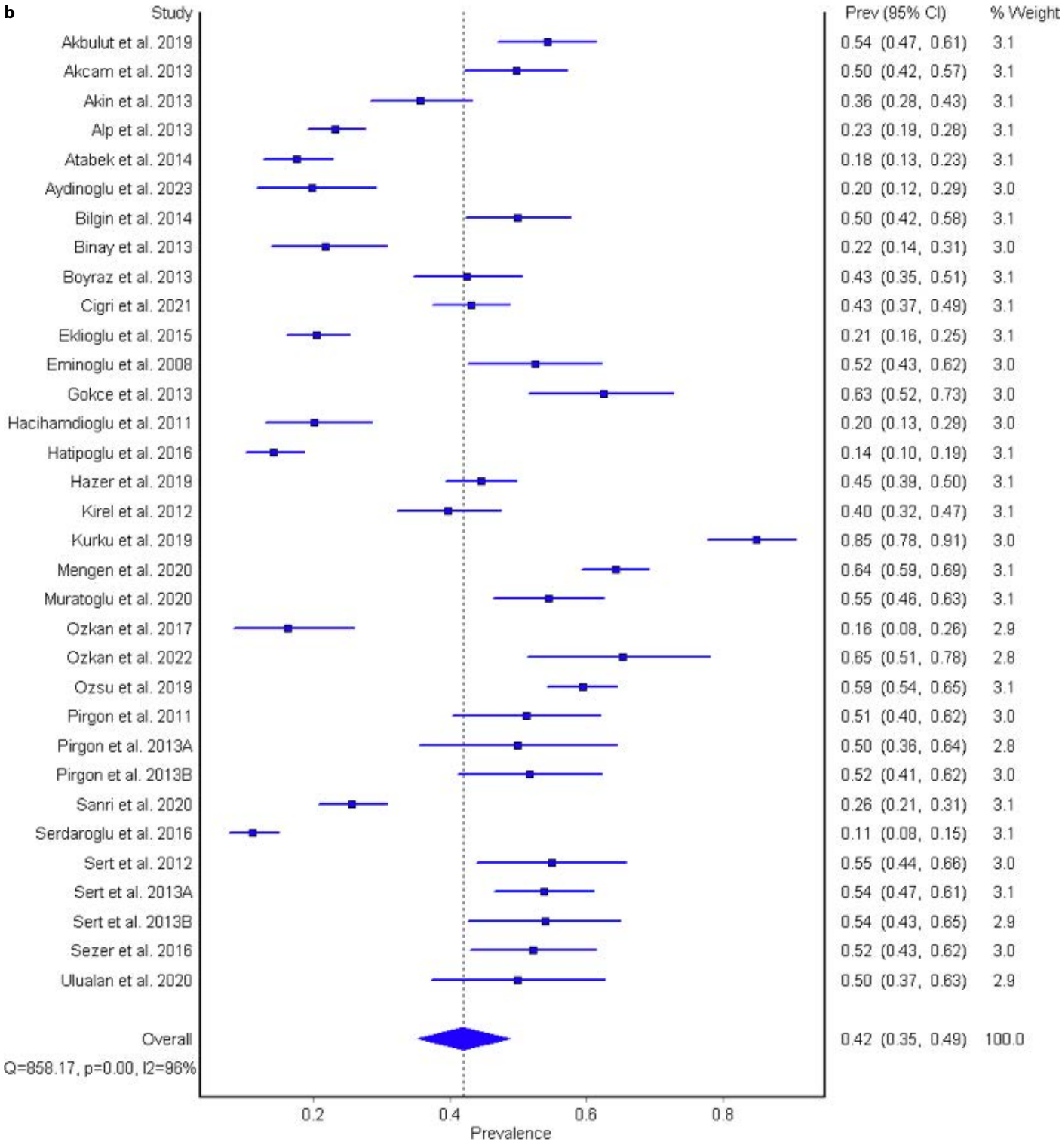


Figure 4. (a) Prevalence of pediatric MASLD in the Marmara and Aegean regions; **(b)** Prevalence of pediatric MASLD in the Black Sea, Mediterranean and Central Anatolia regions.

The metabolic burden originating in childhood often persists into adulthood and is associated with a more severe prognosis compared to acquiring these comorbidities later in life. Patients with pediatric MASLD have a significantly higher likelihood of requiring liver transplantation compared to the general population.[73,74] The trajectory may, in fact, be determined before birth, as even gestational

Table 1. Distribution of included studies and participants by population and publication period

Group	Study population	Subgroup	2005–2009		2010–2014		2015–2019		2020–2023		Total	
			Stu. (n)	Par. (n)	Stu. (n)	Par. (n)	Stu. (n)	Par. (n)	Stu. (n)	Par. (n)	Stu. (n)	Par. (n)
Group 1	Obese	—	3	503	23	3,182	14	2,568	9	1,922	49	8,175
Group 2	Overweight and obese	—	—	—	1	99	1	68	2	184	4	351
Group 3	Other/PCOS	PCOS	—	—	—	—	—	—	1	124	1	124
Group 3	Other/enzyme elevation	Enzyme elevation	—	—	—	—	1	281	3	669	4	950
Overall			3	503	24	3,281	16	2,917	15	2,899	58	9,600

Stu: Studies; Par: Participants; PCOS: Polycystic ovary syndrome. For the Other population, subgroups are displayed explicitly. Participant counts represent the total number of participants reported in the included studies within each population and publication-period category. Counts are presented as number of studies and total participants.

diabetes has been associated with an increased rate of hepatic steatosis among neonates.[75] One important finding from a large retrospective study involving more than 50,000 children identified the ages of 2–6 years as the critical period for weight gain. Beyond this window, the likelihood of obesity persisting into adulthood increases significantly.[76] In line with these data, MASLD in the pediatric age group should be screened among obese children or children at high risk with specific conditions, as indicated.[77,78] Among adults, the recommended target population for MASLD screening is largely similar to that in the pediatric population. However, in adults, the screening strategy relies on the application of the FIB-4 index, which allows for the exclusion of patients at low risk for advanced fibrosis, who can then be followed in primary care settings.[79] FIB-4 has been well validated among adult MASLD patients, including in the Turkish population, across different settings such as diabetes, obesity, and both normal and abnormal liver function profiles. Indeed, lean and morbidly obese patients appear to be less suitable for screening with FIB-4 or NAFLD fibrosis score-based algorithms. Nevertheless, the conclusion from these studies was that such scoring systems are valuable in excluding high risk for advanced fibrosis, due to their strong negative predictive value.[80–82] In contrast, screening in pediatric patients primarily relies on alanine transaminase (ALT)-based algorithms, applied in the presence of cardiometabolic risk factors or obesity, beginning at 10 years of age or earlier.[83] Such an approach may not be suitable for the pediatric population, as abnormal ALT thresholds are not universally valid across different populations. Defining what constitutes an abnormal value is therefore challenging, and this limitation may result in missing some children at high risk for MASLD.[84] At present, there is growing interest in screening children with imaging modalities. However, there is also a need for non-invasive diagnostic algorithms that can be applied in primary care settings to enable timely and targeted intervention.[83] In our meta-analysis, ultrasonography was almost universally used as the diagnostic method for MASLD. In two studies, transient elastography–based methods/algorithms were also applied. This approach may be particularly useful in children, as FibroScan is easy to perform and has higher sensitivity for detecting hepatic steatosis compared with ultrasonography. Moreover, its ability to identify increased liver fibrosis provides an important advantage in detecting children at high risk of developing severe liver-related outcomes.[68] A recent analysis of National Health and Nutrition Examination Survey data reported a MASLD prevalence of 20% among adolescents aged 12–17 years, increasing to as high as 70% in adults.[85] These findings suggest that FibroScan can also be feasibly applied in children, where its high sensitivity may allow for the detection of a greater number of cases of hepatic steatosis. Although imaging-based algorithms are associated with higher costs, the vulnerability of obese children and the projected long-term burden of untreated disease often leading to more severe outcomes in adulthood suggest that these approaches should be more strongly encouraged in pediatric practice.

Another significant challenge is the treatment of patients with MASLD, particularly regarding who should be treated and at what stage. Until recently, no pharmacological treatment options were available for MASLD. The recent approvals of resmetirom and semaglutide have opened a new era in the medical management of MASLD. For MASH, both have been approved only for adults.[86–88] However, glucagon-like peptide-1 receptor agonists are also being considered for the treatment of obesity in children aged 12 years and older.[77] A recent clinical trial conducted in children aged 6–12 years compared liraglutide with placebo, with both groups receiving lifestyle modification counseling. The study revealed that the liraglutide group achieved significant weight loss without adversely affecting development, whereas the placebo group continued to gain weight.[89] Interestingly, the success rate was even higher compared to the adolescent trial of liraglutide.[89,90] After discontinuation of the medication, weight regain remained a considerable problem, and the prospect of lifelong use of these agents in children requires careful evaluation. Nevertheless, these results indicate that intervening in childhood obesity as early as possible enhances treatment effectiveness and reduces the burden in adulthood, including the risk of MASLD.

This study should be interpreted in light of its strengths and limitations. To the best of our knowledge, this is the first meta-analysis to demonstrate the burden of MASLD among Turkish children and adolescents. We were able to include a large number of studies spanning a considerable period of time. However, all included studies were conducted in children and adolescents with specific conditions such as obesity and increased transaminases. Therefore, the prevalence of MASLD in the general pediatric population could not be

estimated. Moreover, ultrasonography was the most commonly used method for the detection of hepatic steatosis, with only a few studies employing additional methods such as transient elastography. The low sensitivity of ultrasonography for detecting mild steatosis, as well as its operator dependency and inter-observer variability, may have affected our results. Also, the high degree of heterogeneity (I2 = 96%) indicates marked clinical and methodological diversity among the included studies, including differences in patient selection, underlying risk conditions, and diagnostic approaches. Consequently, the pooled prevalence should not be viewed as a universal estimate for all children in Türkiye, but rather as a summary measure reflecting the burden of MASLD across heterogeneous at-risk pediatric populations. These findings also warrant consideration alongside additional limitations, including possible cohort overlap among included studies, group sizes potentially driven by study design rather than true prevalence, restrictions in search language and terminology, and diagnostic heterogeneity arising from the transition from the NAFLD to the MASLD nomenclature. Although we conducted an exploratory analysis by publication period, these results should be interpreted cautiously. The number of studies was uneven across periods, particularly in 2005–2009, and differences in study populations, clinical settings, and diagnostic approaches limited our ability to draw robust conclusions about temporal changes in pediatric MASLD prevalence in Türkiye.

Conclusion

This study is the first to systematically demonstrate the alarming prevalence of MASLD among overweight/obese and at-risk children and adolescents in Türkiye. This high prevalence underscores the increasing burden and severity of the disease as affected children transition into adulthood. Early intervention and timely diagnosis should therefore be critically evaluated and integrated into routine pediatric care. There is a need for epidemiological studies in the general pediatric population to better estimate prevalence and to inform the development of appropriate screening policies for children.

Online Appendix Link: https://file.paplino.com/hepatologyforum/files/1786537058-appendix-en.pdf

Ethics Committee Approval: As this study was a systematic review and meta-analysis based exclusively on previously published data, ethics committee approval and informed consent were not required.

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SYSTEMATIC REVIEW

The effect of silymarin (milk thistle) on cirrhosis: A systematic review and meta-analysis of clinical trials

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Points to Note

- **Synthesis of Current Evidence:** Silymarin may improve AST, ALT, and albumin levels in cirrhosis, with no serious adverse effects reported.
- **Major Controversies:** Evidence remains limited by few studies, small samples, heterogeneity, and lack of control groups in some trials.
- **Future Directions:** Larger, well-designed randomized controlled trials are needed to confirm efficacy, optimal dose, and clinical relevance.

ABSTRACT

Background and Aim: Cirrhosis is a fatal liver disease. Silymarin, by improving inflammation, oxidative stress, and the regeneration of liver cells, can improve cirrhosis. Therefore, this study aimed to conduct a systematic review and meta-analysis of silymarin in cirrhosis.

Materials and Methods: PubMed, Scopus, and Web of Science were systematically searched up to 16 May 2025 to find clinical trials that investigated the effect of silymarin on cirrhosis. No time or language limitations were considered.

Results: Eight clinical trials with nine intervention arms were included. The results of this study showed that silymarin significantly reduced aspartate aminotransferase (AST) (weighted mean difference [WMD]: −5.41 IU/L, 95% confidence interval [CI]: −8.92, −1.91; I^2=89.4%, P for heterogeneity<0.001) and alanine aminotransferase (ALT) (WMD: −6.07 IU/L, 95% CI: −11.31, −0.84; I^2=96.1%, P for heterogeneity<0.001), and increased albumin (WMD: 0.08 g/dL, 95% CI: 0.03, 0.14; I^2=0.0%, P for heterogeneity=0.691) in cirrhosis, but had no significant effect on ALP (WMD: −14.45 IU/L, 95% CI: −30.45, 1.55; I^2=0.0%, P for heterogeneity=0.610) and bilirubin (WMD: −0.03 mg/dL, 95% CI: −0.18, 0.12; I^2=78.6%, P for heterogeneity=0.001). No significant side effects were reported in any of the studies. Only some studies reported very limited and negligible complications in a very limited number of patients.

Conclusion: The results of the present study showed the favorable effects of silymarin on reducing AST and ALT and increasing albumin levels in cirrhosis. Although due to the small number of included studies, findings should be interpreted with caution, based on the results of this meta-analysis, silymarin might be considered a safe, inexpensive, and available agent for the treatment of cirrhosis.

Keywords: Cirrhosis, meta-analysis, milk thistle, silymarin, systematic review.

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Introduction

Cirrhosis is one of the most important causes of death worldwide.[1] Alcohol abuse, metabolic disorders, viral hepatitis, and non-alcoholic fatty liver disease (NAFLD) are among the most important factors leading to cirrhosis.[2,3] Cirrhosis causes the imbalance of many inflammatory factors, especially C-reactive-protein (CRP), and tumor necrosis factor-α (TNF-α). Also, glutathione (GSH), one of the most important antioxidants, decreases significantly in cirrhosis.[4–7] In many liver problems, including cirrhosis, reactive oxygen species increase excessively, which can cause DNA damage and imbalance in the regulation of genes of inflammatory factors and disturbance in the transmission of cell signals. Also, free radicals may cause lipid peroxidation and damage to proteins inside liver cells, resulting in liver dysfunction.[8–10]

Cirrhotic patients are at high risk of hepatocellular carcinoma.[11,12] In addition, if the disease progresses, the need for a liver transplant is very likely.[13,14] Therefore, it is very important to help these patients to prevent the need for a liver transplant. This can be done by preventing the development of the disease and also by intervening in the affected people.[1] Some of the strategies available to help patients with cirrhosis include the administration of branched-chain amino acids to improve hypoalbuminemia, antiviral treatments in case of cirrhosis caused by viral hepatitis, diuretics to reduce ascites, steroids, and beta blockers, but none of these cases are not a definitive solution. Furthermore, many of these treatments have contraindications in some conditions and may cause hepatotoxicity.[13,15–18] Therefore, the high prevalence of liver diseases, especially liver cirrhosis, and the lack of a definite treatment solution for it, indicates the need to provide new cost-effective and useful treatment solutions.[19]

Silymarin is an extract from milk thistle (Silybum marianum), which contains flavonolignan and flavonoid polyphenolic.[20,21] This herbal extract helps establish oxidative balance by inhibiting free radicals and increasing intracellular glutathione. This action reduces lipid peroxidation and also protects other compounds in the cell, including DNA and proteins, from oxidative damage.[22–25] Oxidative stress causes excessive stimulation of inflammatory factors genes and aggravates liver damage, therefore silymarin reduces inflammatory responses and stabilizes the liver condition by improving oxidative stress.[22,26]

Silymarin by regulating the permeability of the liver cell membrane reduces the entry of hepatotoxic agents into the liver cells. It is also effective in stimulating the regeneration of liver cells, so it improves liver damage.[27,28] Several studies have suggested the safety of silymarin supplementation in many liver problems, including cirrhosis.[22,27,29,30] Hence, a decrease in cytotoxicity, especially in the liver, can be expected after consuming silymarin. Also, this plant extract can reverse the destruction of liver cells and prevent its progression, so it can be useful and effective in modulating the damage caused by liver fibrosis and cirrhosis.[22]

With regard to the importance of the issue, and considering the lack of a definite treatment solution for cirrhotic patients and the potential therapeutic effects of silymarin on liver diseases, so far, several trials have been conducted to investigate the effect of silymarin on cirrhosis. However, the results of these studies are somewhat contradictory and there is no systematic review and meta-analysis to fill this gap. Therefore, this study aims to systematically review and meta-analyze clinical trials that investigated the effect of silymarin supplementation on cirrhosis.

Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki.

Search Strategy

The present systematic review was conducted based on the preferred reporting items for systematic reviews and meta- analyses (PRISMA) guidelines.[31] A detailed and comprehensive systematic search was conducted in PubMed, ISI Web of Science, and Scopus databases to find trial studies investigating the effect of silymarin on cirrhosis up to 16 May 2025. Google Scholar was also searched to find the relevant articles. There were no restrictions on language, time of publication, and place of study. The keywords used in the search are as follows: ((“Silymarin” OR “Silybin” OR “milk thistle” OR “milk-thistle” OR “thistle plant” OR “thistle-plant” OR “Silybum marianum” OR “Silybum-marianum” OR “Silybum” OR “silibinin” OR “silydianin” OR “silychristin” OR “cardus marianus” OR “cardus-marianus” OR “isosilibinin” OR “silichristin”) AND (“cirrhotic ascites” OR “cirrhosis” OR “hepatic cirrhosis” OR “liver cirrhosis” OR “decompensated liver cirrhosis” OR “cirrhotic-ascites” OR “hepatic-cirrhosis” OR “liver-cirrhosis” OR “decompensated liver-cirrhosis” OR “decompensated-liver cirrhosis”)). In addition, Medical Subject Headings terms were used for PubMed.

Databases were reviewed by two independent authors (S.A. and M.B.). If there was a difference of opinion between the researchers, a common opinion was obtained by face-to-face discussion. Population, intervention, comparator, and outcome were as shown in Table 1.

Inclusion and Exclusion Criteria

Clinical trials in all languages that investigated the effect of silymarin on cirrhosis patients were included. We excluded the following

Table 1. Detailed information about population, intervention, comparator, and outcome (PICO)

PICO Items	Definition
Population	Cirrhotic patients
Intervention	Silymarin
Comparison	Placebo or standard therapy (do not take silymarin) or no control group
Outcome	AST, ALT, ALP, bilirubin, and albumin

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase.

Table 2. The main characteristics of included clinical trials

ID	First author (publication year), Country	Sample size included in analyses		Gender		Mean Age (or range of age)	Subjects	Study design	Intervention of experimental group	Intervention of control group	Duration	Side effects
		Intervention	Control	Male	Female							
1	Ferenci (1989), Austria[36]	87	83	123	47	57.4±11.9	Liver cirrhosis	Prospective, randomized trial	420 mg/day of silymarin (140 mg three times/day)	Placebo	24 months	Nausea and epigastric discomfort (2 in the silymarin and 2 in the placebo group).
2	M Velussi (1993), Italy[37]	30	30	42	18	62.5±3.5	Diabetic patients with cirrhosis	Clinical trial (parallel)	600 mg /day of silymarin+ standard therapy	Standard therapy (Do not take silymarin)	6 months	No side effects
3	Mario Velussi (1997), Italy[38]	30	30	Not mentioned		62.5±3.5 (45–70)	Diabetic patients with cirrhosis	Clinical trial (parallel)	600 mg /day of silymarin+ standard therapy	Standard therapy (Do not take silymarin)	12 months	No side effects
4	Parés (1998), Spain[39]	58	67	Not mentioned		50.4±10.7	Alcoholics with liver cirrhosis	Clinical trial (parallel)	450 mg/day of silymarin (150 mg/3 times daily)	Placebo	24 months	Eleven patients had side effects (7 in the treatment group and 4 in the placebo group). Complications included arthralgias and pruritus, headache and urticaria, and unspecified complications.
5	Angulo (2000), USA[40]	27	0	Not mentioned		51.6 ±1.4 (38–71 years)	Primary Biliary Cirrhosis With a Suboptimal Response to UDCA	Clinical trial	420 mg/day of silymarin (140 mg 3 times daily)+UDCA (13-15 mg/kg/day)	No control group	12 months	Transitory GI adverse events occurred in 2 patients
6	Lucena (2002), Spain[41]	24	25	48	1	49±13 (20–70)	Alcoholic liver cirrhosis	Clinical trial (parallel)	450 mg/day of silymarin (150 mg t.i.d./day)	Placebo	6 months	One patient in the treatment group reported impotence.
7	Fallah Huseini (2005), Iran[42]	30	30	40	20	48.6±2.4	Liver cirrhosis caused by chronic hepatitis B.	Clinical trial (parallel)	435 mg/day of silymarin (145 mg t.i.d./day)	Placebo	12 months	No side effects
8a	Fathalah (2017), Egypt[43]	31		NM (The gender in each group is not mentioned, but in 62 patients there were 38 male and 24 female)		48.9±7.7 (20–75)	Chronic HCV-decompensated cirrhotic patients	Clinical trial	1,050 mg/day of silymarin	No control group	3 months	Among 62 patients: 10 patients: Diarrhea 7 patients: GI discomfort 7 patients: Attack of hematemesis
8b	Fathalah (2017), Egypt[43]	31		NM (The gender in each group is not mentioned, but in 62 patients there were 38 male and 24 female)		48.9±7.7 (20–75)	Chronic HCV-decompensated cirrhotic patients	Clinical trial	420 mg/day of silymarin	No control group	3 months	Among 62 patients: 10 patients: Diarrhea 7 patients: GI discomfort 7 patients: Attack of hematemesis

GI: Gastrointestinal; UDCA: Ursodeoxycholic acid.

Table 3. Main results of the included studies

ID	First author (publication year), Country	Child-Pugh score	Survival rate	Ascites	MDA	TC	HDL	Fasting insuline-mia	Glycosuria	C peptide	FBS	HbA1C	Creatinine	Albumin	Bilirubin	ALP	AST	ALT	Other outcomes
1	Ferenci (1989), Austria[36]		↑												↔	↔		↔	
2	M Velussi (1993), Italy[37]				↓	↔		↓	↓	↓	↓	↓					↔	↔	
3	Mario Velussi (1997), Italy[38]				↓	↔	↑	↓	↓	↓	↓	↓	↔		↔	↔	↓*	↓*	
4	Parés (1998), Spain[39]		↔											↔	↔	↔	↔	↑	↔ Encephalopathy
5**	Angulo (2000), USA[40]													↔	↔	↔	↔		
6	Lucena et al.(2002), Spain[41]	↔			↓								↔	↔	↔	↔	↔	↔	↑ GSH
7	Fallah Huseini et al. (2005), Iran[42]	Improve		↓										↔	↔		↓	↓	
8***	Fathalah (2017), Egypt[43]	Improve		↔										↑	↓		↓	↓	Both groups showed a significant decline in ALT and AST. Moreover, group A showed a significant decline than group B. INR showed a significant decline in both groups with a significantly different pattern in favor of group A

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; HbA1C: Hemoglobin A1C; FBS: Fasting blood sugar; HDL: High-density lipoprotein; TC: Total cholesterol; INR: International normalized ratio; MDA: Malondialdehyde; GSH: Glutathione; ↓: Decreasing effect; ↑: Increasing effect; ↔: No significant effect. All the changes mentioned are compared to the control group, except *, **, and ***. *: There was a slow and continuous decrease in ALT and AST values in the silymarin-treated group compared to baseline ($p<0.01$). **: All results for this study are reported in comparison to the baseline, as there was no control group. ***: The results are related to the comparison of the group receiving a higher dose of silymarin (1,050 mg/day) (group A) compared to the group receiving a lower dose of silymarin (450 mg/day) (group B).

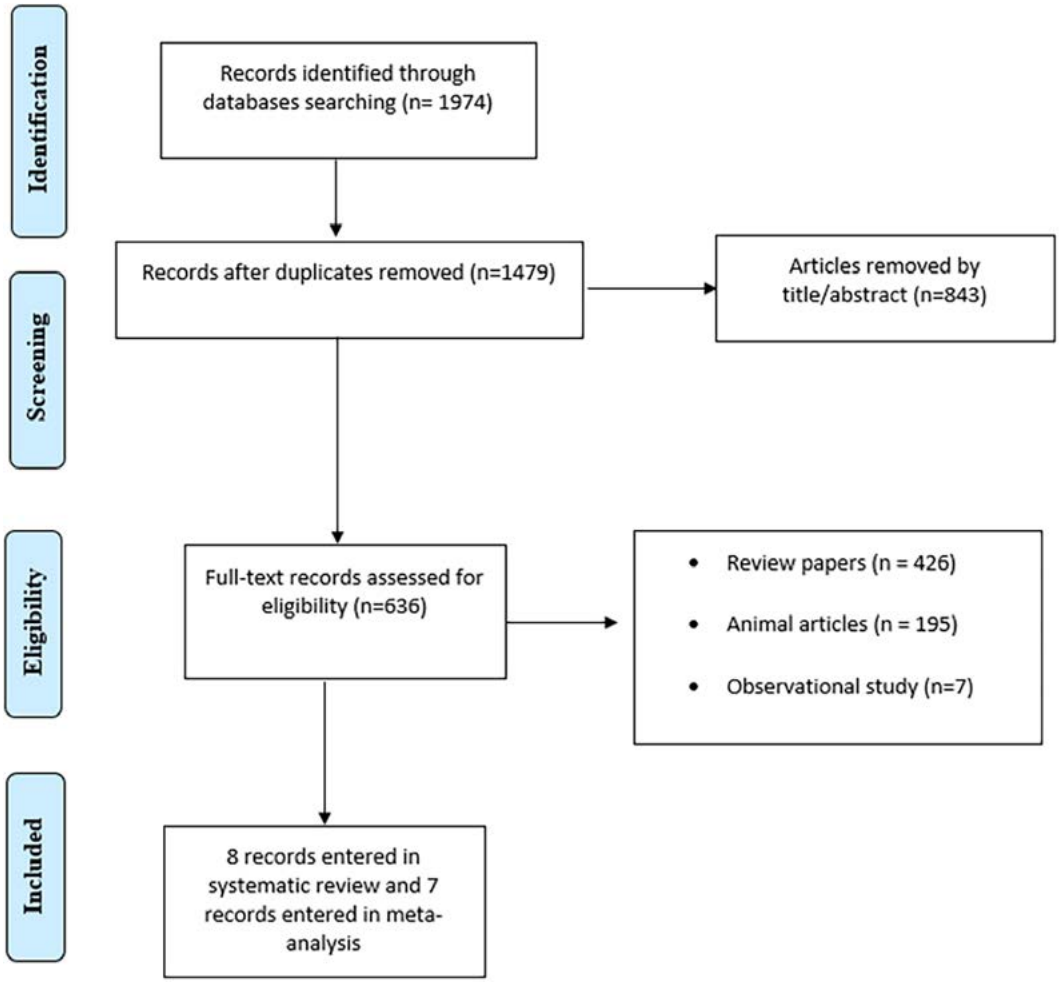


Figure 1. Flow diagram of the literature selection process.

studies: (1) Animal studies, (2) Studies that did not report sufficient data, (3) Observational studies, (4) Reviews, letters, study protocol, editorial articles, or case reports, and (5) Studies that had less than one week of intervention.

Data Extraction

The information extracted from the articles was as follows: the name of the first author, publication year, country, sample size, sex, and mean age of participants, subjects, design of the study, intervention of experimental and control groups, and duration of intervention and side effects (Table 2). Furthermore, the changes in AST, ALT, alkaline phosphatase, bilirubin, albumin, and other factors related to cirrhosis were extracted (Table 3). Data extraction was done by two independent researchers (S.A. and M.B.).

Quality Assessment of Studies

The Cochrane Collaboration tool was used to assess the risk of bias in clinical trials. According to this tool, studies in terms of random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, Selective reporting, and other sources of bias were assessed. The overall assessment result was as follows: good (low risk for more than 2 items), fairly good (low risk for 2 items), or poor (low risk for less than 2 items).[32]

Statistical Analysis

STATA statistical software version 13 (Stata Corporation, College Station, TX, USA) was used to perform the meta-analysis. Whole effects with the $p<0.05$ were considered statistically significant. The mean and standard deviation (SD) of AST, ALT, alkaline phosphatase, bilirubin, and albumin were used to calculate the effect size between intervention and control groups. In studies that reported standard errors (SE), SD was obtained by the formula $SD = SE \times \sqrt{N}$. None of the studies reported the data with a 95% confidence interval (CI). The overall effect size was reported by a random effects model as a weighted mean difference (WMD) in all results. To investigate the influence of each study or a specific group of studies on the total effect, sensitivity analysis was used, and Begg's[33] and Egger's[34] tests and funnel plots were used to check publication bias. We used the I2 statistic to assess heterogeneity between studies.[35]

Table 4. Risk of bias assessment for included randomized controlled clinical trials

ID	The first author (publication year)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other risks of bias	Overall quality
1	Ferenci (1989)[36]	L	L	U	U	L	L	U	Good
2	M Velussi (1993)[37]	U	U	H	H	H	L	L	Relatively good
3	Mario Velussi (1997)[38]	U	U	H	H	L	L	L	Good
4	Parés (1998)[39]	L	L	U	U	L	L	U	Good
5	Angulo (2000)[40]	H	H	H	H	L	L	U	Relatively good
6	Lucena (2002)[41]	U	U	H	H	L	L	U	Relatively good
7	Fallah Huseini (2005)[42]	U	U	U	U	L	L	U	Relatively good
8	Fathalah (2017)[43]	L	L	U	U	L	L	U	Good

L: Low risk of bias; H: High risk of bias; U: Unclear risk of bias. Good quality; Relatively good quality.

In cases where heterogeneity was observed between the studies, the data were included in subgroup analysis based on the dose of silymarin supplementation (<600 mg/day or ≥600 mg/day), having or not having a control group, and based on the fact that only silymarin was used as an intervention or silymarin was used in combination with other compounds. The fixed-effects model was used to investigate between-subgroup heterogeneity.

Results

Search Results and Study Selection

As shown in Figure 1, 1974 studies were found in the initial search (PubMed: 416, ISI Web of Science: 395, and Scopus: 1163). Duplicates were removed, so 1479 studies remained. The first 100 records in Google Scholar were also searched and screened. After reviewing the title and abstract of the remaining studies, 843 unrelated studies were excluded. The remaining studies were reviewed for full text; Review papers (n=426), animal articles (n=195), and observational studies (n=7) were excluded. Finally, 8 clinical trials that investigated the effect of silymarin on cirrhosis were included in the current study.[36–43]

Characteristics of the Included Studies

Eight trials[36–43] with 9 intervention arms conducted between 1989 and 2017 were included. One study had two intervention arms[43] and the other studies had one intervention arm.[36–42] The characteristics of the studies are detailed in Table 2. The minimum period of study intervention was 3 months[43] and the maximum period was 24 months.[36,39] The amount of silymarin received varied between 420mg/day and 1050mg/day. All studies were conducted on adult patients with cirrhosis. The average age of the patients was between 48 and 62 years. Seven studies were in English[36–41,43] and one was in Persian.[42] The total sample size included 613 patients. Two studies were conducted without a control group,[40,43] and 4 studies had a control group that received a placebo,[36,39,41,42] and in 2 studies, the control group did not take any placebo.[37,38] Three studies[38,39,43] had control groups but did not report quantitative data for them. Thus, we referred to them as without control groups in the text, but included them as having control groups in Table 2 and reported their qualitative comparisons in Table 3. Three studies did not report gender[38–40] and the rest included both genders.[36,37,41–43] In 7 studies, only silymarin was used as an intervention,[36–39,41–43] and in one, silymarin plus Ursodeoxycholic Acid (UDCA)[40] was used as an intervention.

Side Effects

According to Table 2, none of the studies reported significant side effects of silymarin consumption. Three studies did not observe any side effects,[37,38,42] and other studies reported very mild and minor complications[36,39–41,43] including gastrointestinal complications, arthralgias and pruritus, headache and urticaria and unspecified complications in a limited number of patients.

Study Quality

The results of the quality assessment based on the Cochrane Collaboration tool determined that 4 studies are of good quality[36,38,39,43] and 4 studies are relatively good[37,40–42] (Table 4).

Main Results

Effect of silymarin on AST

So far, seven studies including 8 arms have investigated the effect of silymarin on AST among cirrhosis patients.[37–43] Pooled analysis of these studies showed that supplementation with silymarin significantly reduces AST (WMD:-5.41 IU/L, 95% CI:-8.92, -1.91;

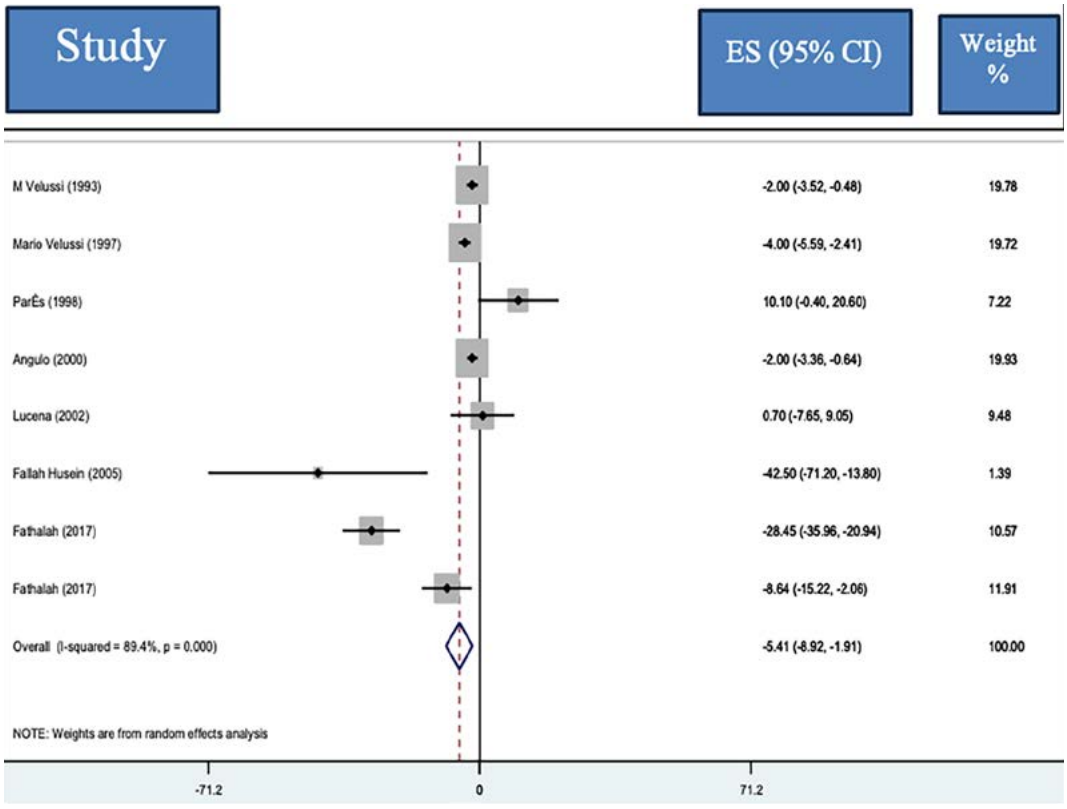


Figure 2. The effect of silymarin on aspartate aminotransferase in cirrhotic patients.

I^2=89.4%, p<0.001) (Fig. 2). Due to the existence of heterogeneity between studies, we performed several subgroup analyses to find the source of heterogeneity, which are as follows (Table 5).

Subgroup analyzes were performed based on the presence or absence of a control group, dose, and intervention with silymarin or silymarin plus other compounds.

In the subgroup analysis based on having or not having a control group, a significant decrease in AST was observed in studies without control (WMD:-7.36 IU/L, 95% CI:-11.12, -3.61; I^2=91.6%, P for heterogeneity<0.001), but the result of the analysis of studies with control did not show a significant change (WMD: 4.84 IU/L, 95% CI: -4.31, 13.98; I^2=47.0%, P for heterogeneity=0.170). According to Figure 3, subgroup analysis based on having or not having a control group detects the heterogeneity sources.

Subgroup analysis based on the dose of silymarin was also performed, which showed that receiving a dose ≥ 600 mg/day causes a significant decrease in AST in cirrhosis (WMD: -9.29 IU/L, 95% CI:-15.54, -3.05; I^2=95.7%, P for heterogeneity<0.001). However, silymarin supplementation of less than 600 mg/day did not show a significant effect on AST (WMD: -2.79 IU/L, 95% CI: -9.56, 3.99; I^2=76.5%, P for heterogeneity=0.002) (Fig. 4).

Subgroup analysis based on intervention with silymarin (WMD:-6.68 IU/L, 95% CI:-11.63, -1.72; I^2=90.5%, P for heterogeneity<0.001) or silymarin plus other compounds (WMD:-2 IU/L, 95% CI:-3.36, -0.64; I^2=0.0%, P for heterogeneity<0.001) showed that in both cases, AST significantly decreases (Fig. 5).

No publication bias was observed in these studies through the Egger (p=0.277) and Begg (p=0.322) tests and the appearance of the funnel plot. In the results of the sensitivity analysis, the exclusion of any study had no significant effect on the overall effect size of the findings.

Effect of Silymarin on ALT

Six trials with 7 arms have reported the effect of silymarin on ALT in patients with cirrhosis. Pooled analysis of these studies showed that silymarin significantly reduces ALT in these patients (WMD: -6.07 IU/L, 95% CI: -11.31, -0.84; I^2=96.1%, P for heterogeneity <0.001) (Fig. 6). Due to the high heterogeneity, we performed several subgroup analyses to find the source of heterogeneity (Table 5).

Subgroup analysis based on having or not having a control group detects the heterogeneity source. This subgroup analysis showed that silymarin causes a significant decrease in ALT in uncontrolled studies (WMD:-11.14 IU/L, 95% CI:-16.71, -5.58; I^2=96.4%, P for heterogeneity<0.001), but no reduction effect was observed in the analysis of controlled studies (WMD:6.66 IU/L, 95% CI:1.12, 12.19; I^2=25.7%, P for heterogeneity=0.246) (Fig. 7).

Subgroup analysis based on the dose of silymarin showed that receiving ≥600 mg/day caused a significant decrease in ALT (WMD: -10.91 IU/L, 95% CI: -17.45, -4.37; I^2=98.1%, P for

Table 5. Results of subgroup analysis

Subgroup	Effect size (n)	Pooled effect	I^2	p heterogeneity	p between subgroup heterogeneity
AST (IU/L)					
Control group					
Have a control group	2	4.84 (-4.31, 13.98)	47.0	0.170	0.028
Don't have a control group	6	-7.36 (-11.12, -3.61)	91.6	<0.001	
Dose					
<600 mg/day	5	-2.79 (-9.56, 3.99)	76.5	0.002	0.106
≥600 mg/day	3	-9.29 (-15.54, -3.05)	95.7	<0.001	
Intervention					
Only silymarin	7	-6.68 (-11.63, -1.72)	90.5	<0.001	0.094
Silymarin+other compounds	1	-2.00 (-3.36, -0.64)	0.0	<0.001	
ALT (IU/L)					
Control group					
Have a control group	2	6.66 (1.12, 12.19)	25.7	0.246	<0.001
Don't have a control group	5	-11.14 (-16.71, -5.58)	96.4	<0.001	
Dose					
<600 mg/day	4	-1.96 (-13.02, 9.09)	86.2	<0.001	<0.001
≥600 mg/day	3	-10.91 (-17.45, -4.37)	98.1	<0.001	
Bilirubin (mg/dL)					
Intervention					
Only silymarin	4	-0.09 (-0.18, -0.00)	0.0	0.465	<0.001
Silymarin+other compounds	1	0.1 (0.08, 0.12)	0.0	<0.001	

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

heterogeneity<0.001), but less than 600 mg/day did not show a significant effect (WMD: -1.96 IU/L, 95% CI: -13.02, 9.09; I^2=86.2%, P for heterogeneity<0.001) (Fig. 8).

No publication bias was observed in these studies through the Egger (p: 0.606) and Begg (p=0.652) tests and the appearance of the funnel plot. In the results of the sensitivity analysis, the exclusion of Parés et al.[39]'s study had a significant effect on the overall effect size of the findings. By excluding this study, the overall effect size was "95% CI: -0.16, 9.77."

Effect of Silymarin on Alkaline Phosphatase

Three studies have investigated the effect of silymarin on alkaline phosphatase in patients with cirrhosis.[39–41] Pooled analysis of these studies did not show significant changes in ALP (WMD:-14.45 IU/L, 95% CI:-30.45, 1.55; I^2=0.0%, P for heterogeneity=0.610) (Fig. 9). No heterogeneity was observed between the studies, so subgroup analysis was not performed. According to the Egger (p=0.206) and Begg (p=0.117) tests and the appearance of the funnel diagram, no publication bias was observed in these studies. In the sensitivity analysis, no significant effect on the overall effect size of the findings was observed during the exclusion of any study.

Effect of Silymarin on Bilirubin

So far, 4 studies[39–41,43] including 5 arms have investigated the effect of silymarin on bilirubin in patients with cirrhosis. Pooled analysis of these studies did not show a significant change in bilirubin (WMD: -0.03 mg/dL, 95% CI:-0.18, 0.12; I^2=78.6%, P for heterogeneity=0.001) (Fig. 10). Due to the heterogeneity of the studies, subgroup analysis was performed based on whether the intervention was done with silymarin or silymarin plus other compounds. With this subgroup analysis, the source of heterogeneity was found (Table 5).

This subgroup analysis showed that silymarin alone can significantly reduce bilirubin in cirrhosis (WMD:-0.09 mg/dL, 95% CI:-0.18, –0.00; I^2=0.0%, P for heterogeneity=0.465), but silymarin plus other compounds did not cause significant changes (WMD:0.1 mg/dL, 95% CI:0.08, 0.12; I^2=0.0%, P for heterogeneity<0.001) (Fig. 11).

Subgroup analyses based on the dose of silymarin showed that receiving more equal to 600 mg/day caused a significant decrease in bilirubin (WMD:-0.12 mg/dL, 95% CI:-0.24, –0.00; I^2=0.0%, P for heterogeneity<0.001), but <600 mg/day did not show a significant effect (WMD: 0.02 mg/dL, 95% CI:-0.12, 0.16; I^2=54.6%, P for heterogeneity=0.086) (Fig. 12).

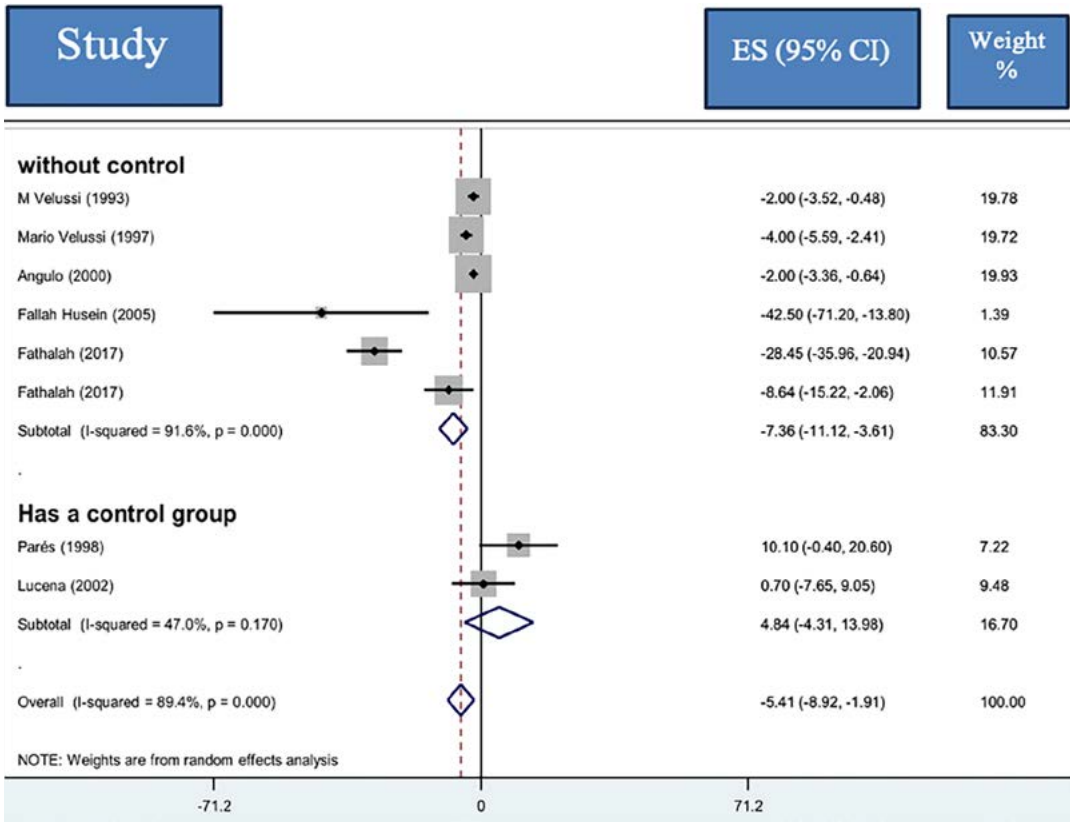


Figure 3. The effect of silymarin on aspartate aminotransferase in cirrhotic patients. Subgroup analysis based on having or not having a control group.

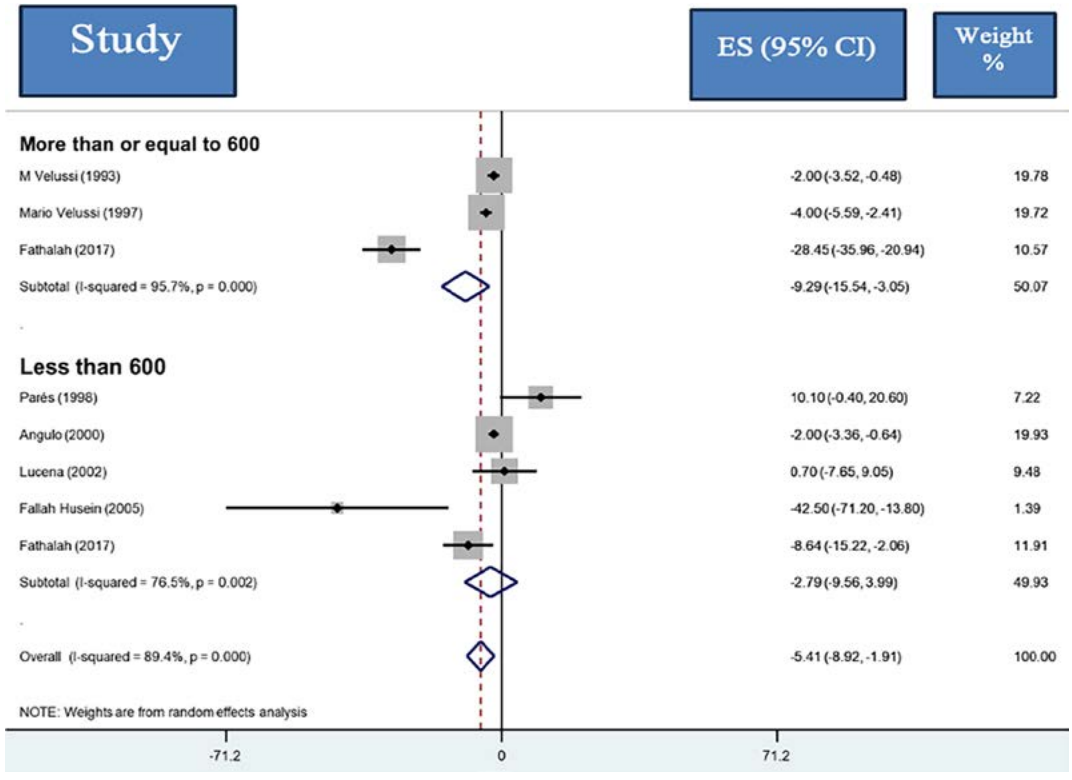


Figure 4. The effect of silymarin on aspartate aminotransferase in cirrhotic patients. Subgroup analysis based on dose (<600 mg/day or ≥600 mg/day).

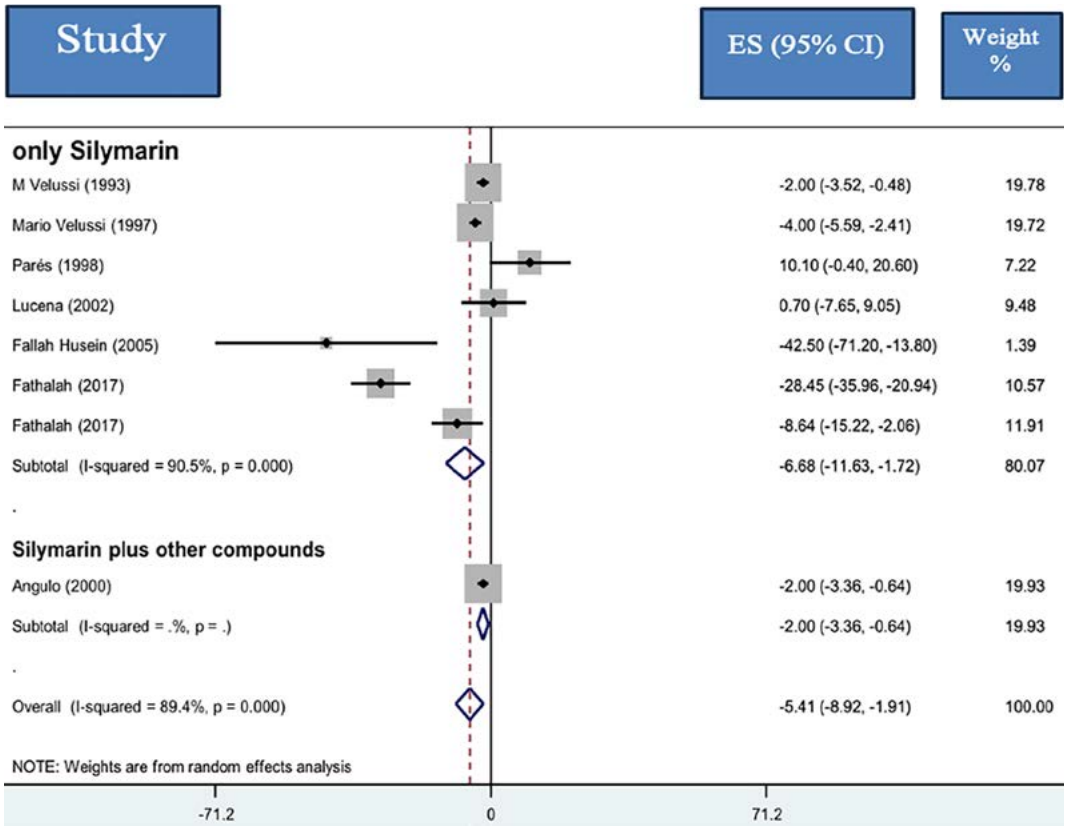


Figure 5. The effect of silymarin on aspartate aminotransferase in cirrhotic patients. Subgroup analysis based on intervention with silymarin or silymarin plus other compounds.

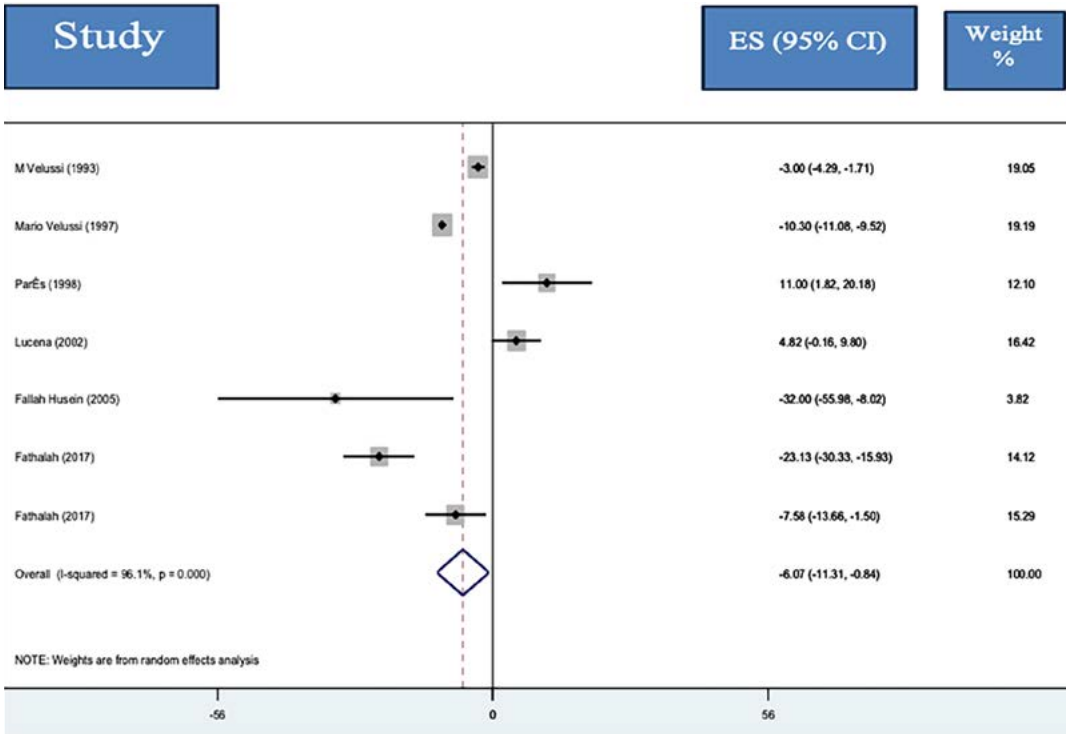


Figure 6. The effect of silymarin on alanine aminotransferase in cirrhotic patients.

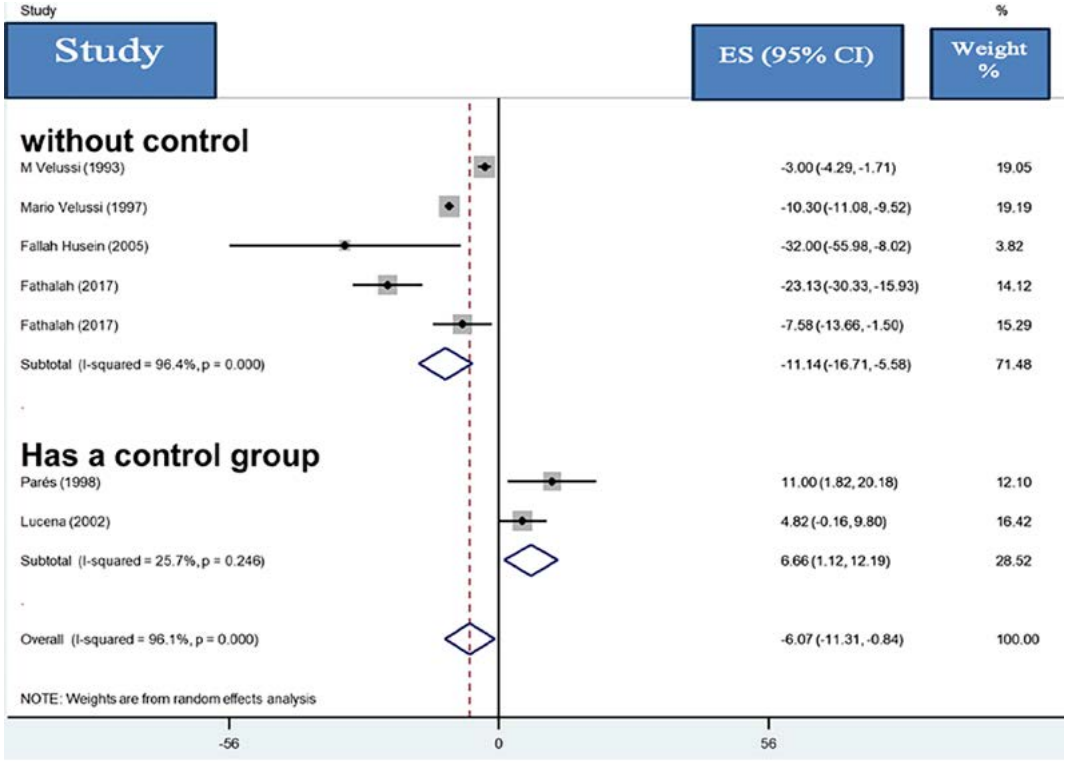


Figure 7. The effect of silymarin on alanine aminotransferase in cirrhotic patients. Subgroup analysis based on having or not having a control group.

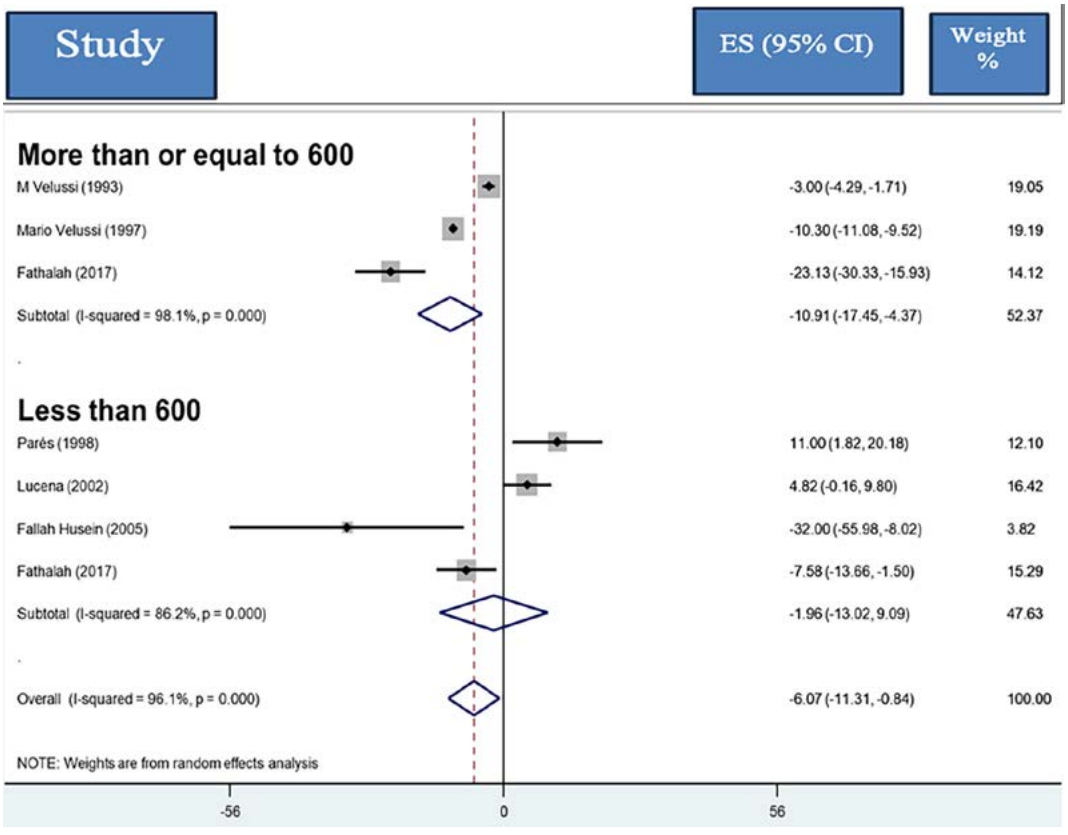


Figure 8. The effect of silymarin on alanine aminotransferase in cirrhotic patients. Subgroup analysis based on dose (<600 mg/day or ≥600 mg/day).

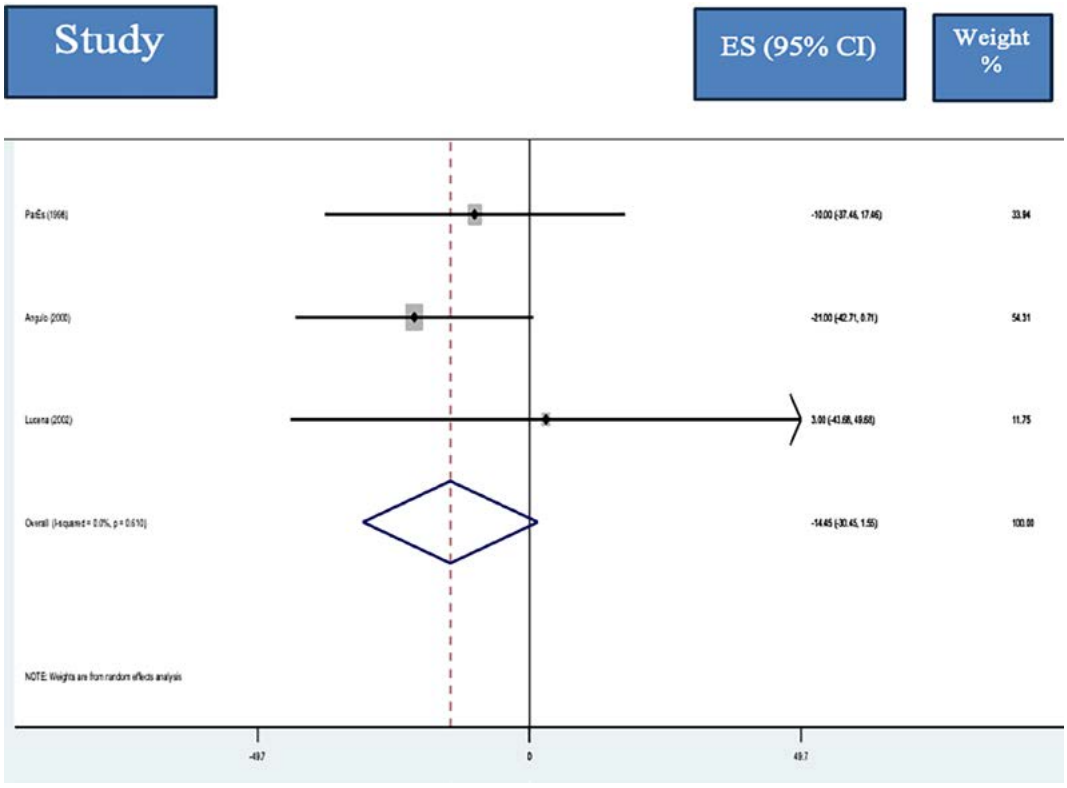


Figure 9. The effect of silymarin on alkaline phosphatase in cirrhotic patients.

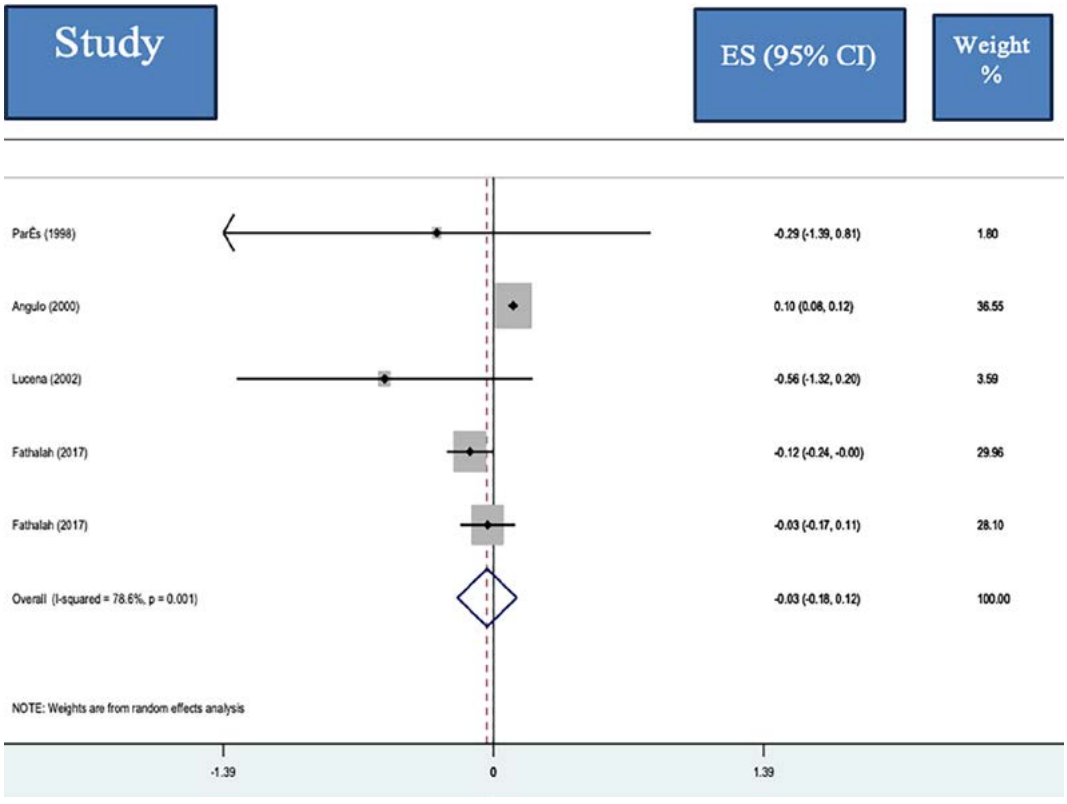


Figure 10. The effect of silymarin on bilirubin in cirrhotic patients.

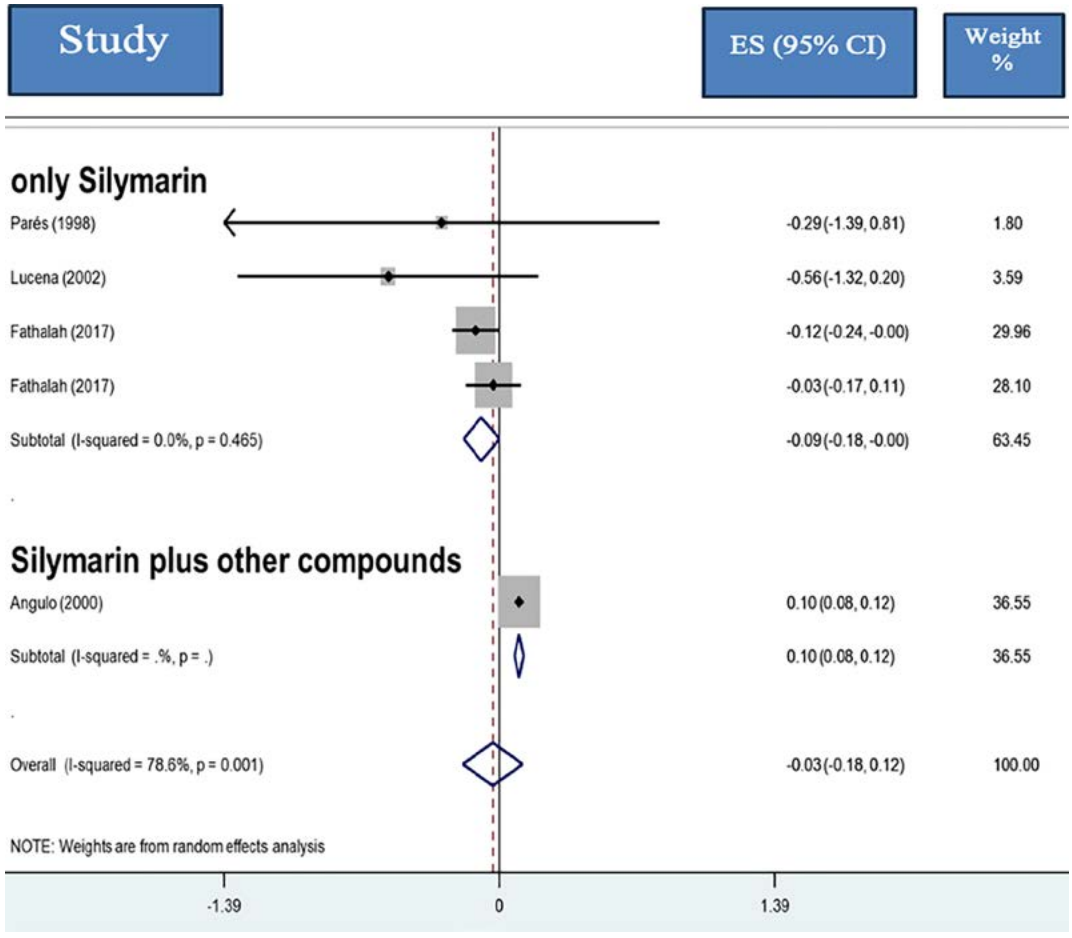


Figure 11. The effect of silymarin on bilirubin in cirrhotic patients. Subgroup analysis based on intervention with silymarin or silymarin plus other compounds.

In the subgroup analyses based on having or not having a control group, no significant results were reported in bilirubin changes; with control: (WMD: -0.47 mg/dL, 95% CI: -1.1, 0.15; I^2=0.0%, P for heterogeneity=0.692); without control: (WMD: -0.01 mg/dL, 95% CI: -0.16, 0.14; I^2=87%, P for heterogeneity<0.001) (Fig. 13).

No publication bias was observed in these studies through the Egger (p=0.076) and Begg (p=0.624) tests and the appearance of the funnel plot. In the results of the sensitivity analysis, the exclusion of Angulo et al[40]'s study had a significant effect on the overall effect size of the findings. By excluding this study, the overall effect size was "95% CI: -0.18, -0.01".

Effect of Silymarin on Albumin

In general, 4 studies with 5 arms investigated the effect of silymarin on albumin in cirrhotic patients[39–41,43] The meta-analysis of these studies showed that albumin increased significantly in response to the silymarin supplementation (WMD: 0.08 g/dL, 95% CI:0.03, 0.14; I^2=0.0%, P for heterogeneity=0.691) (Fig. 14). Due to the lack of heterogeneity between studies, no subgroup analysis was performed. No publication bias was observed in these studies after performing the Egger (p=0.891) and Begg (p=0.624) tests and the appearance of the funnel plot. In the results of the sensitivity analysis, no significant effect on the overall effect size of the findings was observed during the exclusion of any studies.

Discussion

The present systematic review and meta-analysis were conducted to investigate the effect of silymarin supplementation on cirrhosis. In general, eight trial studies with nine arms were included in this review. The results showed a significant decrease in AST and ALT and a significant increase in albumin. However, silymarin did not have a significant impact on alkaline phosphatase or bilirubin levels. Importantly, no serious adverse effects were reported, indicating a favorable safety profile. So far, many studies have suggested the safety of silymarin in many liver diseases, including cirrhosis.[22,27,29,30]

The observed reductions in AST and ALT levels after silymarin supplementation are of considerable clinical significance, as these enzymes serve as well-known biochemical markers of liver cell injury. In the context of cirrhosis, persistent elevations in AST and ALT levels indicate ongoing liver cell injury and inflammatory necrotic activity in the liver parenchyma.[44] Therefore, the reductions in these

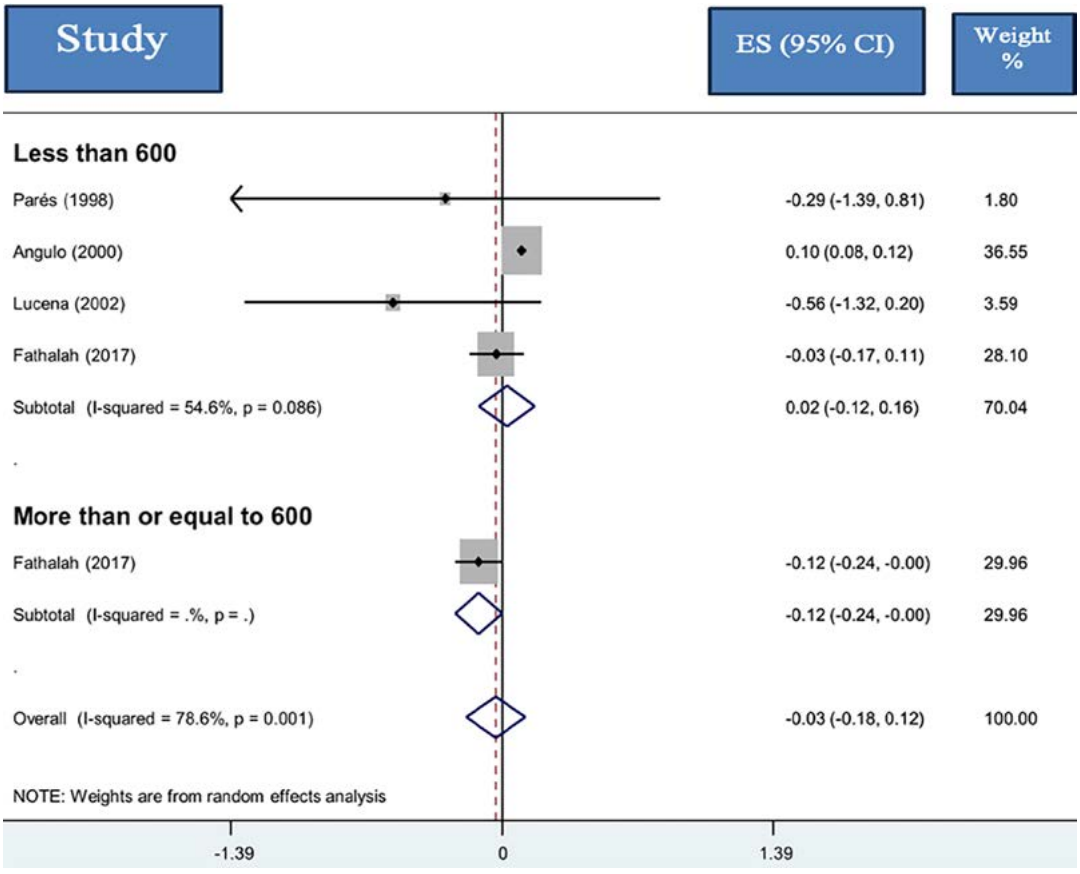


Figure 12. The effect of silymarin on Bilirubin in cirrhotic patients. Subgroup analysis based on dose (<600 mg/day or ≥600 mg/day).

enzymes, as demonstrated in our analysis, may indicate a reduction in the extent of liver cell injury. These reductions could also indicate an improvement in the regenerative capacity of liver cells, as lower levels of transaminases may indicate stabilization or even reversal of some aspects of liver injury.[45]

Silymarin scavenges harmful free radicals produced during the liver's detoxification processes, increases levels of glutathione (a major intracellular antioxidant), and stimulates enzymes such as superoxide dismutase (SOD) that neutralize oxidative stress. This reduces oxidative damage to liver cells, which is the main cause of elevated transaminases.[46] Silymarin also inhibits the activation of NF-kB, a transcription factor that increases the expression of pro-inflammatory cytokines such as TNF-alpha and IL-6. By suppressing these inflammatory pathways and leukotriene formation, silymarin reduces liver inflammation, which helps to reduce AST and ALT levels.[23,47] In addition, silymarin inhibits the activation of hepatic stellate cells, which are responsible for the development of fibrosis, and modulates matrix metalloproteinases involved in tissue remodeling. It also enhances liver cell regeneration by stimulating protein synthesis and cell proliferation. These effects help stabilize or even reverse liver damage, as reflected by normalization or reduction of transaminase levels.[48,49]

In addition, the observed increase in serum albumin levels is particularly noteworthy. Hypoalbuminemia is a frequent and serious complication in patients with cirrhosis, resulting from a decrease in the liver's capacity to synthesize proteins as the disease progresses. Low albumin levels not only indicate impaired hepatic synthetic function, but are also strongly associated with adverse clinical outcomes, including an increased risk of ascites, edema, and a worse overall prognosis.[50] Therefore, improved albumin synthesis, as indicated by higher serum albumin concentrations, may indicate a significant increase in hepatic synthetic function. This could potentially lead to better clinical outcomes for patients, such as improved nutritional status, reduced complications related to fluid retention, and possibly even improved survival.[50] Taken together, these findings highlight the potential of silymarin as a supportive therapy in the management of cirrhosis, by helping to reduce liver cell damage and restore essential liver functions.

The lack of significant changes in alkaline phosphatase (ALP) and bilirubin levels after silymarin treatment suggests that its effects are more focused on protecting hepatocytes rather than improving cholestatic or excretory liver functions. ALP and bilirubin are markers typically elevated when bile flow is obstructed or impaired, indicating cholestasis.[51,52] Since these parameters did not improve significantly, it implies that silymarin primarily acts on liver cells themselves by reducing oxidative stress, inflammation, and stabilizing cell membranes, rather than directly affecting bile

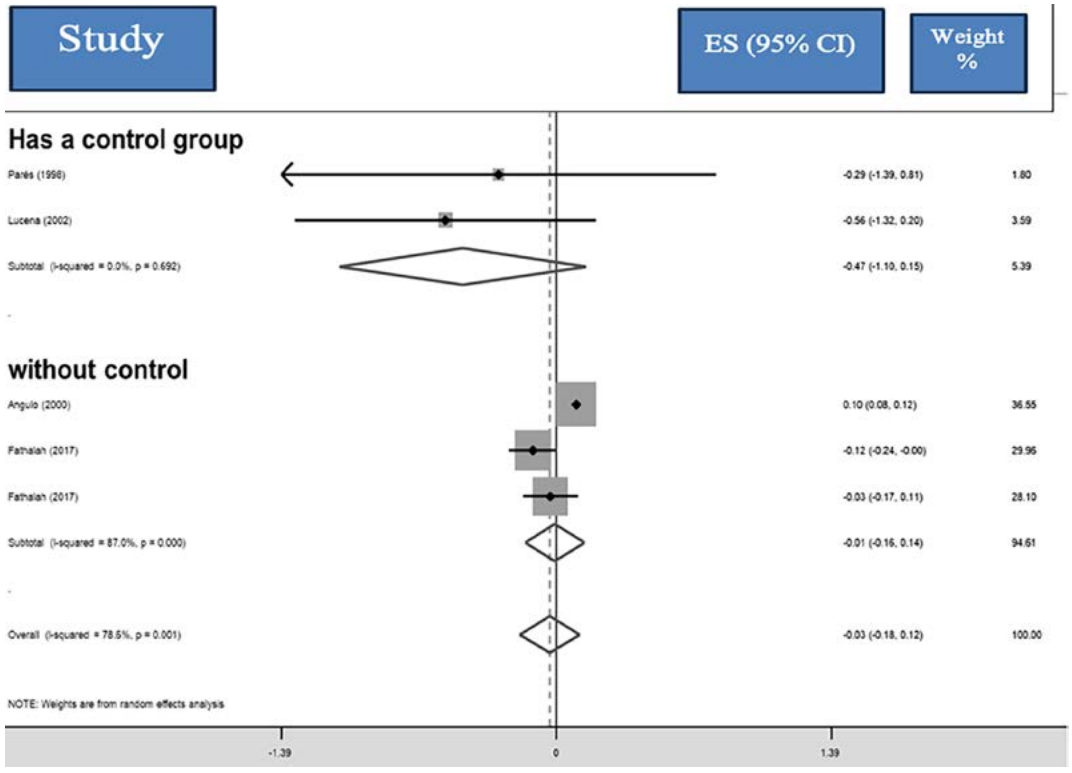


Figure 13. The effect of silymarin on Bilirubin in cirrhotic patients. Subgroup analysis based on having or not having a control group.

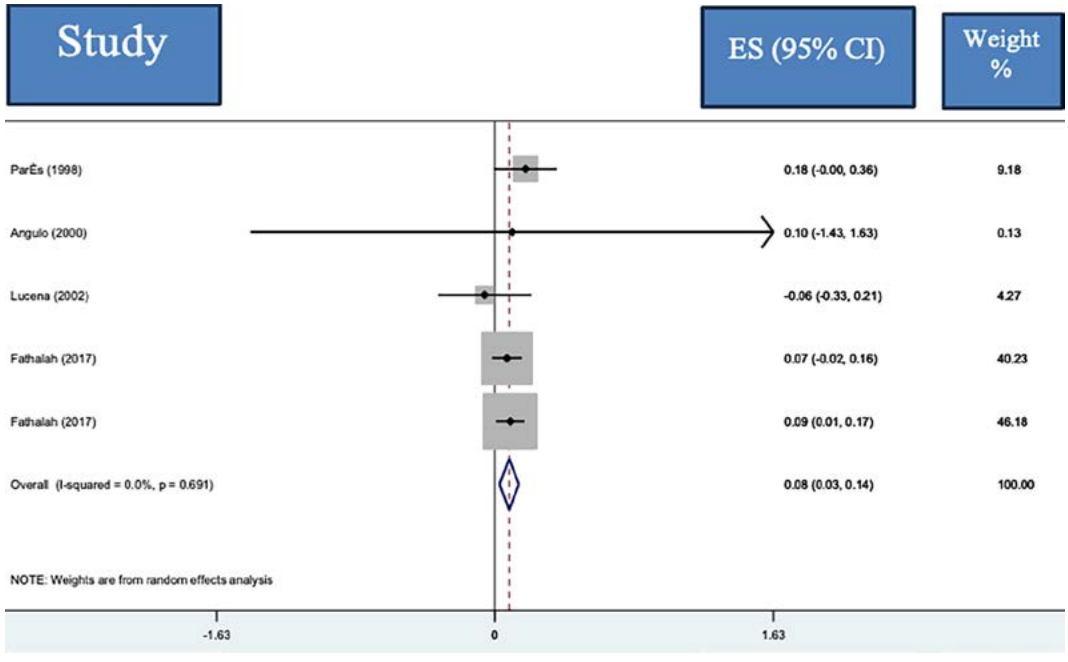


Figure 14. The effect of silymarin on the albumin in cirrhotic patients.

ducts or bile secretion pathways. This aligns with silymarin's well-documented antioxidative, anti-inflammatory, and membrane-stabilizing properties, which mainly target hepatocyte health and function rather than biliary processes.[53]

Inflammation can increase liver enzymes.[54] Two pro-inflammatory lipids, Platelet-activating factor (PAF) and lysophosphatidylcholine-PAF (lyso-PAF), are increased in liver cirrhosis and accelerate the disease process.[55] Lysophosphatidylcholine acyltransferases 1-4

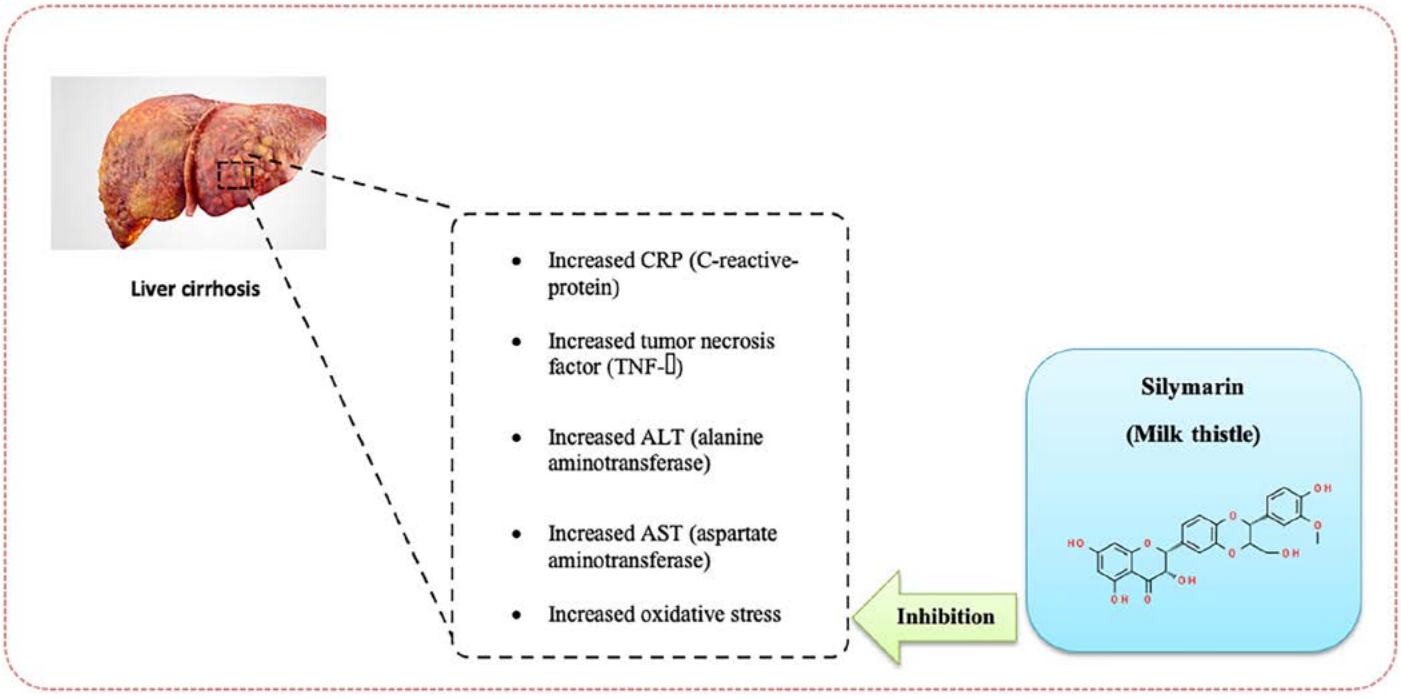


Figure 15. Possible mechanism of silymarin (milk thistle) on liver cirrhosis.

(LPCAT) are involved in PAF regeneration during inflammation.[56,57] silybin can decrease PAF and lyso-PAF in cirrhotic liver rats. This effect was attributed to the role of silybin in reducing the activity and expression of LPCAT1 and LPCAT2.[58] Therefore, silymarin is effective in improving liver enzymes by controlling inflammation, so it has hepatoprotective effects.[59,60] Also oxidative stress increases in cirrhosis.[61] Harmful oxidative factors caused by oxidative stress can increases bilirubin by destabilizing the red blood cell membrane.[62] A study reported that receiving oral silymarin at a dose of 200 mg/kg body weight, twice a week, for 8 weeks in rats with liver cirrhosis, improves cirrhosis and reduces its progression. This effect was attributed to a significant decrease in total bilirubin and ALT and an increase in antioxidant factors including SOD, MDA, and GSH.[24] In general, patients with cirrhosis have high inflammation (including increased CRP and TNF-α),[63,64] oxidative stress,[10,65] and an imbalance of liver enzymes.[66–68] Therefore, the improvement of each of the mentioned factors can slow down the course of the disease and even improve these patients.[16,69] Silymarin, a plant extract in milk thistle, with its antioxidant and anti-inflammatory effects, reduces harmful oxidative and inflammatory factors[70–73] and can regulate liver enzymes such as AST and ALT.[74–77] Therefore, this herbal extract will be useful in liver diseases, including cirrhosis[78,79] (Fig. 15).

In the sensitivity analysis of the studies that investigated ALT changes, there was a significant change in the overall effect size with the exclusion of Parés et al.'s study.[39] In this study, there is a longer period of supplementation (24 months)[39] compared to other studies in this field (3 to 12 months).[37,38,41–43] In the results of the sensitivity analysis of the studies that examined bilirubin, the exclusion of Angulo et al.'s study[40] had a significant effect on the overall effect size of the findings. In this study, silymarin along with UDCA was used as an intervention and there was no control group.

In our results, it was mentioned that the intervention with silymarin can cause a significant decrease in bilirubin, but silymarin plus other compounds did not have a significant effect. Importantly, only one study had an intervention with silymarin plus other compounds.[40] In this study, the intervention included silymarin plus UDCA and the patients in this study were primary biliary cirrhosis with a suboptimal response to UDCA. Considering the existence of only one study in this field, which has limitations such as the absence of a control group and a small sample size (n=27), it cannot be concluded that the combination of silymarin with other compounds cannot improve bilirubin in cirrhosis.

Subgroup analysis based on the dose of silymarin supplement showed that silymarin, only in ≥600 mg/day, caused a significant decrease in AST and ALT.

A recent meta-analysis examined the effect of silymarin in patients with liver diseases. The dose of silymarin received in the studies included in this meta-analysis was 210 to 700 mg/day. The results of this study showed the reducing effect of silymarin on transaminases (AST and ALT).[76] Another meta-analysis reported the effect of silymarin on the reduction of AST and ALT levels in NAFLD. The amount of silymarin received in the studies included in this meta-analysis was 140 to 2100 mg/day.[80]

A detailed and comprehensive search to find trials investigating the effect of silymarin on cirrhosis and performing subgroup analyses to find the sources of heterogeneity of studies are among the strengths of the present study. Limitations of our study include the lack of a control

group in some studies or the failure to report changes in the control group. Also, the small sample size of the studies, the small number of studies, and the lack of studies conducted within the last 8 years are limitations of this study. Therefore, according to the mentioned limitations, it is better to interpret the results of this study with caution.

Conclusion

The results of the present study showed that supplementation with silymarin in cirrhosis can cause a significant decrease in AST and ALT and a significant increase in albumin, but no significant changes in alkaline phosphatase and bilirubin in cirrhotic patients. In general, silymarin with a dose equal to or more than 600 mg/day has a better impact on ALT and AST. Although due to the small number of included studies, findings should be interpreted with caution, based on the results of this meta-analysis, silymarin might be considered as a potentially safe, inexpensive, and available agent for the treatment of cirrhosis, particularly with the dose ≥ 600 mg/day. The small number of studies, the small sample size, and the absence of a control group in many studies make it difficult to make a conclusive conclusion. Therefore, more well-designed randomized controlled trials with a higher sample size are needed to clarify the findings of this study.

Ethics Committee Approval: Ethics committee approval was not required because this study was a systematic review based solely on previously published data.

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

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

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REVIEW ARTICLE

Primary cilia orchestrate the multi-organ network in metabolic dysfunction-associated steatohepatitis

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Points to Note

- **Synthesis of Current Evidence:** Primary cilia may coordinate liver-gut-pancreas and brain-gut-liver axes in MASH by regulating metabolic, inflammatory, and fibrotic pathways.
- **Major Controversies:** Direct evidence in MASH remains limited, and whether ciliary dysfunction is a cause or consequence of disease is unclear.
- **Future Directions:** Studies should validate cilia-based biomarkers and test targeted therapies in MASH models and patient subgroups.

ABSTRACT

Metabolic dysfunction-associated steatohepatitis (MASH) is an increasingly prevalent cause of chronic liver disease and a major driver of cirrhosis and hepatocellular carcinoma worldwide. Although its pathogenesis involves complex interactions among metabolic, inflammatory, and neuroendocrine processes across multiple organs, current therapeutic strategies remain largely liver-centric and fail to address this systemic complexity. Primary cilia (PC) are evolutionarily conserved microtubule-based organelles that function as cellular sensory hubs, integrating extracellular signals and coordinating metabolic and inflammatory pathways. Emerging evidence from studies of ciliopathies, obesity, and neurodegeneration suggests that ciliary dysfunction may contribute to metabolic disorders affecting multiple organ systems. Here, we synthesize current evidence to propose a cilia-centered conceptual framework for MASH pathogenesis. We outline a dual-axis model in which PCs coordinate a horizontal metabolic axis linking the liver, gut, and pancreas to regulate glucose and lipid homeostasis, and a vertical neuro-metabolic axis connecting the brain, gut, and liver to integrate neural and endocrine signaling. Within these networks, cilia-associated pathways, including mammalian target of rapamycin, Hedgehog, Wnt/β-catenin, Notch, and transforming growth factor beta signaling, modulate key processes underlying steatosis, inflammation, and fibrogenesis. Dysfunction of PCs in hypothalamic neurons, pancreatic β-cells, intestinal stromal cells, and hepatic stellate cells may collectively amplify metabolic imbalance and inflammatory signaling, thereby promoting MASH progression. Understanding the systemic regulatory role of PC provides a unifying perspective on the multi-organ nature of MASH and highlights cilia-associated pathways as potential targets for therapeutic intervention.

Keywords: Liver-gut axis, metabolic dysfunction-associated steatohepatitis, microbiota-neuron-metabolism axis, primary cilia.

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Introduction

Metabolic dysfunction-associated steatohepatitis (MASH) is rapidly reshaping the landscape of chronic liver disease worldwide. Globally, over one-third of adults are affected by metabolic dysfunction-associated steatotic liver disease (MASLD).[1] As a progressive stage of MASLD, MASH has become a significant driver of cirrhosis and hepatocellular carcinoma (HCC),[2] while also exacerbating the risk of cardiovascular events,[3] chronic kidney disease,[4] and neurodegenerative disorders.[5] This creates a cross-organ pathological network. Recent evidence suggests that single-target interventions are insufficient to address the complex, multi-axial pathology of MASH. However, primary cilia (PC) – organelles once regarded as "evolutionary relics" – mediate information transduction and cellular process regulation across multiple systems.[6] Consequently, the PC may serve as a critical hub for trans-systemic regulation.

Overview of PC

Cilia are microtubule-based structures, evolutionarily highly conserved, present on nearly all mammalian cells. They serve as crucial signaling hubs in energy metabolism and inflammation, participating in processes such as the cell cycle, signal transduction, and autophagy.[6] Cilia protrude from the cell surface as finger-like projections, consisting of a microtubule axoneme covered by a specialized plasma membrane anchored by a basal body or centriole. A dichotomous classification of cilia is based on motility differences arising from "9+2" to "9+0" microtubule configurations: motile cilia and non-motile cilia, the latter also termed PC.[7] The PC's capacity for sensing and modulating information has long been recognized.[6,8] Defects in ciliary structure or function can lead to ciliopathies, whose core manifestations or major complications include metabolic diseases such as obesity and diabetes.[9]

As a significant early warning sign of metabolic syndrome,[10] MASH is associated with abnormalities in PC structure and function: the loss of cilia on hepatic stellate cells (HSCs) exacerbates fibrosis progression through multiple pathways,[11,12] while ciliary dysfunction in the intestinal system not only worsens metabolic disturbances but also promotes brain functional decline.[13] As detailed in Section 4, PCs are present in HSCs, cholangiocytes, pancreatic islets, enteric neurons, and hypothalamic neurons. These nodes position the PC as an overlapping component of relevant networks, a common pathological nexus for the microbe-metabolism-neuron axis, and a potential therapeutic target for MASH.

Pathogenesis of MASH and Evidence for PC Abnormalities

The traditional exclusion-based term "non-alcoholic" has been superseded, with MASLD and MASH now adopted as standard nomenclature. MASLD requires the presence of hepatic steatosis plus at least one cardiometabolic risk factor, while MASH additionally involves inflammation and hepatocyte ballooning.[14,15] This review uses MASLD/MASH uniformly, retaining non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) when citing pre-2023 studies.[16]

MASH is a chronic liver disease driven and progressively aggravated by metabolic dysregulation. Its core pathogenesis involves a series of pathological processes including insulin resistance (IR), lipotoxicity, oxidative stress, organelle dysfunction, and apoptosis.[17] These processes can be exacerbated by metabolic abnormalities such as obesity, hypertension, and hypertriglyceridemia.[18,19] During disease progression, lipid accumulation in hepatocytes induces mitochondrial dysfunction and excessive reactive oxygen species generation, subsequently activating the JNK pathway and endoplasmic reticulum stress. This ultimately triggers hepatocyte apoptosis through pathways such as caspase-3, further activating HSCs and promoting fibrosis.[20–22]

Notably, the PC, as a ubiquitous organelle, mediates vital physiological and pathological signals in different organs. In the liver, PCs on cholangiocytes have been established as key mechano- and chemosensors. Through proteins like polycystin-2, they perceive changes in bile composition and flow, regulating intracellular Ca^{2+} and cAMP balance, thereby influencing cell proliferation and secretion.[23,24] Studies show that in genetic polycystic liver disease and experimental cholestasis models, PC functional defects (e.g., downregulation of polycystin-2) can lead to aberrant activation of vascular endothelial growth factor (VEGF) signaling, promoting angiogenesis and inflammatory-fibrotic responses.[25] Furthermore, in fibropolycystic liver disease models, defects in cilia-associated proteins can activate β-catenin signaling, driving the expression of chemokines such as CXCL10, recruiting macrophages, and exacerbating periportal fibrosis.[26]

In biliary atresia and most fibrocystic liver diseases, bending, shortening, loss, and genetic defects of PCs have been clearly associated with disease progression.[27–29] Notably, these diseases share a hypoxic microenvironment with MASH. Existing studies have observed an association between hypoxia-inducible factor 1-alpha (HIF-1α) activation and ciliary loss in cholangiocytes.[27,30] *In vitro* experiments exposing cholangiocyte epithelial cells to hypoxic conditions (0.5% O_2) directly reduced PC number and shortened their length. This suggests that hypoxia, a prevalent microenvironmental alteration in MASH and many chronic liver diseases,[31,32] likely causes similar physical disruption to PCs in intrahepatic cells. Therefore, hypoxia-induced PC dysfunction may be a potential mechanism for ductular reaction and fibrosis in MASH.

In a mouse model with cholangiocyte-specific knockout of the key PC gene Kif3a, PC-deficient cholangiocyte epithelial cells exhibited upregulation of senescence and DNA damage response pathway genes and downregulation of proliferation-related genes at the transcriptome level. These cells showed significantly reduced proliferative capacity and increased senescence markers (SA-β-Gal). When transplanted into injured livers, their engraftment and repair capacity were severely impaired. This indicates that PC dysfunction is sufficient to drive cells into senescence and deprive them of

regenerative potential. Notably, a self-reinforcing vicious cycle exists among hypoxia, PC damage, and cellular senescence.

Devarbhavi et al.,[33] showed that hypoxia can directly induce biliary epithelial cell (BEC) senescence; conversely, inducing cholangiocyte senescence significantly reduced the proportion of ciliated cells. Simultaneously, PC loss upregulated genes like HIF Hif1a. Therefore, in the pathological context of MASH, local hepatic hypoxia and metabolic stress may act as initial hits, damaging PC structure and function. Impaired PCs then push cholangiocytes or other liver cells into a senescent state. Inflammatory factors (senescence-associated secretory phenotype) secreted by senescent cells worsen the microenvironment, exacerbating hypoxia and metabolic abnormalities, and further inhibiting PC function, creating a negative feedback loop that impedes tissue repair.

Furthermore, the activated mammalian target of rapamycin (mTOR) pathway in MASH has been shown to bidirectionally regulate PC dynamics; mTOR inhibition enhances autophagy and promotes ciliary elongation, whereas its activation shortens cilia.[34] Thus, mTOR dysregulation in MASH may contribute to metabolic disturbances and disruption of cellular homeostasis by affecting PCs.

However, research on the role of PCs in MASH is still in its infancy. Although the aforementioned studies in related liver disease models have identified PC involvement in key pathways regulating inflammation and fibrosis, and MASH similarly features metabolism stress-induced inflammation and fibrosis, direct experimental evidence proving that PC structural or functional changes are a cause rather than a consequence of MASH onset remains very limited. Future studies need to systematically investigate PC morphological changes and their direct impact on hepatocyte lipid metabolism and inflammatory signaling pathways, specifically in MASH animal models or patient samples, to clarify their precise role in the MASH liver-gut-brain axis.

Multi-Axis Metabolic Imbalance in MASH Pathogenesis

A growing body of recent research recognizes the association between the "gut-liver axis" and MASH,[35] yet therapeutic breakthroughs remain scarce. We therefore summarize a more comprehensive framework of organ axes, including the "gut-liver-microbiota axis," the horizontal gut-liver-pancreas axis, and the vertical brain-gut-liver axis. This will serve as contextual background for subsequent discussion on leveraging PCs for MASH treatment.

Dysregulation of the Gut-Liver-Microbiota Axis

Microbial abundance, metabolites, and gut permeability play crucial roles in MASH development. Studies show that the gut microbiota of MASH patients has significantly higher abundances of Proteobacteria and Fusobacteria compared to healthy individuals.[36] Microbial metabolites also critically influence MASH. The gut microbiota converts primary bile acids (BAs, e.g., CA and CDCA) into secondary BAs, thereby activating the farnesoid X receptor (FXR) and the membrane receptor TGR5.[37] However, downregulated FXR expression in MASH patients leads to uncontrolled BA synthesis and exacerbates hepatic inflammation.[38] Furthermore, increased intestinal permeability allows harmful substances like endotoxins to reach the liver, activating immune responses and ultimately triggering hepatic inflammation.[39] These three factors interact and collectively contribute to MASH pathology, information vital for its treatment.

Dysfunction of the Liver-Gut-Pancreas Axis as a Metabolic Axis

Metabolic aspects of the liver-gut-pancreas axis relate to glucose and lipid homeostasis, reflected in increased risks of human comorbidities. MASH can induce IR, impairing insulin action (e.g., through reduced insulin receptor expression, ineffective receptor binding, or impaired insulin signaling).[40] Insulin regulates neuronal development and can induce neurodegeneration in the central nervous system (CNS) through signaling pathways such as the phosphatidylinositol-3-kinase (PI3K) and mitogen-activated protein kinase pathways, suggesting a bottom-up influence from MASH. Epidemiological studies indicate that MASH patients are at greater risk for type 2 diabetes (T2D).[41] The "twin-cycle" hypothesis proposes that fat accumulation in the liver and pancreas exacerbates IR, impairs pancreatic regulation of glucose homeostasis, and ultimately leads to T2D.[42] T2D significantly increases the risk of MASH in obese adults and accelerates progression from MASH to fibrosis, cirrhosis, and even HCC.[43] Related mechanisms primarily involve glucose and lipid metabolism (including glucotoxicity and lipotoxicity[44]), IR (increased lipolysis, FFA delivery to the liver, hepatic fatty acid β-oxidation causing oxidative stress[45]), and alterations in insulin secretion.

Dysfunction of the Brain-Gut-Liver Axis as a Neural Axis

The brain-gut-liver axis connects the CNS with gut microbiota, the enteric nervous system, and the neuroendocrine system, participating in the vertical systemic effects of MASH in the body. Direct evidence links MASH to brain function: Within the bidirectional regulatory mechanism of the vagus nerve, intrahepatic vagal afferent fibers sense lipid metabolism signals and provide feedback through the brainstem nucleus tractus solitarius to regulate hepatic very-low-density lipoprotein secretion; the CNS (e.g., hypothalamus) inhibits hepatic lipid synthesis through the leptin-vagal axis, a pathway often characterized by leptin resistance in MASH patients.[46] Chronic MASH leading to varying degrees of liver fibrosis can cause white matter lesions, thereby reducing cognitive function. Concurrently, in this chronic inflammatory state, reduced vagal tone further amplifies intrahepatic inflammatory responses.[47] In the gut, microbial metabolites such as short-chain fatty acids (SCFAs) directly regulate sympathetic nervous system activity through G protein-coupled receptor (GPCR)41,[48] which can promote microglial overactivation, leading to neuronal damage.[49]

Table 1. Impact of PC effect size in different organs on MASH progression

Object	PC effect size	Impact on MASH	Key processes	Evidence notes	Source
Hypothalamus	Inhibition of development/length shortening (depletion of IFT88/KIF3A)	Leads to adult-onset obesity and glucose dysregulation, presumed to increase MASH risk	Impairs degradation of lysosomal proteins, disrupts formation of embryonic POMC neuronal circuitry, causing lifelong adverse effects on food intake and energy metabolism	Indirect evidence; mouse model	[51]
Hepatocytes	Loss of function (KIF12 mutation/deletion)	Promotes hepatic steatosis, MASH, and early cirrhosis	Dysregulated degradation of KIF12-mediated lipogenic enzymes	Direct evidence; mouse model	[52]
HSCs	Structural disruption/ dysfunction (IFT88 knockout)	Drives liver fibrosis	IFT88 degradation destroys HSC cilia, stimulating HSC activation and fibrosis	Direct evidence; mouse model	[50]
Pancreatic β-cells	Structural loss/ disruption (TULP3 knockout)	Significantly impairs insulin secretion, potentially causing a severe diabetic phenotype, greatly increasing MASH risk	Mislocalizes G protein-coupled receptors (GPCRs) like free fatty acid receptor 4 (FFAR4) and prostaglandin E2 receptor, preventing response to downstream metabolic signals	Indirect evidence; mouse model	[53]
Intestinal cells (primarily lamina propria fibroblasts)	Structural loss/signaling abnormality (e.g., Wnt pathway dysregulation)	Increases risk of intestinal and systemic metabolic inflammation, promoting MASH fibrogenesis	PC disruption can dysregulate Wnt signaling, leading to gut barrier impairment and microbiota dysbiosis, key pathogenic factors in MASH	Indirect evidence; extrapolation from literature	[54–56]

PC: Primary cilia; MASH: Metabolic dysfunction-associated steatohepatitis; HSC: Hepatic stellate cell; POMC: Pro-opiomelanocortin.

PC: A Metabolic Hub for Cross-System Regulation in MASH

Within the liver, PCs prominently protrude from the apical surface of cholangiocytes, being present in BECs (BECs, also called cholangiocytes). PCs are also found on quiescent HSCs, where they disassemble during HSC activation and hepatic fibrogenesis.[50] Notably, a key mechanism in liver fibrosis is HSC activation. Although biopsy evidence for PCs on hepatocytes is currently lacking, this does not preclude the potential role of the PC as a metabolic hub regulating MASH pathological progression. Viewing MASH through the lens of the PC links it to metabolic syndrome, highlighting its therapeutic potential.

Before a detailed discussion, we first provide a succinct summary of how alterations in PC parameters (e.g., changes in length, functional gain or loss) within various organs discussed herein influence MASH progression, as detailed in Table 1.

PC and the Liver-Gut-Pancreas Axis: Regulation of the Energy Metabolism Axis

Within the gut-liver-pancreas axis, PC-mediated regulation of insulin secretion in β-cells (through GLP-1/FFAR4/GPCR signaling) and HSC activation are mechanisms most directly linked to MASH fibrosis.

In the pancreas, PCs exhibit motility,[57] enabling them to more effectively sense dynamic changes in microenvironmental metabolites like glucose. Axon-cilium synapses form between β-cell cilia and cholinergic islet innervation.[58] Internally, this allows real-time regulation of insulin secretion; externally, it facilitates signal transmission and linkage. This precise regulation depends, at least partly, on the enriched GPCR signaling platform on cilia, including the GLP-1 receptor sensing the gut hormone glucagon-like peptide-1 and FFAR4 sensing long-chain fatty acids.[59,60] PC function is also crucial for overall pancreatic development and homeostasis. Expression of the intraflagellar transport protein gene Ift88 in pancreatic ducts and islets, whose loss causes ciliary assembly defects, leads to exocrine tissue cyst formation, acinar cell apoptosis, and pancreatic atrophy.[61] Arrest or loss of PC formation is a hallmark across stages of pancreatic ductal adenocarcinoma, underscoring the necessity of PCs for normal pancreatic structure and function. Evidence indicates that PC structural abnormalities impair β-cell paracrine signaling and insulin secretion, ultimately correlating with diabetes development.[59,62] This review aims to explore and connect how PCs influence various stages of MASH; in this context, we posit this step as the initiating event in energy metabolism axis dysregulation.

We propose that dysregulation of PC signaling at the pancreatic end triggers a cascade of reactions throughout the liver-gut-pancreas axis, driving MASH progression. Impaired PC signaling in β-cells disrupts the timing and quantity of insulin secretion, inducing IR. PCs are key nodes integrating downstream PI3K/ protein kinase B (Akt)/ mTOR signaling from leptin and insulin; their absence or dysfunction disrupts this pathway, exacerbating both leptin and IR.[62] The resulting systemic metabolic disturbances – elevated free fatty acids and blood glucose – persistently burden the liver. Within the liver, metabolic stresses such as lipotoxicity and ER stress, along with the ensuing inflammatory state, impair PC function in hepatocytes and HSCs.[63] PC damage not only weakens cellular homeostasis maintenance (e.g., by affecting autophagic flux to exacerbate cellular stress[64–67]) but, more importantly, may release normal inhibition on pro-fibrogenic pathways such as Hedgehog (Hh) and Wnt.[68,69] Quiescent HSCs are

abnormally activated, transforming into myofibroblasts that produce excessive extracellular matrix (ECM), becoming central to fibrosis progression. At the intestinal end of the axis, the abundant PCs in lamina propria fibroblasts decrease in number and exhibit structural defects under inflammatory conditions,[70,71] potentially disrupting the balance of local tissue repair and immune regulation. Abnormal signals from these cells may further impact the liver through the portal system, collectively exacerbating MASH pathology.

Functional loss of PCs within the liver-gut-pancreas axis, as a systemic regulatory network, leads to glucose and lipid metabolism dysregulation. Combined with aberrant signals of intestinal origin, this creates a microenvironment that damages hepatic PC function and promotes HSC activation and fibrosis, thereby driving the irreversible progression from simple steatosis to MASH and fibrosis.

PC and the Liver-Gut-Brain Axis: Integrative Regulation of the Neuro-Metabolic Axis

PCs are present on neurons, where they control neurite growth and development[72] and process energy metabolism signals.[73] Hypothalamic PCs, in particular, regulate feeding behavior, acting as "central sensors" for energy homeostasis. PCs on pro-opiomelanocortin (POMC) and neuropeptide Y (NPY) neurons in the arcuate nucleus (ARC) are especially crucial. Evidence shows that disrupting these cilia (e.g., by knocking out IFT88 or KIF3A) impairs POMC neuron function, leading to adult-onset obesity,[51,74] establishing a causal link between ciliogenesis and body weight regulation. Moreover, central PCs modulate sensitivity to hormones including leptin and insulin.[75] The melanocortin 4 receptor (MC4R) pathway, localized to PCs, plays a central role.[76] POMC neurons release α-melanocyte-stimulating hormone, activating MC4R to suppress appetite;[77] similarly, defective MC4R gene expression can cause obesity.[78]

Thus, the hypothalamic-PC-MC4R axis can be viewed as a high-weight pathway in cilia-related appetite regulation, tightly coupled to leptin signaling. Leptin primarily acts on AgRP and POMC neurons in the ARC, suppressing appetite by activating POMC neurons. The leptin resistance common in obesity may form a vicious cycle with PC defects. For instance, the average length and surface area of hypothalamic cilia are significantly reduced (by over 40%) in obese mice,[79] a shortening phenotype likely both a consequence and an exacerbating factor of impaired signal transduction.

Extending this view to the liver-gut-brain axis, PCs constitute a systemic regulatory network. In the liver, PCs on HSCs and BECs regulate cell activation and proliferation through pathways like Hh, Wnt, and Notch, influencing fibrosis. Modulating Notch signaling can reduce fibrotic deposition.[80] Genetic (e.g., PKD2 mutation) or acquired (inflammatory cytokines, ER stress) damage can impair ciliary function, causing intracellular Ca^{2+}/cAMP signaling imbalance.[81] This triggers VEGF-driven angiogenesis and HSC activation[25] as well as β-catenin-mediated chemokine (e.g., CXCL10) secretion, recruiting macrophages and promoting inflammation and fibrosis.[26] These processes align with the ductular reaction and periportal fibrosis observed in MASH. We hypothesize that dysfunctional PC in intrahepatic cholangiocytes may integrate metabolic stress signals and translate them into VEGF-mediated angiogenesis and β-catenin/chemokine-mediated inflammatory-fibrotic responses, thereby driving progression from simple steatosis to MASH and fibrosis. In the CNS, PCs regulate hormonal activity. Impaired cilia may affect lipid metabolism, worsening MASH. Furthermore, PCs have been confirmed in some subtypes of glial cells and interstitial cells of Cajal within the enteric nervous system.[82] Studies also show that the gut microbiota regulates numerous host metabolic processes, including energy homeostasis, glucose metabolism, and lipid metabolism[83,84] and is even linked to brain regions processing sensory information.[85] This relationship is bidirectional: Brain-derived signals can top-down alter gut microbiota composition, and microbial metabolites can influence human brain structure.

We propose the following hypothesis: Hypothalamic PC dysfunction leading to feeding dysregulation and systemic metabolic disturbances will exacerbate hepatic lipid accumulation and inflammation through circulatory factors (e.g., bile acids, metabolites) or neural signals. Conversely, MASH-associated systemic inflammation and metabolic disturbances may also damage cilia in the hypothalamus and other brain regions, where microglial activation-mediated neuroinflammation is considered a key node linking peripheral metabolic disorder to central ciliopathy and cognitive decline.

Although the local functions of PCs in individual organs are being revealed, the integrated picture of how they synergistically drive MASH progression at the multi-organ axis level remains unclear. We propose an integrative hypothesis: Under genetic predisposition or high-fat diet induction, functional loss or shortening of the hypothalamic PC-MC4R signal is an early event in central regulatory failure, leading to hyperphagia and obesity. The ensuing hyperleptinemia, IR, and gut microbiota dysbiosis collectively create a microenvironment that damages PCs in hepatocytes and hepatic non-parenchymal cells, accelerating hepatic steatosis and inflammation. Simultaneously, peripheral inflammatory signals ascend to the brain, potentially damaging neuronal PC function by activating microglia, forming a vicious cycle that drives progression from simple steatosis to MASH and even extrahepatic complications. Future research should employ causal interventions at the axis level in MASH animal models and quantitatively assess the precise effect size of such interventions on core MASH phenotypes such as hepatic fat content, inflammation score, and fibrosis degree, to validate this hypothesis and elucidate core mechanisms.

Therapeutic Implications of PC-Associated Pathways in MASH

Based on the central role of PCs in MASH pathogenesis, interventions targeting their associated signaling pathways have emerged as a highly promising therapeutic strategy. Restoring or modulating PC function and the key pathways they mediate holds potential to intervene in disease progression across multiple layers, including lipid metabolism, inflammatory responses, fibrogenesis, and neuro-immune regulation.

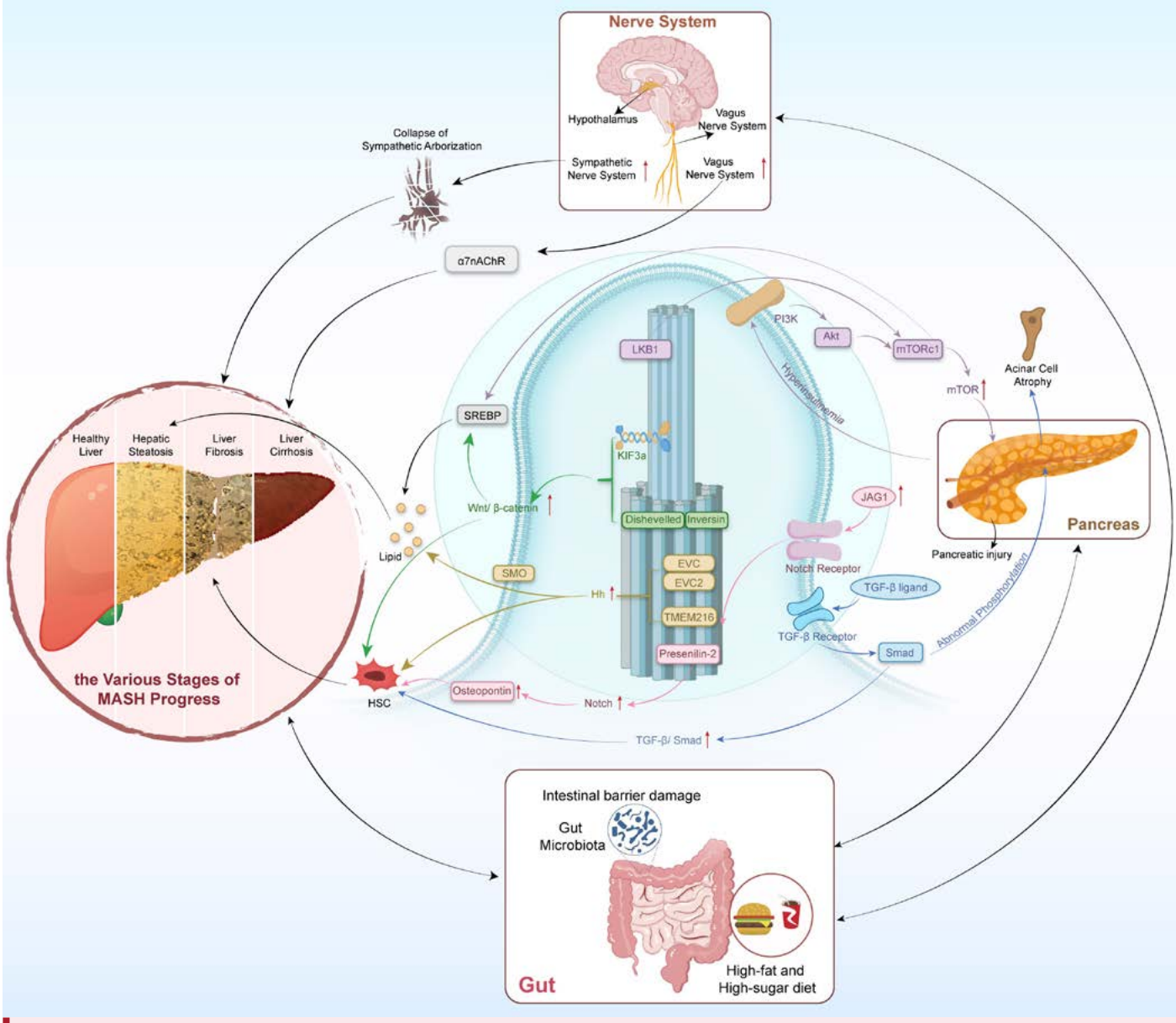


Figure 1. The regulatory pathway of the primary cilia in metabolic dysfunction-associated steatohepatitis. This schematic illustrates the pivotal role of PC as a signaling hub connecting the gut, pancreas, brain, and liver in MASH pathogenesis. PC dysfunction disrupts key pathways – including mTOR, Hh, Wnt/β-catenin, Notch, TGF-β/Smad, and neuro-metabolic axes – exacerbating lipid metabolism dysregulation, IR, inflammation, and fibrosis. This integrated view underscores the mechanistic basis for targeting ciliary function in MASH therapy.

The following sections elaborate on the therapeutic significance of PC-linked pathways – mTOR, Hh, Wnt/β-catenin, Notch, transforming growth factor beta (TGF-β)/Smad, and sympathetic/vagal nerve regulation – in MASH, exploring potential drug intervention directions based on these pathways (Fig. 1).

To further advance the clinical translation of this strategy, future efforts should focus on constructing a PC-based biomarker system (e.g., ciliary-associated proteins, specific imaging features) to enable precise identification and dynamic monitoring of disease status. Concurrently, identifying advantaged patient subgroups likely to benefit from cilia-targeted therapies is crucial. Such subgroups may include obese patients with T2D exhibiting advanced liver fibrosis and severe IR, or patients with metabolic-associated neurocognitive impairment. Implementing precision interventions for these key populations holds promise for breaking the current therapeutic bottleneck and achieving effective translation from mechanistic insight to clinical benefit.

mTOR Signaling Pathway

Liver kinase B1 protein, located within the PC, negatively regulates the mTOR complex 1 (mTORC1), serving as a key molecular link between PC mechanosensation and mTOR signaling.[86] mTORC1 activity correlates

with PC length, with enhanced activity increasing ciliary length.[87] Within the mTOR pathway, mTORC1 is a downstream effector of PI3K/AKT signaling. Following PI3K/AKT activation, phosphorylation and inhibition of the Tuberous Sclerosis Complex 2 (TSC2) relieves its suppression of Rheb, thereby activating mTORC1.[88] Activated mTORC1 promotes lipid synthesis through sterol regulatory element-binding protein (SREBP) transcription factors, fostering hepatic steatosis. Upstream, IR-associated hyperinsulinemia activates the PI3K/AKT/mTOR pathway, leading to lipid accumulation through the above process.[88,89] Concurrently, multiple pathological processes synergistically drive MASH initiation and progression, including oxidative stress[90] and chronic inflammation.[91] During oxidative stress, accumulated hepatic ROS can oxidatively modify the critical Cys124 residue of phosphatase and tensin homolog, inactivating it and thereby removing its negative regulation on PI3K/Akt. This further contributes to persistent aberrant activation of the PI3K/AKT/mTOR pathway. Chronic inflammation and hepatocyte injury activate HSCs, promoting fibrosis. Pro-fibrogenic factors like TGF-β secreted by HSCs continuously stimulate the PI3K/AKT pathway.[92] Collectively, these processes make the PI3K/AKT/mTOR pathway an engine driving progression from MASH to fibrosis and HCC.

Hh Signaling Pathway

Evc and Evc2 are transmembrane proteins that interact at the PC base; their knockout or defective expression attenuates Hh signaling.[93] TMEM216, a transmembrane protein at the ciliary base, also weakens Hh signaling when deficient.[94] Normally quiescent in the liver, the Hh pathway activates upon injury to facilitate regeneration. However, persistent liver damage leads to prolonged Hh signaling.[95] Hepatocytes continuously produce Hh ligands, causing aberrant pathway activation.[96] Overactivation upregulates the long non-coding RNA Hilnc through the downstream transcription factor Gli. Highly expressed Hilnc specifically binds the RNA-binding protein IGF2BP2 in the cytoplasm, stabilizing peroxisome proliferator-activated receptor γ (PPARγ), leading to elevated hepatic PPARγ protein levels and promoting lipogenesis.[96] Concurrently, Hh ligands released from damaged hepatocytes act in a paracrine manner on HSCs, activating their internal Hh pathway, evidenced by nuclear translocation of Gli proteins and target gene expression. Hh-Gli activation drives expression of pro-inflammatory factors (e.g., TNF-α, interleukin-6), exacerbating inflammation and injury, even promoting ballooning,[97] and fosters HSC activation and fibrogenic progression, thereby aggravating MASH.

Wnt/β-Catenin Signaling Pathway

The kinesin KIF3a participates in ciliary assembly, maintenance and regulates Wnt/β-catenin signaling.[98] Inversin acts as a molecular switch for Wnt signaling, forming a protein complex with Dishevelled.[99] A specific Inversin compartment exists within the PC; its absence does not affect PC structure but disrupts the establishment of polarized duct systems in the liver and pancreas.[100] Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection.[101] It can also activate the intestinal Wnt/β-catenin pathway. Moreover, restraint stress similarly disrupts intestinal homeostasis;[102] in this context, compensatory activation of the Wnt/β-catenin pathway can protect the gut-vascular barrier and delay NASH progression.[103] In the liver, liver-specific β-catenin knockout mice exhibit defects in bile acid and cholesterol homeostasis and increased susceptibility to metabolism-driven steatohepatitis.[104] Overactivation of the hepatic Wnt/β-catenin pathway upregulates lipogenic genes (e.g., SREBP-1c) and suppresses fatty acid oxidation genes (e.g., PPARα), collectively promoting hepatic lipogenesis.[105] Furthermore, excessive pathway activation suppresses PPARγ transcriptional activity through regulators such as necdin and DLK1. Decreased PPARγ expression promotes HSC proliferation, activation, and fibrosis.[106]

Notch Signaling Pathway

Notch receptors are located on the PC membrane, while Presenilin-2, the enzyme that cleaves and activates Notch, resides at the ciliary basal body. This spatial proximity provides a structural basis for localized Notch signal activation.[107] Aberrant Notch activation inhibits PC formation, shortening cilia and suppressing function.[108] Activated Notch signaling, through its intracellular domain (NICD), promotes expression of the transcription factor Sox9, which upregulates osteopontin.[109] Osteopontin, a key fibrogenic factor, directly drives HSC activation and promotes liver fibrogenesis.[109] This pathway's abnormal activation stems from increased expression of the upstream ligand Jagged1 (JAG1), a process driven by gut microbiota dysbiosis through the hepatocyte Toll-like receptor 4 (TLR4)-nuclear factor kappa (NF-κB) signaling axis.[110] Human liver biopsies and mouse NASH models show positive correlations between hepatic JAG1 expression and disease activity scores, fibrosis stage, and Notch target gene (HES1, HEYL) levels. Hepatocyte-specific Jag1 knockout protects mice from NASH-induced fibrosis.[111]

TGF-β/Smad Signaling Pathway

In the pancreas, PC deficiency (e.g., Kif3a, Ift88, or Cby1 knockout) leads to ciliary loss in pancreatic ductal cells, upregulates TGF-β1 expression, and activates downstream Smad3 signaling. This promotes pancreatic stellate cell activation and excessive ECM deposition, ultimately causing pancreatic inflammation, fibrosis, and acinar cell atrophy.[112] The PC membrane harbors TGF-β receptors. Upon ligand binding, activated receptors migrate from the ciliary membrane to the ciliary pocket and enter the cell through clathrin-mediated endocytosis. This process is crucial for activating downstream SMAD transcription factors (e.g., SMAD2/3), which then translocate to the nucleus to regulate target gene transcription.[113] In MASH, damaged hepatocytes and inflammatory cells release TGF-β1. Binding to receptors on HSCs activates downstream Smad2/3 phosphorylation. The resulting Smad complex translocates to the nucleus, promoting excessive ECM deposition.[114] In addition, TGF-β1 induces epithelial-mesenchymal transition in hepatic oval cells, converting them to HSCs and aggravating fibrosis.[115]

Table 2. Pharmacological modulators of primary cilia-associated metabolic signaling pathways relevant to MASH

Target pathway	Key preclinical/ clinical drug examples	Effects on MASH phenotype and considerations	PC-dependency for MASH effect?	PC-related notes	Current evidence level	Source
mTOR	Rapamycin	mTORC1 inhibitor; limits MASH progression across stages, induces autophagy, and insulin sensitivity.	Partially dependent	Promotes PC formation but shortens PC length.	Preclinical rodent studies; some clinical trials.	[132]
Hedgehog	GDC-0449; LDE225	Blocks Smoothened (Smo) activity, inhibits Gli1 transcription, and alleviates MASH inflammation.	Partially dependent	SMO enriches at the PC membrane upon Hh pathway activation.	Preclinical rodent studies.	[133]
Wnt/β-catenin	Niclosamide	Inhibits Dvl2, reduces β-catenin stability, blocks Wnt signaling; applicable across MASH stages.	Partially dependent	Dvl2 protein localizes to the PC basal body region.	Preclinical rodent studies.	[134,135]
Notch	DAPT	Improves MASH pathology by inhibiting Notch1 activity, reducing lipid accumulation, and hepatocyte injury.	Partially dependent	Notch1 is a transmembrane receptor also located on the PC membrane.	Preclinical rodent studies.	[136]
	siJag1	Inhibits hepatic JAG1 expression, suppressing the Notch pathway and attenuating liver fibrosis.	Partially dependent	Receptor for JAG1 is present on the PC membrane.	Preclinical rodent studies.	[111]
TGF-β/Smad	SB431542-Loaded Liposomes	Inhibits TGF-β signaling, alleviates liver fibrosis; achieves high local concentration in the liver.	Possibly dependent	TGF-β receptors are located on the PC membrane.	Preclinical rodent studies.	[131]

PC: Primary cilia; MASH: Metabolic dysfunction-associated steatohepatitis; TGF-β: Transforming growth factor beta; mTOR: Mammalian target of rapamycin.

Sympathetic Nervous System Regulatory Pathway

In the nervous system, most neurons possess a single PC, which has been shown to be crucial for maintaining excitatory-inhibitory balance in neural circuits.[73] Animal studies indicate that PC loss or dysfunction in the ventromedial hypothalamus reduces sympathetic nerve tone and causes central leptin resistance, lowering energy expenditure and leading to obesity,[116] a high-risk factor for MASH. Investigations using three-dimensional (3D) immunoimaging to explore liver innervation integrity across NAFLD stages revealed degenerative features in sympathetic nerves, including collapsed dendritic arborization, with degeneration severity correlating with NAFLD pathology.[117] This results from chronic sympathetic over-excitation.[118] In this context, reducing aberrant hepatic sympathetic nerve activation can effectively counteract liver steatosis.[119] Therefore, both sympathetic suppression and chronic over-excitation are MASH risk factors, and intact PC structure likely exerts a positive influence on neuronal electrical activity.

Vagus Nerve System Regulatory Pathway

Muscarinic acetylcholine receptor 3 (mAChR M3) is present in the PCs of cerebrovascular cells,[120] a key target of the vagus nerve. Activating mAChR M3 enhances ciliary length[121] and delays MASH progression.[122] Hepatic macrophages, particularly Kupffer cells, are major immune players in MASH. Some studies indicate that reducing Kupffer cells by inhibiting inflammatory pathways (e.g., NF-κB) improves hepatic IR and alleviates MASH.[123] From a vagal perspective, research shows that vagus nerve stimulation activates the α7 nicotinic acetylcholine receptor (α7nAChR), which directly suppresses inflammation through cholinergic signaling and indirectly modulates the unfolded protein response (UPR) pathway in Kupffer cells to inhibit ER stress.[124] This suppresses three UPR arms: PERK/eIF2-α, ATF6, and IRE1/TRAF2/IKK,[125] thereby inhibiting inflammation. Activating α7nAChR inhibits hepatic necroptosis and alleviates acute liver injury,[126] suggesting a potential to delay MASH progression. Furthermore, the vagus nerve establishes streamlined direct connections between the brainstem and gut,[127] also influencing MASH progression.

Potential MASH Therapeutics Based on PC Pathways

At present, no MASH therapeutics explicitly developed based on PCs exist. However, potential links to PCs can be found among known preclinical or clinical drugs. For instance, Histone deacetylase 6 (HDAC6) mediates autophagy-dependent PC disassembly. HDAC6 overexpression in cholangiocarcinoma reduces PC expression and promotes tumor growth, while HDAC6 inhibition restores cilia, which may slow disease progression. The HDAC6 inhibitor ricolinostat inhibits cholangiocarcinoma cell proliferation, an effect enhanced when combined with ciliogenesis-promoting agents like the SCFAs

Table 3. Therapeutic modulation of primary cilia-related neuro-metabolic pathways in MASH

Target pathway	Key preclinical/ clinical drug examples	Effects on MASH phenotype and considerations	PC-dependency for MASH effect?	PC-related notes	Current evidence level	Source
Sympathetic Nervous System	Pegozafermin (PEGylated FGF21 analog); FGF21 and analogs (e.g., Efruxifermin)	Acts on CNS Vglut2+ glutamatergic neurons to increase hepatic sympathetic nerve activity, inhibiting de novo lipogenesis, reducing triglycerides, and fibrosis.	Not explicitly stated	Not explicitly stated.	Preclinical rodent studies; Clinical Phase IIb (HARMONY trial); Phase III.	[137–139]
Vagus Nerve System	Vagus nerve stimulators (e.g., 2-DG)	Vagal excitation releases ACh, acting on α7nAChR on Kupffer cells and HSCs, inhibiting NF-κB, etc., reducing hepatic inflammation/ fibrosis.	Not explicitly stated	Not explicitly stated.	Preclinical rodent studies.	[140,141]
	Cholinergic receptor agonists (e.g., M3 mAChR agonists; selective α7nAChR agonists)	Mimics the cholinergic anti-inflammatory pathway, inhibits hepatic innate immune cell activation, potentially blocking the inflammatory and fibrotic progression of MASH. Moreover, activation of cholinoceptors on hepatocytes may directly influence glucose and lipid metabolism.	Not explicitly stated	Not explicitly stated.	Preclinical rodent studies.	[141,142]

PC: Primary cilia; MASH: Metabolic dysfunction-associated steatohepatitis; CNS: Central nervous system; NF-κB: Nuclear factor kappa; HSCs: Hepatic stellate cells; α7nAChR: Alpha-7 nicotinic acetylcholine receptor.

butyrate.[128,129] Other studies show Ricolinostat can delay renal fibrosis through the TGF-β pathway.[130] This evidence suggests Ricolinostat might exert anti-fibrotic effects in MASH through PC-related mechanisms. Therefore, we posit that adding PC-restoring agents to conventional MASH treatment strategies could yield superior clinical efficacy, ideally through more precise selection based on specific PC pathways. It is also worth noting that lipid-based nanoparticles possess high liver-targeting efficiency, stability, and safety.[130] Their co-administration with relevant drugs (e.g., SB431542-Loaded Liposomes, as shown in the following tables)[131] may further improve therapeutic outcomes.

Tables 2 and 3 list drugs validated in clinical trials or animal studies to improve hepatic pathology and illustrate their relationship to PC pathways.

Limitations and Future Directions

While targeting PC offers a novel therapeutic avenue for MASH, significant limitations remain. The foremost bottleneck is the lack of longitudinal human data on PCs in the MASH context, primarily due to technical challenges in achieving high-resolution, high-throughput detection of PCs in clinical samples (especially paraffin-embedded tissues), making dynamic assessment of their signaling activity difficult. Furthermore, PC-associated signaling pathways exhibit considerable crosstalk, posing a risk of off-target effects during intervention. However, advances in detection technologies, such as novel elastography methods including ultrasound-based acoustic radiation force impulse imaging, can already assess liver fibrosis in ciliopathy patients. Future, more sensitive PC detection methods hold promise for revealing associations between different ciliary gene variants and fibrosis risk, and for identifying MASH subgroups more responsive to PC-targeted therapy.[143] Therefore, PCs may serve not only as therapeutic targets but also as biological indicators for disease monitoring and prognosis.

Conclusion

Regarding drug development, future efforts should focus on screening or designing compounds that can specifically modulate PC assembly, length, or signal transduction, based on known PC pathways, followed by systematic functional validation in MASH models. Studies should incorporate dynamic monitoring of PC-related biomarkers (e.g., ciliary structural proteins, signaling activity molecules) to clarify the correlation between drug efficacy and PC status. This would provide more compelling preclinical evidence for PC-targeted MASH therapy. Integrating cross-technology, cross-model research has the potential to gradually overcome current limitations and advance PC-targeted strategies from mechanistic exploration towards clinical translation.

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REVIEW ARTICLE

Prevention of alcohol relapse in post-liver transplant patients with alcohol use disorder

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Points to Note

- **Synthesis of Current Evidence:** Alcohol relapse after liver transplantation worsens graft and patient outcomes; prevention requires pre-LT risk assessment, biomarker-based monitoring, and combined pharmacologic and psychosocial care.
- **Major Controversies:** The 6-month abstinence rule, relapse definitions, and early LT for severe alcohol-associated hepatitis remain debated.
- **Future Directions:** Standardized relapse criteria, validated risk tools, multicenter studies, and transplant-specific trials of AUD therapies are needed.

ABSTRACT

Alcohol-associated liver disease has become the most common reason for liver transplantation (LT) in many regions, including the US. This shift reflects the declining hepatitis C-related LTs and rising prevalence of harmful alcohol use, which increased substantially, especially during COVID-19 pandemic. Post-LT alcohol relapse leads to poor clinical outcomes, including medication non-adherence, graft dysfunction (steatosis and alcohol-related hepatitis), recurrent cirrhosis, and decreased overall survival. For patients with severe alcohol-associated hepatitis, early or expedited LT can offer a survival advantage in carefully selected candidates compared with traditional approaches requiring six months of pre-LT abstinence, without a substantial increase in hazardous relapse. Pre-LT risk assessment is essential for the candidate selection and combines psychosocial factors with validated tools such as Stanford Integrated Psychosocial Assessment for Transplantation, Hopkins psychosocial scale, sustained alcohol use post-LT, harmful alcohol use post-LT, and high-risk alcoholism relapse. Post-LT monitoring utilizing direct biomarkers (e.g., phosphatidylethanol, ethyl glucuronide) with indirect markers of alcohol-use to widen the detection window and capture both low-level and heavy use should be considered. Optimal management of alcohol-use disorder (AUD) relies on combining pharmacologic and psychosocial interventions. Among pharmacologic options, naltrexone and acamprosate are considered first-line options, whereas disulfiram is less commonly used after LT given concerns about its drug interactions. Psychosocial aspects of the management are as important as the pharmacologic aspects to maintain abstinence and reduce relapse risk. Potential barriers to participation, such as hepatic decompensation, hepatic encephalopathy, or logistical challenges, should also be recognized and addressed. This narrative review summarizes current management strategies for AUD with emphasis on the post-LT setting.

Keywords: Alcohol-related hepatitis, alcohol-use disorder, liver transplantation, relapse after liver transplant.

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Introduction

Alcohol-associated liver disease (ALD) has become the most common reason for liver transplantation (LT) in many regions.[1,2] This shift reflects the widespread adoption of antiviral therapies that have markedly reduced hepatitis C virus-related transplant demand, as well as an increase in harmful alcohol consumption, which particularly escalated during the COVID-19 pandemic.[3] Data provided by Nielsen National Consumer Panel demonstrates substantial growth, 34%, in retail alcohol sales during the pandemic.[4] This surge in alcohol consumption led to the increased prevalence of alcohol use disorder (AUD), and ultimately, to a rise in ALD and LT waiting list addition.[5,6] AUD is defined as a chronic disease of unhealthy alcohol use despite adverse social, occupational, or health consequences.[7] ALD comprises a continuum of liver injury, evolving from steatosis to steatohepatitis and ultimately cirrhosis.[8] For selected patients with advanced ALD, LT remains the only therapeutic option. However, due to the standard 6-month abstinence rule implemented by most LT programs, many patients die before qualifying for a LT. This is reflected by the high mortality rate of 70% at 6 months in those unresponsive to corticosteroid treatment who would have otherwise benefited from a liver transplant.[9] Data show that deaths specifically linked to alcohol in the US increased by 25% from 2019 to 2020, while deaths attributed explicitly to ALD increased by about 22.4% during the same period.[3]

Because available donor organs remain limited and allocation carries ethical implications, transplant programs must carefully evaluate candidates with ALD to determine which individuals are most likely to remain abstinent following LT, thereby reducing the likelihood of recurrent alcohol use, associated complications, and ultimately graft loss. The pandemic-era spike in alcohol use further amplifies the relapse risk in the already vulnerable transplant recipient population. A critical challenge is how to prevent alcohol relapse in a post-pandemic world where access, stressors, and societal norms have changed.

Materials and Methods

A thorough literature review was conducted to gather relevant information for this narrative review of the prevention of AR in post-liver transplant patients with AUD. The search strategy included a combination of keywords related to post-transplant AR, its clinical impact, monitoring, prevention, and treatment. English-language studies published between 2000 and 2025 were identified through electronic databases including PubMed/MEDLINE, Embase, and Google Scholar. Titles and abstracts were screened initially for relevance, followed by pertinent sections of the body and full-text review of relevant articles. We included English literature publications coming from experienced institutions, as well as high-volume liver transplant centers, and also incorporated the authors' clinical experience from their routine practice. We prioritized recent clinical practice guidelines, systematic reviews/meta-analyses, randomized trials when available, and large transplant cohort studies.

Clinical Impact of Relapse in Transplantation

AR after LT is associated with many adverse outcomes, including medication non-adherence, histopathological changes such as steatosis, steatohepatitis, and advanced fibrosis, as well as shortened survival after LT.[10,11] Graft steatosis and alcohol-associated hepatitis (AH) were found to be increased by four- to ninefold in patients who have AR.[12] These changes can lead to graft cirrhosis, graft loss, and ultimately patient mortality. At present, there is no standard definition for AR. This poses several significant challenges and undermines the consistency of clinical care. A major challenge is the clinical ambiguity, the policy, and the ethical implications. Since many LT programs often use AR as a criterion for listing or delisting patients, without a clear, shared definition, this process can become arbitrary or biased, raising concerns about fairness and equity.[13] In addition, the lack of consensus leads to inconsistent assessments and management strategies among providers, complicating eligibility decisions for LT and post-transplant care.[14] Therefore, to improve patient management and care, a classification system consisting of three AR categories was proposed:[8] (1) Mild relapse, referring to infrequent episodes of alcohol use, typically under once monthly; (2) moderate relapse, characterized by ongoing alcohol consumption that falls within drinking quantities considered acceptable by the National Institute on Alcohol Abuse and Alcoholism (NIAAA, generally no more than 4 daily or 14 weekly drinks for men, and 3 daily or 7 weekly drinks for women) and (3) severe relapse, marked by sustained intake exceeding NIAAA recommendations or accompanied by clinical complications such as pancreatitis, acute alcohol-related hepatitis, graft failure, or other medical consequences linked to resumed drinking. Per World Health Organization criteria, severe AR corresponds to self-reported consumption exceeding approximately 20 g daily in women or 30 g daily in men over a period of 6 months or longer.[15]

Of these three types of relapses, severe relapse carries the most significant risk as it can promptly result in recurrent alcohol-associated cirrhosis (RAC) in the transplanted liver.[16] RAC is one of the primary causes of mortality in transplanted patients with ALD, alongside *de novo* malignancies, and cardiovascular events.[17] Therefore, the selection of LT candidates with AUD is heavily influenced by their risk of AR after transplantation. AR can be predicted by multiple scoring systems, which will be discussed later. Utilizing these scoring systems and using the correct definitions of relapse is crucial in identifying patients at high-risk patients and implementing targeted follow-up programs to help prevent AR.

The Role of Early LT (ELT) in AH

Despite increasing acceptance, ELT practice still remains controversial. The traditional 6-month abstinence requirement has been questioned repeatedly, as several studies report comparable AR rates regardless of pre-transplant abstinence duration. ELT was first systematically described by Mathurin et al.,[18] who reported the data of LT for carefully selected patients with the first episode of severe

AH (SAH) and <6 months of abstinence using strict psychosocial and medical criteria across seven centers in France and Belgium. In this cohort, patients unresponsive to medical therapy had an estimated 6-month survival of ~30% without LT, which improved to 77% among those who underwent ELT.[18] However, despite improved survival rates, ELT was associated with a higher incidence of post-LT alcohol use.[11] In contrast, a recent retrospective cohort study of 163 patients was evaluated for differences in 1-year overall survival, graft survival, and hazardous relapse–free survival. Hazardous relapse was further categorized into binge, at-risk, or frequent drinking. The study showed no significant difference in AR rates between patients who underwent ELT and those who underwent standard LT. Data showed a 1-year relapse-free survival in ELT as 80.4% versus standard LT as 83.5% (p=0.41), and the 1-year hazardous relapse–free survival in ELT as 85.8% versus standard LT as 89.6% (p=0.41). The only significant factor associated with worse survival was early relapse, referring to resumption of alcohol consumption within the first 90 days following transplantation, particularly with hazardous drinking patterns.[19] Another recent benchmark study did a retrospective chart review of 69 adults who underwent LT for ALD from 2018 to 2021, and AR rates did not differ between those who achieved 6 months of sobriety before LT and those who had not.[20] Although longer pre-LT sobriety correlated with reduced likelihood of AR, no definitive minimum abstinence period emerged as a reliable predictive threshold.[20]

Another concern raised in broader literature and the transplant community is whether ELT patients might have a higher risk of acute graft rejection. A meta-analysis study compared 228 ALD-associated LT patients in two groups: Those with fewer than 6 months of sobriety versus those exceeding 6 months. The main endpoint evaluated was the rate of biopsy-proven acute rejection (BPAR) during the 1st year after LT. They found that a sobriety duration under 6 months did not correlate with a higher incidence of BPAR in the first post-LT year,[21] indicating that ELT does not increase the risk of immune-mediated graft rejection. Therefore, given the consistent evidence from multiple studies showing that achieving a 6-month sobriety period does not meaningfully alter the likelihood of AR after LT or improve overall survival, ELT may be considered a reasonable option for carefully selected patients with severe ALD, within appropriate ethical and institutional frameworks and guided by the factors discussed in the following sections. It should also be noted that ELT practices vary by region and center due to differences in organ availability, regulatory context, addiction-care resources, and sociocultural norms. Ongoing ethical considerations include equitable access, transparent selection criteria, and consistent post-transplant support; policies should therefore be tailored locally and periodically reassessed.

Strategies for Preventing AR Post-Liver Transplant

Pre-Transplant Interventions

To improve clinical outcomes in patients undergoing LT for ALD, management efforts to prevent AR in the post-LT period should be initiated well in advance of the transplant procedure.

Managing Alcohol Withdrawal

Participation in an alcohol abstinence program, such as Alcoholics Anonymous (AA), is usually mandated by most LT centers. These programs assist patients in achieving and sustaining sobriety using psychosocial support and teaching patients how to cope with emotional stressors, triggers, and the mental hurdles of addiction. However, it is important to realize the challenges that come with abstinence in AUD and to address them. Withdrawal is a major event that can challenge a patient's progress and recovery. Alcohol withdrawal syndrome (AWS) has been shown to occur to some degree in about 50% of patients with chronic excessive alcohol use after abrupt cessation or significant reduction of alcohol intake.[22] AWS typically begins within 1–3 days of admission and lasts for about 5 days.[23] One study on the relationship of pre-LT AWS and post-LT relapse showed that patients with pre-LT AWS had a significantly higher risk of post-LT relapse (subdistribution hazard ratio =6.37; 95% confidence interval 1.33–30.62; p=0.02).[24] Moreover, this study reported AWS to confirm the severity of AUD, and suggests that future evaluations should place greater emphasis on DSM-5 diagnostic standards and detailed alcohol-use histories to better identify risk factors for AR.[24]

Predicting Risk of AR

Predicting the risk of patient AR post-LT is the most crucial step in pre-LT evaluation. After identifying a medically appropriate candidate for LT, identifying their risk for AR is the next step. Categorizing patients as high or low risk is crucial for establishing close monitoring, support, and immediate intervention to prevent graft injury and loss. Several risk factors have been identified as being associated with the post-LT AR risk. A retrospective study showed that factors like being younger at LT, a history of AR, notable psychiatric disorders, alcohol consumption after cirrhosis was diagnosed, a shorter sobriety period before listing for LT, and participation in prior substance use treatment programs were statistically significant in association with AR.[20] Other studies showed coexisting psychiatric disorders, such as anxiety, depression, or personality-related conditions, were likewise linked to an increased risk of AR.[25,26] Risk prediction models and scoring systems are other important tools that can be used.

The Stanford integrated psychosocial assessment for transplantation (SIPAT) was first published in 2012. It assesses 4 categories: readiness and illness self-management, quality of social support, psychosocial stability and psychiatric status, and lifestyle factors including substance use. It assigns patients scores from 0 to 110, with higher scores indicating a higher psychosocial risk for AR. However, it was later found in a validation study that it demonstrated only moderate ability to predict overall psychosocial outcomes.[27]

The Hopkins psychosocial scale (HPSS) is a model that integrates factors specific to patients with AH along with recognized predictors of AR. An HPSS score <0 predicts sustained AR, which is derived based on the balance of protective versus high-risk factors. Protective factors contributing to the score include voluntary hospital presentation, pre-sobriety daily alcohol consumption, awareness of illness, duration of sobriety before LT, and marital status.[28]

Table 1. Scoring systems

Scoring/Meaning of abbreviation	Target patient subgroups	The most suitable clinical scenario and timing
Hopkins Psychosocial Scale (HPSS)	HPSS predicts AR for individuals who are candidates of LT due to SAH. This scale benefits from unique factors specific for SAH patients additionally known risk factors for AR in AUD.	This scale is used in pre-transplant patient selection by classification in psychosocial assessment and considering ethical appropriateness.
Sustained alcohol use post-LT (SALT)	SALT predicts brief AR ("slip") and sustained AR to alcohol usage in individuals receiving ELT for SAH.	This scale is used in pre-transplant period for post-transplant sustained alcohol usage prediction.
Harmful Alcohol use Post-Liver Transplant (HALT)	HALT is used in LT candidates with ALD or AH.	This scale is used in pre-transplant period for post-transplant harmful drinking risk prediction.
Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT)	SIPAT, as a comprehensive psychosocial evaluation tool, predicts psychosocial consequences in individuals who are receiving solid organ transplant. This scale is nonspecific for AUD.	This scale is used in pre-transplant (in LT candidates with ALD) psychosocial assessment globally.
High-Risk Alcoholism Relapse (HRAR) (scale)	HRAR predicts AR and time of AR for individuals with AUD. In addition, this scale is nonspecific for organ transplantation.	This scale is used in relapse risk prediction in pre-transplant period (in LT candidates with ALD) by evaluating the addiction severity and AR related risk factors.[58]

SAH: Severe alcohol-associated hepatitis; AR: Alcohol relapse; LT: Liver transplantation; AUD: Alcohol-use disorder; ELT: Early liver transplantation; AH: Alcohol-associated hepatitis; ALD: Alcohol-associated liver disease. Adapted from Dienstag et. al.[59] with an additional column by the authors.

The sustained alcohol use post-LT (SALT) score is a risk stratification tool, which integrates four variables to identify low-risk patients and has a score range of 0–11. These are: more than ten drinks per day at the initial admission (+4), a history of multiple rehabilitation attempts (+4), previous legal problems related to alcohol (+2), and past illicit substance abuse issues (+1 points). Per this scoring system, about 95% of those with a score under 5 remain abstinent of alcohol post-LT, while about 25% of those with a score of 5 or more continue drinking post-LT.[29]

The harmful alcohol use post-LT score is a multivariable regression-based model designed to estimate the likelihood of harmful alcohol use following LT. It incorporates age at the time of LT, history of non–alcohol-related legal offenses, duration of abstinence before LT, and average daily alcohol consumption.[30]

The high-risk alcoholism relapse (HRAR) scale predicts the risk of AR after LT in patients with ALD. It stratifies patients for more intensive follow-up or rehabilitation support; however, it does not account for factors like social support, mental health, or motivation to stay sober. Therefore, it is often used alongside other psychosocial evaluations like SIPAT. It is composed of three variables: Duration of heavy drinking, number of drinks per day, and number of prior inpatient treatments for alcoholism. An HRAR score of 4 or more indicated an increased risk for harmful alcohol use after LT.[25]

Notably, only the SALT and HPSS scores were designed specifically for patients undergoing ELT for SAH; however, neither has a consistent outcome measure or external validation.[31,32] Table 1 clarifies the relapse risk-prediction tools for specific clinical scenarios and patient subgroups briefly.

Post-Transplant Interventions

Monitoring and therapeutic approaches used to prevent post-LT AR are summarized in Figure 1 and further detailed in the following sections below.

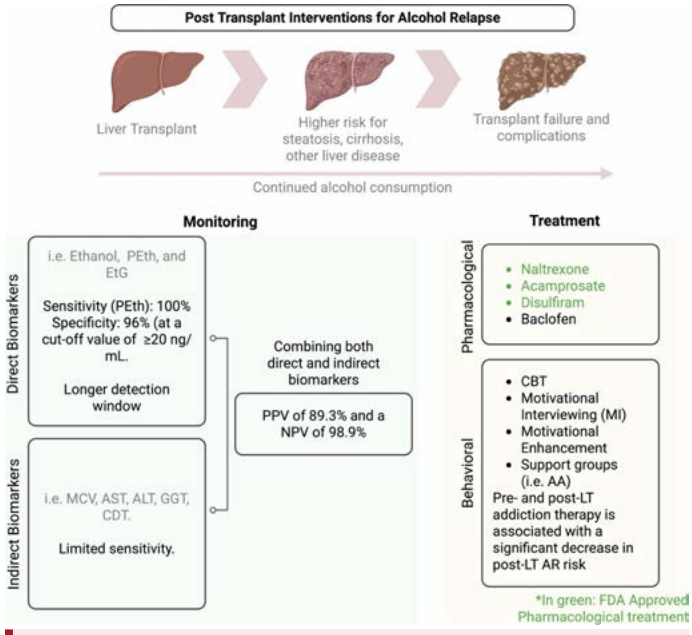


Figure 1. Overview of post-LT alcohol-relapse prevention strategies.

AA: Alcoholics anonymous; ALT: Alanine transaminase; AR: Alcohol relapse; AST: Aspartate transaminase; CBT: Cognitive behavioral therapy; CDT: Carbohydrate-deficient transferrin; EtG: Ethyl glucuronide; FDA: Food and drug administration; GGT: Gamma-glutamyl transferase; LT: Liver transplant; MCV: Mean corpuscular volume; MI: Motivational interviewing; NPV: Negative predictive value; PEth: Phosphatidylethanol; PPV: Positive predictive value.

Monitoring for Alcohol Use

Early detection of AR after LT cannot be overstated. As mentioned previously, post-LT AR is associated with many adverse outcomes that may lead to graft dysfunction. To prevent that, it is important for clinicians to have the tools to assess patients for alcohol intake and initiate intervention immediately. Random testing for alcohol through analysis of blood, urine, or breath samples continues to be the preferred

method for detecting AR; however, its utility is limited by alcohol's rapid metabolism and short detection window. Consequently, clinicians have increasingly relied on biochemical markers as more sensitive and specific tools for AR detection. These biomarkers are broadly classified into two categories: direct and indirect. Direct biomarkers are metabolites of alcohol, such as ethanol, phosphatidylethanol (PEth), and ethyl glucuronide (EtG), which specifically indicate recent alcohol consumption. PEth is a phospholipid that is formed only when phosphatidylcholine, a component of cell membranes, is metabolized by phospholipase D in the presence of ethanol. It can be detected in fresh whole blood or dry blood spots and is highly sensitive, capable of identifying even minimal alcohol consumption, as little as a single drink within the preceding 1–2 weeks.[33] In a cohort study, PEth was found to have a sensitivity of 100% and a specificity of 96% at a cut-off value of ≥20 ng/mL,[34] making it a reliable marker for the detection of alcohol use. On the other hand, indirect biomarkers reflect the physiological consequences of chronic alcohol use rather than alcohol itself. Common examples include aspartate transaminase/alanine transaminase ratio, gamma-glutamyl transpeptidase (GGT), mean corpuscular volume, and carbohydrate-deficient transferrin (CDT). These markers are practical and cost-effective screening tools for detecting heavy alcohol use; however, they lack sensitivity for identifying occasional lapses or minor drinking episodes.[32] Moreover, GGT and CDT can indicate alcohol use even in the absence of hepatitis; however, both may be elevated due to other causes such as hepatitis C infection, smoking, sepsis, or pulmonary diseases.[35] In comparison to indirect biomarkers, direct biomarkers represent the metabolic products of the non-oxidative pathways of ethanol metabolism and therefore demonstrate substantially higher specificity. Moreover, direct biomarkers have a substantially longer detection window, making them particularly valuable for confirming recent alcohol intake.[36] It was shown that combining both types achieved a positive predictive value of 89.3% and a negative predictive value of 98.9%.[37] Therefore, combining both direct and indirect biomarkers optimizes the detection of both chronic heavy drinking and low-level alcohol consumption.

Treatment of AR

Pharmacological Therapy

Medications for AUD (MAUD) play a key role in managing this condition as an additional treatment alongside psychosocial interventions.[7] Naltrexone, acamprosate, and disulfiram are currently the three FDA-approved medications for treating AUD. The effectiveness of these medications has been well established across multiple studies over recent years. Use of MAUD has been shown to reduce mortality and rehospitalization rates by 42%.[38] Despite the strong evidence, they are still surprisingly underused. Only 2% of the 30 million people with AUD are ever prescribed MAUD.[39] Their proven effectiveness supports wider use and integration into the management of appropriately selected post-LT patients with AUD. Similarly, direct comparative effectiveness data for MAUD in post–LT recipients are very limited. To date, no head-to-head trials have compared naltrexone, acamprosate, and baclofen specifically in post-LT populations, and the only randomized study in LT recipients is a recent pilot trial evaluating acamprosate versus standard of care without pharmacotherapy.[40]

Naltrexone is a μ-opioid receptor blocker that diminishes alcohol-induced reward signaling within the mesolimbic dopamine pathway, helping with the urge and craving to drink. However, the primary safety concern is its boxed warning, noting the risk of hepatocellular injury at high doses.[41] A new study investigated the use of an injectable extended-release naltrexone (XR-NTX) to overcome this adverse effect. A retrospective case series evaluated 14 adults with advanced ALD who received at least one 380 mg dose of XR-NTX between 2023 and March 2025. They concluded that none of these patients developed hepatotoxicity or hepatic decompensation and maintained stable liver function test results (MELD and Child-Pugh) throughout a minimum follow-up period of 12 weeks.[42]

Acamprosate is an N-methyl-D-aspartate (NMDA) receptor antagonist that attenuates the pleasurable effects of alcohol.[43] It was found to be a safe, feasible, and effective treatment with promising adherence and no signs of AR or liver-related complications for post-LT AUD patient.[40] It significantly increases cumulative abstinence duration and continuous abstinence rates compared with placebo.[44] In post-LT populations, comparative effectiveness data are extremely limited; nevertheless, acamprosate is the only MAUD formally studied in a randomized trial in LT recipients. In a recent pilot randomized trial (n=30), acamprosate 666 mg three times daily was safe and feasible over 14 weeks, with similar adverse event rates compared with standard of care (92.3% vs. 90.0%) and no grade 4/5 adverse events. No biochemical or reported AR occurred in either group; however, baseline craving scores were low, limiting conclusions regarding efficacy.[40] Its side effects are generally mild and dose-dependent, most commonly including transient diarrhea, while suicidal ideation has been reported rarely.[45] However, it is contraindicated in patients with severe renal impairment as it is renally eliminated.

Disulfiram is the first pharmacologic agent approved by the US Food and Drug Administration (FDA) for the treatment of AUD. Its pharmacologic effect is mediated through inhibition of aldehyde dehydrogenase, thereby disrupting alcohol metabolism and resulting in acetaldehyde accumulation. Acetaldehyde is the component that causes the aversive symptoms of drinking, like nausea, vomiting, hypotension, chest pain, and flushing. This negative reinforcement discourages patients from subsequent alcohol use. The main concern with this drug is acute liver injury. Aminotransferase elevation occurs in 25% of patients.[45] Because disulfiram is hepatically metabolized and moderately inhibits CYP 2C9, it carries a potential risk for significant drug-drug interactions with other agents metabolized by this pathway.[46] Therefore, disulfiram usage is limited in post-LT AUD patients.

Although Baclofen, a gamma-aminobutyric acid type B (GABA-B) receptor agonist, is not yet approved by FDA nor recommended by the American Psychiatric Association. Its effectiveness and safety as a potential pharmacotherapy are still being studied. A randomized clinical trial evaluated the effectiveness of baclofen to

manage AUD. The 16-week study compared baclofen 30 and 90 mg/day versus placebo in 120 patients, examining the effects of dose, sex, and pretreatment drinking levels. The analysis demonstrated that baclofen treatment was associated with a reduction in heavy drinking and an increase in abstinent days. Specifically, baclofen resulted in 13.6 fewer heavy drinking days (p=0.018) and 12.9 more abstinent days (p=0.028) compared with placebo.[46] In addition to its role in the prevention of AR, baclofen also showed efficacy in managing AWS by activating GABA-B receptors and thereby effectively counterbalancing AWS-associated and NMDA-mediated glutamatergic excitatory neurotransmission.[47]

A comparative study evaluating pharmacotherapies for AUD showed that naltrexone produced the greatest reduction in alcohol craving and consumption, the lowest AR rate, but also the most adverse effects. On the other hand, baclofen exhibited the most favorable tolerability profile, with relatively stable liver function parameters and fewer reported adverse effects. The highest dropout rate was observed in the acamprosate group.[48]

In terms of transplant-specific considerations, no formal interaction studies between MAUD and immunosuppressants have been performed in LT recipients. Based on pharmacokinetics, clinically significant interactions appear unlikely for acamprosate (renal elimination, no hepatic metabolism), while naltrexone and baclofen also have no established interactions with calcineurin or mechanistic target of rapamycin inhibitors; however, evidence is limited, and vigilance is warranted. Accordingly, medication choice should be individualized with attention to renal function (acamprosate), hepatic injury monitoring (naltrexone), and sedation/neurocognitive risk (baclofen), with close follow-up.

GLP-1 receptor agonists (GLP-1RAs) are being explored as a potential adjunctive therapy for AUD. In a large VA EHR analysis, GLP-1RA exposure was associated with modest reductions in AUDs Identification Test-Consumption (AUDIT-C) scores compared with both propensity-score–matched unexposed patients and DPP-4 inhibitor users, with larger reductions observed among patients with baseline AUD.[49] In another VA EHR analysis of patients with harmful alcohol use, GLP-1RA exposure was associated with a lower risk of liver-related outcomes and mortality, as well as a lower likelihood of a positive AUDIT-C during follow-up.[50] Randomized evidence remains limited but encouraging: in a phase 2 trial in patients with AUD, weekly low-dose semaglutide reduced overall alcohol consumption and decreased drinks per drinking day and craving, without significant changes in overall drinking days in total. However, it should be noted that these data were generated while patients were under active surveillance.[51] Complementing these findings, a Swedish registry study reported a lower risk of AUD-related hospitalization during periods of semaglutide or liraglutide use compared with nonuse.[52] A recent systematic review and meta-analysis found heterogeneous, non-significant effects on alcohol consumption, but suggested fewer alcohol-related events and improved liver-related outcomes with GLP-1RA use.[53] Taken together, these findings are encouraging and support further studies to clarify the clinical effectiveness of GLP-1RAs for AUD and identify the patients most likely to benefit.

Behavioral Therapy

In conjunction with pharmacological therapy, behavioral therapy must be integrated into every patient's management plan. Psychological interventions incorporate concepts from psychological theories, such as operant conditioning and cognitive theory, to disrupt AR loop. Cognitive behavioral therapy (CBT) is a behavior-focused approach that examines thought patterns to identify triggers that contribute to drinking and subsequently replaces maladaptive responses with alternative, non-drinking behaviors. CBT requires the patient's active participation and sustained commitment, as it spans over 10 or more sessions. It is the most widely implemented behavioral intervention for AUD and is supported by robust evidence from randomized controlled trials and observational studies demonstrating its efficacy in promoting and maintaining abstinence.[54]

Motivational interviewing (MI) is another strategy. This technique emphasizes enhancing a patient's internal awareness of the consequences of alcohol use. MI is guided by five principles: (1) demonstrating empathy to build connection; (2) highlighting discrepancies between patients' goals and behaviors; (3) avoiding direct confrontation; (4) working collaboratively with, rather than opposing, resistance; and (5) reinforcing self-efficacy.[55]

Motivational enhancement (MET) uses the principles of MI but aims to evoke the patient's intrinsic motivation for behavioral change.[56] In a study comparing patients who received MET with those who did not, MET was found to reduce both the quantity and frequency of pre-transplant alcohol consumption among LT candidates with alcohol dependence.[57]

Participation in mutual support groups, such as AA, is widely recommended both pre- and post-transplantation. It is reported that a combination of both pre- and post-LT addiction therapy is associated with a significant decrease in post-LT AR risk (p=0.002).[58] Mutual support programs provide the additional benefit of social support, which is less prominent in CBT and MI/MET.

Active participation is a typical requirement for listing in most transplant programs; however, it is important to consider the many barriers that may limit a patient's ability to participate, including: (1) frequent hospital admissions related to decompensated liver disease; (2) decreased ability to engage meaningfully due to cognitive deficits; and (3) practical difficulties attending appointments, such as inability to drive resulting from encephalopathy or significant ascites-related volume overload.[59]

Conclusion

Alcohol recidivism remains a significant challenge post-LT, impacting long-term outcomes. The COVID-19 pandemic worsened alcohol use, contributing to higher ALD-related mortality and increased transplant demand. Early detection of high-risk patients and targeted interventions are essential for improving post-LT success. Strong psychosocial support and continuous follow-up can help reduce relapse risk. Policy changes should focus on individual patient risk

rather than rigid sobriety timelines (i.e., 6-month rule). Accordingly, the level of therapeutic intervention should be customized for each LT recipient. Future strategies should incorporate integrated behavioral health, telehealth, and predictive modeling to enhance care. Future research should include prospective, multicenter studies with standardized relapse definitions and external validation of relapse risk–prediction tools across diverse settings. Transplant-specific trials and real-world comparative effectiveness studies are also needed to clarify the efficacy and long-term safety of MAUD and to optimize post-LT monitoring strategies.

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HEPATOLOGY FORUM

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CASE REPORT

Primary hepatic T-cell lymphoma presenting with unexplained liver dysfunction in a young female: A diagnostic challenge

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Clinical Pearls

- **Unique Features of the Case:** A rare primary hepatic T-cell lymphoma occurred in a 37-year-old woman with unexplained liver dysfunction, cytopenia, no classic risk factors, and initially non-specific biopsy findings.
- **Primary Lesson for Clinicians:** PHTCL should be considered when liver dysfunction and cytopenia persist despite negative routine workup, as repeat biopsy and early hematology/oncology involvement may prevent diagnostic delay.

ABSTRACT

Primary hepatic T-cell lymphoma (PHTCL) is a rare, aggressive extranodal non-Hodgkin lymphoma confined to the liver, often presenting with non-specific symptoms and leading to delayed diagnosis. A 37-year-old female presented with progressive jaundice, pruritus, and abdominal discomfort, accompanied by markedly elevated transaminases and mixed-pattern cholestasis. Extensive serological, infectious, and autoimmune work-up was non-contributory. Despite the introduction of a gluten-free diet following the incidental diagnosis of celiac disease, the patient's liver function deteriorated, accompanied by persistent cytopenia. Initial liver biopsy demonstrated non-specific inflammatory changes. A repeat biopsy, prompted by worsening clinical status, revealed extensive infiltration of atypical T-lymphocytes with a high proliferative index and diffuse CD3 positivity, consistent with high-grade peripheral T-cell lymphoma. Rapid hepatic decompensation ensued, and the patient died before receiving oncologic treatment. PHTCL should be considered in patients with unexplained liver dysfunction and cytopenia, even without classic risk factors or imaging abnormalities, to enable timely diagnosis and management.

Keywords: Cytopenia, diagnostic delay, liver biopsy, liver dysfunction, primary hepatic T-cell lymphoma.

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Introduction

Abnormalities in liver function tests are often found in patients who are otherwise asymptomatic, as these tests are commonly included in a routine blood screening panel.[1] Liver dysfunction can occur from a variety of etiologies, ranging from autoimmune conditions to malignancies.

In cases of liver dysfunction requiring further etiological evaluation, hepatic biopsies can occasionally reveal underlying systemic hematopoietic disorders, with rare occurrences of primary hepatic lymphoma (PHL) being among the potential findings.[2]

This case underscores the importance of considering rare but aggressive malignancies, such as primary hepatic T-cell lymphoma, a subtype of extranodal lymphoma comprising a mere 0.016% of all cases.[3] Although primarily observed in individuals in their fifth decade of life[4] and predominantly affecting men, this aggressive neoplasm should be considered in the differential diagnosis of patients presenting with unexplained liver dysfunction and cytopenia, due to its significant mortality rate.

Case Report

A 37-year-old female patient presented to the hospital with complaints of abdominal pain, nausea, generalized pruritus, and jaundice that had been ongoing for 1 month and had worsened in the past 2 weeks. Liver function tests revealed significant abnormalities, and she was hospitalized in the Hepatology Department with a preliminary diagnosis of toxic hepatitis. Her medical history was unremarkable except for two previous miscarriages. The patient had no history of herbal product or supplement use, except for occasional use of non-steroidal anti-inflammatory drugs within the past 6 months. Her family history included Behçet's disease in a sibling. On physical examination, she had scleral icterus and diffuse abdominal tenderness; her vital signs were stable.

Initial laboratory tests revealed markedly elevated liver enzymes: Aspartate transaminase (AST) 1490 IU/L, alanine transaminase (ALT) 875 IU/L, alkaline phosphatase 428 IU/L, gamma-glutamyl transferase 46 IU/L, total bilirubin 6.5 mg/dL, and direct bilirubin 5.3 mg/dL, indicating a mixed hepatocellular and cholestatic pattern of injury. International Normalized Ratio (INR) was 1.7. Hemoglobin was 11.4 g/dL, white blood cell count 31,000/mm^3, platelet count 266,000/mm^3, urea 19 mg/dL, and creatinine 0.51 mg/dL. C-reactive protein was 2 mg/L, sedimentation rate 8 mm/h, ferritin 37.4 ng/mL, and lactate dehydrogenase 384 IU/L. Abdominal ultrasonography revealed a liver of normal size and contour with increased periportal echogenicity. The gallbladder was normal in size but had a thickened wall (5 mm) and echogenic bile sludge within the lumen. The intrahepatic and extrahepatic bile ducts were of normal caliber.

Etiological work-up revealed a normal ceruloplasmin level (29.8 mg/dL) and 24-h urinary copper excretion (48.95 µg/g creatinine). TORCH, Epstein-Barr virus (EBV) immunoglobulin (Ig)M/IgG, and Brucella serologies were negative. Purified-protein derivative was

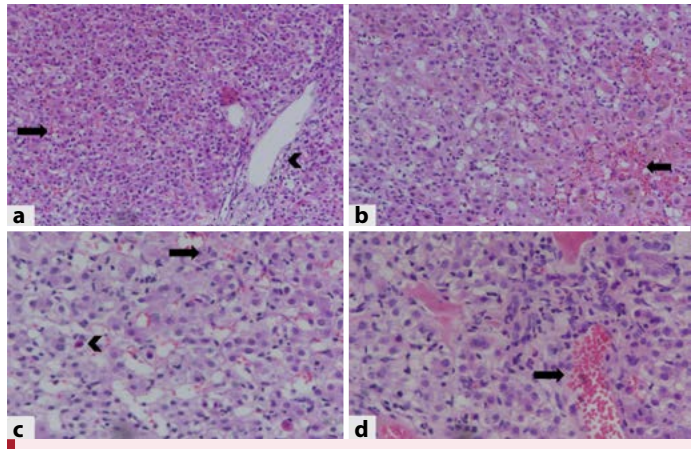


Figure 1. (a) Apoptotic hepatocytes (arrow) and mild portal inflammation (arrowhead) are visible. **(b)** Prominent hepatocellular cholestasis is observed (arrow). **(c)** Presence of eosinophils (arrow) and single-cell hepatocyte necrosis (arrowhead). **(d)** Congestion in the hepatic parenchyma is evident (arrow). (Hematoxylin and Eosin stain; [a and b]: ×200, [c and d]: ×400)

10 mm. Haptoglobin was 0.295 g/L, and the Coombs test was negative. Peripheral smear showed leukocytosis, anisocytosis, and poikilocytosis. Viral hepatitis markers (HBsAg, Anti-HBc Total) and autoimmune hepatitis autoantibodies (Antinuclear antibodies, anti-smooth muscle antibody, liver kidney microsomal antibodies, anti-mitochondrial antibody) were all negative. Serum immunoglobulins were within normal limits: IgA 4.2 g/L, IgM 2.28 g/L, and IgG 15.7 g/L.

Screening for celiac disease revealed a markedly elevated tissue transglutaminase IgA level (>200 U/mL). Upper gastrointestinal endoscopy demonstrated patchy, white-exudate-covered ulcerations involving the bulb and second part of the duodenum, consistent with active celiac disease. A gluten-free diet was initiated. However, no significant improvement was observed in liver function tests despite dietary adherence. AST was 1203 IU/L, ALT 544 IU/L, total bilirubin 16.3 mg/dL, direct bilirubin 12.6 mg/dL, and INR 1.6. The white blood cell count decreased to 2690/mm^3, while the platelet count increased to 401,000/mm^3.

The patient was evaluated by the Hematology Department due to persistent cytopenia and suspicion of a hematologic malignancy. Peripheral lymphadenopathy was not detected, and bone marrow biopsy – performed in anticipation of possible liver transplantation – was reported as normocellular. Immunodeficiency was ruled out by the allergy-immunology team. Behçet's disease was excluded based on the absence of oral ulcers, a negative pathergy test, and a lack of uveitis.

The initial liver biopsy revealed portal inflammation, hepatocellular cholestasis, apoptosis, single-cell necrosis, congestion, and eosinophilic infiltration (Fig. 1). Although autoimmune hepatitis was not strongly supported histologically, no clear toxic etiology could be identified either. Based on these findings, the patient was started on intravenous methylprednisolone (40 mg/day) for presumed toxic hepatitis. However, no clinical or biochemical response was observed. The corticosteroid dose was tapered and discontinued in the 4th week, and the patient was discharged with outpatient monitoring and a plan for re-biopsy if needed.

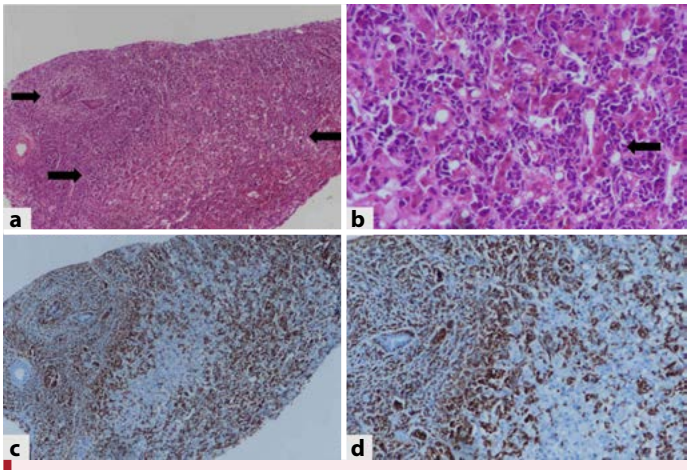


Figure 2. (a) Low-power view showing dense lymphoid cell infiltration extending from the portal areas into the hepatic parenchyma, leading to disruption of the porto-parenchymal interface (black arrows) (Hematoxylin and Eosin stain, ×100). **(b)** High-power view of atypical lymphoid cells with hyperchromatic nuclei, irregular contours, and larger size compared to normal lymphocytes (black arrow) (Hematoxylin and Eosin stain, ×400). **(c, d)** Immunohistochemical staining with CD3 shows strong and diffuse positivity in infiltrating atypical T-lymphocytes, confirming T-cell lineage (CD3 immunostain, ×100 [c], ×200 [d]).

A repeat liver biopsy performed at another center showed infiltrates of neoplastic lymphoid cells that stained strongly positive with CD3, indicating T-cell lineage. Immunophenotyping demonstrated a dominant abnormal T-cell population expressing CD3, CD7, CD43, HLA-DR and TCRγδ, with loss of CD4 and CD8 expression. CD19 and CD20 positive B cells were virtually absent. These findings were consistent with a clonal T-cell lymphoproliferative disorder. Shortly afterward, the patient was re-admitted to the emergency department with worsening nausea, vomiting, and abdominal pain. On examination, she appeared cachectic, lethargic, and disoriented, with signs of hepatic decompensation including ascites and coagulopathy. Despite intensive supportive treatment, the patient died on the 3rd day of admission to the intensive care unit.

Following her death, a retrospective review of her medical records, initial liver biopsy, and bone marrow biopsy revealed no evidence of T-cell lymphoma at the time of the earlier evaluations. The diagnosis of PHTCL was made only after disease progression, and unfortunately, the patient died before the initiation of any specific oncologic treatment (Fig. 2).

Discussion

Primary hepatic T-cell lymphoma represents one of the rarest subtypes of non-Hodgkin lymphomas, characterized by its exclusive involvement of the liver without nodal or peripheral blood involvement at presentation.[5,6] The clinical course of PHTCL is often aggressive, and the non-specific symptoms and laboratory findings associated with this malignancy contribute to diagnostic delays, as demonstrated in this case. The patient's presentation with jaundice, pruritus, and abdominal pain, accompanied by significant elevations in liver enzymes, initially suggested a hepatobiliary disorder such as toxic hepatitis or autoimmune hepatitis. However, the progression of the disease, despite initial treatments, necessitated further investigation.

The patient's clinical deterioration, characterized by persistent hyperbilirubinemia and progressive cytopenia, prompted a multidisciplinary evaluation, including hematology consultation. The subsequent liver biopsy, showing hepatic involvement by neoplastic T cells with a high proliferative index (Ki-67 ~80%), was instrumental in establishing the diagnosis of PHTCL. Immunohistochemical staining further supported the diagnosis, with diffuse positivity for CD3, confirming T-cell lineage, and negativity for markers such as CD20, ruling out B-cell lymphoma.

PHTCL is extremely rare, comprising <0.016% of all extranodal lymphomas, and is typically associated with poor clinical outcomes.[3] Interestingly, despite its aggressive nature,[6] recent studies have revealed that patients with PHL can have 5-year survival rates as high as 77–83%, indicating a more favorable prognosis than previously anticipated.[7–9]

The literature suggests that most patients with PHTCL present with non-specific hepatic symptoms, including jaundice, hepatomegaly, and deranged liver function tests, as seen in this case. Importantly, PHTCL often mimics other causes of liver dysfunction, leading to misdiagnosis. While chronic viral infections such as hepatitis B, hepatitis C, and EBV have been implicated as potential risk factors,[5,8,9] this patient tested negative for these infections, further complicating the diagnostic process.

Histologically, PHTCL often demonstrates a diffuse infiltration of malignant T cells within the hepatic parenchyma, with frequent findings of hepatocellular damage and cholestasis.[10,11] In this case, the initial liver biopsy did not reveal any findings suggestive of lymphoma, emphasizing the diagnostic challenges posed by this malignancy. The absence of typical risk factors and the non-specific clinical presentation contribute to the complexity of diagnosing PHTCL at an early stage.

Therapeutic options for PHTCL are limited. The disease typically responds poorly to conventional chemotherapeutic regimens, and overall survival rates remain unsatisfactory. Given the aggressive nature of PHTCL, early diagnosis is paramount, though, in this case, the diagnosis was made late in the disease course, after the patient had already experienced significant liver damage and multi-organ involvement.

This case underscores the importance of considering rare hepatic malignancies in the differential diagnosis of patients with unexplained liver enzyme abnormalities, particularly when common etiologies such as viral hepatitis, autoimmune hepatitis, and toxic hepatitis have been excluded. The early involvement of a multidisciplinary team, including hematology and oncology, may aid in the timely diagnosis of such rare entities. Furthermore, the use of advanced diagnostic modalities, including immunohistochemistry and molecular testing, is essential in differentiating PHTCL from other hepatic pathologies.

Conclusion

In conclusion, PHTCL is an exceedingly rare and aggressive neoplasm with a poor prognosis. The diagnostic complexity and rapid disease progression highlight the need for increased awareness and consideration of this entity in patients presenting with unexplained liver dysfunction. It should be kept in mind that diagnosis may be challenging in the early stages due to patchy involvement in the liver biopsy. Further research is necessary to elucidate the pathophysiology of PHTCL and to develop more effective therapeutic strategies to improve patient outcomes.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

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HEPATOLOGY FORUM

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CASE REPORT

Reverse hepatitis B seroconversion without immunosuppression: A case report and literature review

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Clinical Pearls

- **Unique Features of the Case:** Reverse HBV seroconversion occurred in an 88-year-old woman more than a decade after HCV cure, despite previously resolved HBV infection, previously documented high anti-HBs levels, and no identifiable immunosuppression or trigger.
- **Primary Lesson for Clinicians:** HBV reactivation can occur years after apparent clearance even without immunosuppression. Long-term vigilance is warranted in patients with resolved HBV, particularly older individuals and those with prior HCV coinfection.

ABSTRACT

We report a case of reverse hepatitis B seroconversion in an 88-year-old woman with previously resolved hepatitis B virus (HBV) infection and sustained virologic response to hepatitis C virus (HCV) therapy. She presented with decompensated cirrhosis and was found to have newly positive hepatitis B surface antigen, hepatitis B e-antigen, and high HBV DNA levels, despite no recent immunosuppression. Entecavir was initiated with clinical and virologic improvement. This case highlights the potential for HBV reactivation years after apparent clearance, even in the absence of immunosuppression, and underscores the need for long-term monitoring in patients with prior HBV infection.

Keywords: Hepatitis B virus, hepatitis C virus, reverse seroconversion.

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Introduction

Reverse seroconversion of hepatitis B virus (HBV), defined as reappearance of hepatitis B surface antigen (HBsAg) in a previously resolved infection, is a well-documented phenomenon in immunocompromised patients. However, its occurrence in immunocompetent individuals without a clear trigger is extremely rare. In patients with HBV-hepatitis C virus (HCV) coinfection, suppression of HBV replication by HCV has been observed. After HCV eradication, latent HBV may reactivate, though this typically occurs within months.[1] We report an unusual case of delayed HBV reverse seroconversion over a decade after HCV cure, presenting as decompensated cirrhosis. The patient has provided informed consent for publication of the case.

Case Report

An 88-year-old East Asian woman with a remote history of HCV genotype 1b, successfully treated with ledipasvir/sofosbuvir 10 years previously, was referred to the emergency department with progressive bilateral lower limb edema and increasing abdominal girth. Outpatient records from 10 years ago confirmed negative HBsAg, positive hepatitis B core antibody, and high-titer hepatitis B surface antibody (anti-HBs) of 180.5 mIU/mL, consistent with resolved HBV infection and a protective anti-HBs response. She had no recent history of immunosuppression, chemotherapy, or systemic illness. Her home medications included antihypertensives, a bisphosphonate, and a proton pump inhibitor. She denied alcohol or drug use.

On presentation, she was noted to have scleral icterus, pitting edema up to the thighs, and mild abdominal distension. Laboratory workup revealed alanine aminotransferase 494 U/L, aspartate aminotransferase 641 U/L, alkaline phosphatase 120 U/L, gamma-glutamyl transferase 144 U/L, total bilirubin 56 µmol/L, albumin 20 g/L, and international normalized ratio 1.4. Abdominal ultrasound and computed tomography imaging showed a nodular liver contour and perihepatic ascites, without focal hepatic lesions or thrombosis. Esophagogastroduodenoscopy revealed no esophageal or gastric varices.

Notably, viral serology revealed newly positive HBsAg and HBeAg, with an HBV viral load of 797,000 IU/mL. HCV RNA remained undetectable. Autoimmune, vascular, and metabolic workup for alternative causes of liver disease was unremarkable. There was no prior history of chronic HBV infection. A basic immunodeficiency workup, including complete blood count, hemoglobin A1c, immunoglobulin levels, and HIV serologies, was also unremarkable.

She was diagnosed with HBV reactivation with reverse seroconversion, presenting with decompensated cirrhosis. She was initially treated with tenofovir, but this was switched to entecavir because of underlying osteoporosis. Diuretics were initiated for ascites and peripheral edema, and she was discharged in stable condition.

At outpatient follow-up, she showed progressive clinical improvement. Five months later, her liver enzymes had normalized, and HBV viral load had decreased to <100 IU/mL, though remained detectable at 70 IU/mL. Diuretics were discontinued, and she remained stable on entecavir with ongoing laboratory and imaging surveillance. Trends in HBV DNA and liver biochemistry are shown in Figure 1.

Discussion

Reverse seroconversion of HBV is defined as the reappearance of HBsAg in individuals with previously resolved infection, which is most commonly associated with immunosuppressive states, such as chemotherapy, biologic agents, or organ transplantation. However, there is only a limited number of published cases in the literature reporting reverse seroconversion in patients without overt immunosuppression, particularly among elderly or medically frail individuals, as outlined in Table 1.

Several cases have documented spontaneous HBV reactivation in the absence of identifiable triggers. Freudiger et al.[2] reported a 73-year-old hemodialysis patient who developed reverse seroconversion without immunosuppressive therapy, suggesting that uremia and age-related immune decline may have contributed. Other reports have implicated acute physiological stress as a trigger. For example, Deroux et al.[3] and Ozturk Cerik et al.[4] reported HBV reactivation following ischemic and hemorrhagic strokes, respectively, hypothesizing that neurologic injury may induce transient immune dysregulation. Kamitsukasa et al.[5] described a patient who reactivated after coronary artery bypass grafting, again without pharmacologic immunosuppression. Lastly, Kim et al.[6]

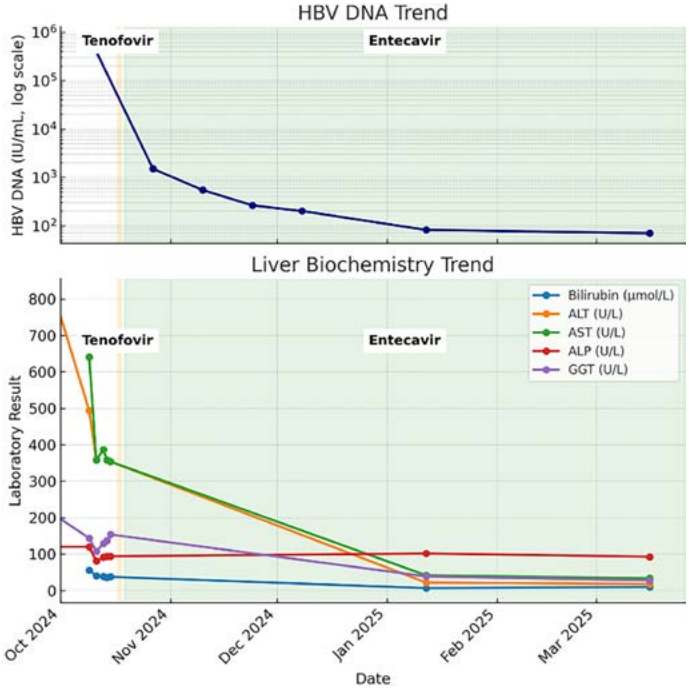


Figure 1. Trends in hepatitis B virus DNA and liver biochemistry.

Table 1. Literature review of case reports of HBV reverse seroconversion in the absence of immunosuppression

Parameter	Current Case Report	Freudiger et al. (2004)[2]	Deroux et al. (2012)[3]	Kamitsukasa et al. (2015)[5]	Kim et al. (2018)[6]	Ozturk Cerik et al. (2025)[4]
Age	88	73	84	74	82	81
Sex	Female	Female	Male	Male	Male	Female
Baseline HBsAg	Negative	Negative	Negative	Negative	Negative	Negative
Baseline anti-HBs (mIU/mL)	180.5	13	212	12.7	Positive (titer not reported)	77.5
Baseline Anti-HBc	Positive	Positive	Positive	Not available	Not available	Positive
Trigger	None identified	None identified	Ischemic stroke	Post-CABG	None identified	Hemorrhagic stroke
Comorbidities/ Clinical characteristics	Advanced age, remote cured HCV	Advanced age, CKD with hemodialysis, COPD, HTN, PVD, osteoporosis	Advanced age, diabetes, HTN, IHD, COPD, sleep apnea	Not reported, advanced age	Iron deficiency anemia, vertebroplasty 5 years ago	Advanced age, COPD, HTN, diabetes

Anti-HBc: Hepatitis B core antibody; Anti-HBs: Hepatitis B surface antibody; COPD: Chronic obstructive pulmonary disease; HTN: Hypertension; PVD: Peripheral vascular disease; CKD: Chronic kidney disease; HCV: Hepatitis C virus; IHD: Ischemic heart disease; CABG: Coronary artery bypass grafting.

presented a case of spontaneous reactivation in an elderly male with no evident trigger, further supporting immune senescence as an independent risk factor.

Our patient shared several features with previously reported cases, including advanced age, no recent immunosuppression, and a long-standing resolved HBV infection with anti-HBs positivity. Her case is unique in that there was no identifiable trigger, she had markedly high anti-HBs, and she was otherwise healthy with minimal medical complexity compared to other reported cases.

Importantly, she also had a history of HCV coinfection that had been successfully treated 10 years previously. HBV–HCV coinfection is not uncommon, given the shared routes of transmission, and is clinically important because it often results in a more severe course of liver disease, faster progression to cirrhosis, and an increased risk of hepatocellular carcinoma compared to monoinfection.[7] At a virological level, HCV often exerts a suppressive effect on HBV replication through direct viral interactions. Clearance of HCV with direct-acting antivirals (DAAs) can remove this suppressive pressure, leading to latent HBV reactivation, which, in rare cases, can progress to fulminant hepatitis requiring a transplant.[1] Conversely, HBV can sometimes suppress HCV replication, though this phenomenon is less well described and less common.[8]

Given these interactions, the European Association for the Study of the Liver (EASL) recommends HBV screening in all patients undergoing HCV treatment, with consideration of prophylactic or preemptive HBV antiviral therapy in those at risk of reactivation who do not otherwise meet criteria for chronic HBV treatment.[9] Most reported cases of HBV reactivation after HCV cure occur within months of DAA therapy, underscoring the importance of close monitoring after HCV eradication. EASL recommends continuing nucleos(t)ide analogue therapy for at least 12 weeks following HCV treatment.[9] In our patient, however, reactivation occurred more than a decade after HCV cure, making it unlikely to be directly attributable to the loss of HCV-mediated suppression. Nevertheless, her history of dual infection may have predisposed her to late reactivation in the setting of immune senescence. This highlights the clinical importance of long-term vigilance in patients with resolved HBV, even when HCV has been eradicated.

Conclusion

In summary, this case adds to the sparse literature showing that reverse HBV seroconversion can occur spontaneously in immunocompetent individuals, particularly the elderly. We suspect that many more cases have been unreported and perhaps even unrecognized. Clinicians should maintain long-term vigilance in patients with resolved HBV infection, especially those with prior HCV coinfection, as immune senescence or subtle physiologic stressors may precipitate reactivation even years after apparent viral control.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: The patient has provided informed consent for publication of the case.

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

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

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Peer-review: Externally peer-reviewed.

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HEPATOLOGY FORUM

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CASE REPORT

Artemisia absinthium (wormwood)–induced toxic hepatitis: First reported cases with contrasting clinical outcomes

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Clinical Pearls

- **Unique Features of the Case:** Two cases of *Artemisia absinthium*-induced toxic hepatitis are described. A 24-year-old woman recovered after 6 days of 5 g daily, while a 52-year-old man developed acute liver failure, required a transplant, and died after 1 week of 10 g twice daily. These are the first documented cases of wormwood-induced hepatotoxicity.
- **Primary Lesson for Clinicians:** These cases highlight the hepatotoxic risk of *Artemisia absinthium*. Clinicians should monitor liver function in patients using herbal products and exercise caution. Further research is needed to define safe usage limits.

ABSTRACT

Artemisia absinthium (wormwood) is a widely used herbal product believed to possess hepatoprotective and anti-inflammatory properties; however, its volatile component, thujone, may cause hepatotoxicity under certain conditions. Reports of *A. absinthium*–induced liver injury in humans are extremely rare. We describe two cases of toxic hepatitis following *A. absinthium* use with contrasting clinical outcomes. The first patient, a 24-year-old woman, consumed 5 g daily for six consecutive days to enhance lactation and recovered completely with supportive treatment. The second patient, a 52-year-old man, used approximately 10 g twice daily for one week to relieve urinary complaints, developed acute liver failure, underwent liver transplantation, and subsequently died. To our knowledge, these are the first documented human cases of *A. absinthium*–associated hepatotoxicity. These cases highlight the potential hepatotoxic risk of uncontrolled herbal use and emphasize the need for further studies to define its hepatotoxic potential.

Keywords: *Artemisia absinthium*; herbal hepatotoxicity; toxic hepatitis.

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Introduction

Herbal remedies are widely used under the assumption that they are "natural" and therefore harmless; however, they may not always be innocuous. Even seemingly safe herbal products can cause serious hepatotoxic events, ranging from mild aminotransferase elevations to fulminant hepatic failure.[1] *Artemisia absinthium* (wormwood) has traditionally been used to stimulate appetite, relieve dyspepsia, treat parasitic infections, and alleviate pain and inflammation.[2]

Although *A. absinthium* has been reported to exhibit hepatoprotective and anti-inflammatory effects, inappropriate or prolonged use has been associated with hepatotoxicity in both experimental and limited clinical observations.[3,4] We report two patients who developed toxic hepatitis following *A. absinthium* ingestion—one recovered fully with supportive treatment, whereas the other developed acute liver failure and died after liver transplantation. To our knowledge, these are the first documented human cases of *A. absinthium*–associated hepatotoxicity.

Case Reports

Case 1

A 24-year-old woman consumed approximately 5 g of *Artemisia absinthium* (wormwood) once daily for six consecutive days by brewing it in hot water to promote lactation. She had no history of concomitant medication or other herbal product use. The patient presented with fatigue and jaundice. On admission, laboratory evaluation revealed aspartate aminotransferase (AST) 1618 U/L, alanine aminotransferase (ALT) 1655 U/L, total bilirubin 15.7 mg/dL, direct bilirubin 8.0 mg/dL, alkaline phosphatase (ALP) 266 U/L, γ-glutamyl transferase (GGT) 144 U/L, lactate dehydrogenase (LDH) 569 U/L, and international normalized ratio (INR) 1.5. Renal function tests were within normal limits.

Serologic markers for viral hepatitis (HAV IgM, HBsAg, Anti-HBc IgM, Anti-HCV, HEV IgM, CMV IgM, EBV VCA IgM, HSV IgM, VZV IgM, Mumps IgM, Rubella IgM, Parvovirus B19 IgM, and SARS-CoV-2 PCR) and autoimmune hepatitis (ANA, ASMA, AMA, LKM-1) were negative, with serum IgG levels within the normal range. Other infectious etiologies of acute hepatitis were serologically excluded. The calculated R-factor of approximately 21 indicated a hepatocellular pattern of liver injury. Wilson's disease and hemochromatosis were ruled out based on clinical and laboratory findings. Abdominal ultrasonography demonstrated parenchymal changes consistent with acute hepatitis without evidence of Budd–Chiari syndrome or vascular pathology. The biliary system was patent, with no gallstones or obstructive lesions, and intrahepatic structures appeared normal.

Supportive management consisted of intravenous N-acetylcysteine, seven sessions of plasmapheresis, and lactulose for constipation prophylaxis. The patient's laboratory course is summarized in Table 1, and dynamic changes in AST, ALT, and total bilirubin levels during hospitalization are shown in Figure 1a. According to the Roussel

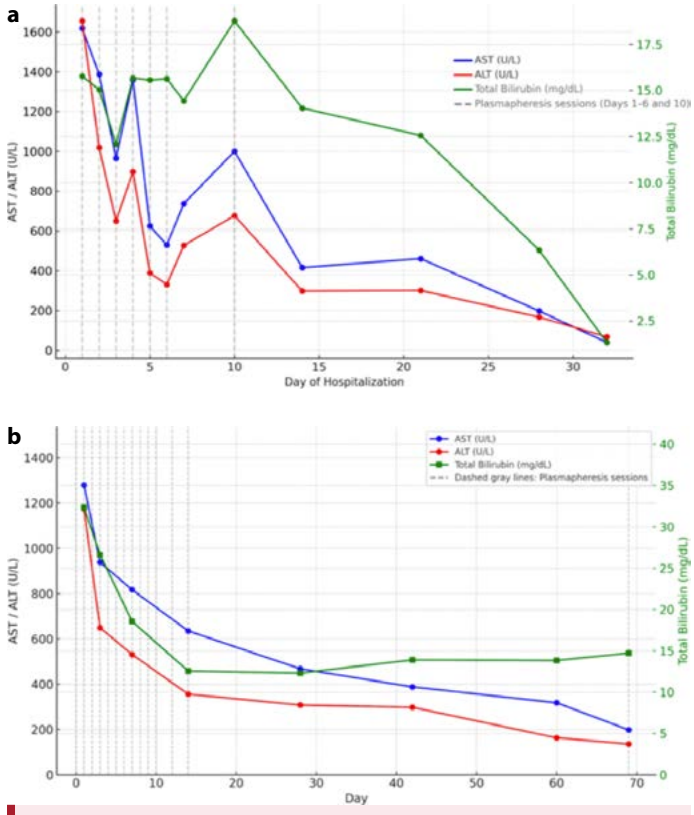


Figure 1. Dynamic changes in liver biochemistry during hospitalization. **(a)** Patient 1 showing progressive decline in AST, ALT, and total bilirubin levels following supportive management. **(b)** Patient 2 showing gradual improvement in AST, ALT, and total bilirubin levels throughout hospitalization with persistent hyperbilirubinemia despite supportive management.

Uclaf Causality Assessment Method (RUCAM), the total score was 9, indicating highly probable causality. After 32 days, she achieved complete clinical and biochemical recovery.

Case 2

A 52-year-old man consumed approximately 10 g of *Artemisia absinthium* (wormwood) twice daily, prepared as an herbal tea by steeping in hot water for one week to relieve urinary complaints. He had no history of concomitant medication or other herbal product use. The patient presented with fatigue and jaundice that developed shortly after the herbal intake. Laboratory evaluation showed markedly elevated AST (1279 U/L) and ALT (1174 U/L), prolonged INR (1.8), and severe cholestasis (total bilirubin 32.3 mg/dL, direct bilirubin 15.3 mg/dL, GGT 113 U/L). The calculated R-factor of approximately 30 indicated a hepatocellular pattern of liver injury.

Vascular and biliary causes were excluded by imaging, and serologic testing for acute viral hepatitis (HAV IgM, HBsAg, Anti-HBc IgM, Anti-HCV, HEV IgM, CMV IgM, EBV VCA IgM, HSV IgM, VZV IgM, Mumps IgM, Rubella IgM, Parvovirus B19 IgM, and SARS-CoV-2 PCR) and autoimmune hepatitis (ANA, ASMA, AMA, LKM-1) was negative, with serum IgG levels within the normal range. Abdominal

Table 1. Laboratory findings and biochemical course of the patients during hospitalization

Day	Total protein (g/dL)	Albumin (g/dL)	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)	INR	Plas.
Case 1										
1	6.0	3.8	15.77	8.02	1618	1655	266	144	1.50	✔
2	5.1	3.1	15.04	8.06	1387	1019	163	79	1.48	✔
3	5.2	3.1	12.08	6.71	965	650	132	50	1.43	✔
4	5.5	3.3	15.67	8.08	1359	898	154	63	1.40	✔
5	5.4	3.3	15.56	7.62	625	389	117	44	—	✔
6	5.4	3.3	15.63	7.75	529	331	104	37	—	✔
7	5.0	3.2	14.43	7.25	737	527	—	—	1.30	—
10	5.0	3.1	18.76	8.71	1000	677	127	—	1.27	✔
14	5.2	3.3	14.04	6.57	416	298	117	31	1.20	—
21	4.9	3.1	12.56	6.12	461	301	122	35	1.20	—
28	4.9	2.9	6.34	2.59	198	167	—	—	1.18	—
32	4.9	2.9	1.34	0.59	40	68	—	—	1.12	—
Case 2										
1	7.0	3.8	32.35	15.31	1279	1174	78	113	1.80	✔
3	5.3	3.2	26.63	13.57	938	649	65	42	1.60	✔
7	5.6	3.6	18.55	9.99	817	531	87	34	1.50	✔
14	5.3	3.5	12.56	6.87	635	356	95	35	1.40	✔
28	5.4	3.4	12.31	7.14	468	308	—	—	1.37	—
42	6.1	3.6	13.90	6.51	388	298	130	75	1.42	—
60	5.4	3.1	13.84	6.53	318	163	138	43	1.38	—
69†	5.1	2.9	14.71	7.13	198	136	89	39	2.20	✔

†Day 69: Development of hepatic encephalopathy before liver transplantation. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ALP: Alkaline phosphatase; GGT: Γ-glutamyl transferase; INR: International normalized ratio; Plas: Plasmapheresis.

ultrasonography revealed findings compatible with acute hepatic failure without vascular obstruction or biliary dilatation. Serial laboratory data during hospitalization are summarized in Table 1, and dynamic trends of AST, ALT, and total bilirubin levels are illustrated in Figure 1b. According to RUCAM, the total score was 9, indicating highly probable causality.

The patient received supportive management for 69 days, including intermittent plasmapheresis, branched-chain amino acid infusions, L-ornithine L-aspartate, lactulose, dextrose infusions, and broad-spectrum antibiotics. Gradual clinical improvement was observed during the first four weeks, followed by a stable course until week 10. On day 69, hepatic encephalopathy developed, and cadaveric liver transplantation was performed on day 71. The patient died 25 days after transplantation due to multiorgan failure. Histopathological examination of the explanted liver revealed extensive hepatocellular loss, marked portal inflammation, cholestasis, ductular proliferation, and pericellular fibrosis, consistent with toxic hepatitis.

Written informed consent was obtained from both patients for publication of this case report.

Discussion

The use of herbal products is a well-recognized cause of drug-induced liver injury.[1] Although *Artemisia absinthium* (wormwood) has often been highlighted for its hepatoprotective properties, we report two cases of toxic hepatitis associated with its use, one of which resulted in death. To our knowledge, this is the first case series describing *A. absinthium*–related herbal hepatotoxicity.

Several experimental studies have demonstrated the antioxidant, anti-inflammatory, and hepatoprotective effects of *A. absinthium*, attributed mainly to its polyphenolic compounds and sesquiterpene lactones such as absinthin.[2,3] However, in an experimental model, Barreto et al.[5] showed that *A. absinthium* reduced profibrogenic markers yet disrupted lipid metabolism and induced cellular stress

by activating detoxification and pro-inflammatory pathways. In our cases, severe hepatocellular injury following high-dose and repeated exposure may represent a clinical correlate of these experimentally observed toxicity mechanisms.

Hepatotoxicity associated with Artemisia species has been previously reported. Artemisia annua–related liver injury was first described by Kumar et al.,[6] and a similar case was later reported by Ruperti-Repilado et al.[7] In both reports, initial hepatocellular enzyme elevations were followed by a predominance of cholestatic features during the clinical course. A comparable trend was observed in our series: in the first patient, short-term, low-dose exposure led to complete recovery without cholestatic progression, whereas the second patient, who had higher and more prolonged exposure, progressed from hepatocellular to cholestatic injury, ultimately requiring liver transplantation. These findings suggest a dose- and duration-dependent pattern of liver injury in *A. absinthium* toxicity.

Among the volatile constituents of *A. absinthium*, thujone and other mono- and sesquiterpene derivatives are considered the main compounds responsible for its toxic potential.[8] Thujone exhibits neurotoxicity through γ-aminobutyric acid (GABA-A) receptor antagonism,[9] but its hepatic effects remain incompletely understood. Experimental models have shown that excessive or prolonged exposure can induce oxidative stress, mitochondrial dysfunction, and hepatocellular apoptosis.[9] The European Medicines Agency (EMA) recommends that daily thujone exposure from *A. absinthium* preparations should not exceed 6 mg per day.[3] Importantly, no standardized dosage or preparation method exists for *A. absinthium*, and considerable variability in thujone concentration depends on geographic origin, harvest time, and extraction technique. Although compound levels were not measured in our patients, the development of severe hepatocellular injury after approximately 10 g twice daily for one week in the second case supports a dose- and duration-dependent toxic effect.

Conclusion

In conclusion, this case series highlights *A. absinthium* as a potential cause of toxic hepatitis. Unsupervised or prolonged use of wormwood preparations may result in severe and irreversible liver injury. Further research is needed to clarify the mechanisms and establish safe dosage limits for this widely used herbal product.

Informed Consent: Written informed consent was obtained from participants.

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

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Peer-review: Externally peer-reviewed.

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CASE REPORT

Mauriac syndrome: A rare complication of uncontrolled type 1 diabetes mellitus in childhood - A case report

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Clinical Pearls

- **Unique Features of the Case:** Mauriac syndrome occurred in a child with poorly controlled T1DM, presenting with hepatomegaly, growth failure, delayed puberty, and elevated liver enzymes.
- **Primary Lesson for Clinicians:** Consider Mauriac syndrome in children with poorly controlled T1DM and hepatomegaly. Early recognition, sustained glycemic control, diabetes education, regular follow-up, psychosocial support, and treatment adherence may prevent recurrence and long-term complications.

ABSTRACT

Mauriac syndrome is a rare but reversible complication of long-standing, poorly controlled type 1 diabetes mellitus (T1DM) in children. It is characterized by growth failure, delayed puberty, hepatomegaly due to hepatic glycogen accumulation, and metabolic abnormalities. An 11-year-old girl with T1DM for 6 years, on irregular insulin therapy, presented with progressive abdominal distension for 1 year, poor linear growth, and visual disturbances. Examination revealed short stature, delayed pubertal development, hypertension, and marked hepatomegaly. Investigations showed poor glycemic control, elevated transaminases, hypertriglyceridemia, delayed bone age, and bilateral diabetic cataracts. Viral, autoimmune, metabolic, and endocrine causes of liver disease were excluded. Imaging revealed hepatomegaly without fibrosis. Liver biopsy demonstrated glycogen-laden hepatocytes, confirming glycogenic hepatopathy. The child was initiated on an intensive basal–bolus insulin regimen with comprehensive diabetes education. On follow-up, there was a significant reduction in hepatomegaly with better glycemic control. Mauriac syndrome should be considered in children with poorly controlled T1DM presenting with hepatomegaly and growth failure.

Keywords: Diabetes, growth failure, hepatomegaly.

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Introduction

Mauriac syndrome is a rare complication of long-standing, poorly controlled type 1 diabetes mellitus (T1DM) in children and adolescents. It is classically characterized by growth retardation, delayed pubertal development, and hepatomegaly secondary to excessive hepatic glycogen accumulation.[1,2] Although the incidence of Mauriac syndrome has markedly declined with the advent of modern insulin regimens and improved glycemic monitoring, sporadic cases continue to be reported, particularly among patients with poor metabolic control or erratic insulin adherence.[3]

There is hepatic glycogenesis, which manifests clinically as hepatomegaly and biochemically as mild-to-moderate elevations in serum transaminases.[4,5] In addition, disruption of the growth hormone–insulin-like growth factor-1 (GH–IGF-1) axis and relative hypercortisolism are thought to contribute to growth failure and delayed pubertal development observed in affected children.[6]

Despite its rarity in the current era, recognition of Mauriac syndrome remains clinically important because of its reversible nature. Optimization of insulin therapy and sustained glycemic control have been shown to result in regression of hepatomegaly, normalization of liver enzymes, and improvement in growth parameters.[7] This report aims to highlight the clinical features, diagnostic challenges, and therapeutic implications of Mauriac syndrome in contemporary pediatric diabetes care.

Case Report

An 11-year-old female child with a normal birth and development history was diagnosed with T1DM since 5 years of age and is on insulin therapy, but non-adherent to treatment. She presented with complaints of abdominal distension for 1 year, poor height gain for the last 5 years and blurring of vision for 2 months. Abdominal distension was not associated with jaundice, abdominal pain, bleeding manifestations, chronic diarrhea or constipation. She was started on regular insulin and long-acting insulin (glargine) at 1 unit/kg/day at diagnosis; however, she was not compliant due to financial constraints. She had poor glycemic control for the last 5 years, requiring four admissions to hospitals with complaints of vomiting and respiratory difficulty. The mother was being treated for hypothyroidism. On examination, she had pallor but no icterus, cyanosis, clubbing, edema, or lymphadenopathy. Anthropometry revealed short stature with a height-for-age Z score of -3.17. Midparental height could not be calculated as the father had died 5 years earlier due to alcoholic liver disease. Lipohypertrophy was noted at insulin injection sites. She had sexual maturity rating, Tanner stage 1. Blood pressure recordings at regular intervals with a digital sphygmomanometer showed hypertension (average systolic pressure above 95th percentile for her age, sex and height as per the Indian Academy of Pediatrics blood pressure charts).

Abdominal examination revealed a soft, distended abdomen with dilated superficial veins. The liver was palpable 8–12 cm below the right costal margin, firm, non-tender, with a smooth surface. The spleen was not palpable. The rest of the systemic examinations were normal. Investigations revealed poor glycemic control with hemoglobin A1c (HbA1c) of 11%. IGF-1 levels were not done due to financial constraints. Liver transaminases were elevated (aspartate aminotransferase 216 IU/L, alanine aminotransferase 462 IU/L) with normal serum bilirubin, serum albumin and coagulation profile. Her kidney function tests were normal. Triglyceride levels were elevated (485 mg/dL). Viral hepatitis markers and autoimmune hepatitis panel (antinuclear antibodies, anti-smooth muscle antibodies, and anti-liver kidney microsomal antibodies) were negative. Ophthalmological evaluation showed no Kayser–Fleischer ring with normal serum ceruloplasmin levels. Thyroid function tests and celiac serology were normal. Bone age was delayed (8–9 years). Other laboratory values are depicted in Table 1. Ultrasonography of the abdomen showed hepatomegaly with normal portal venous flow. FibroScan with M probe revealed steatosis with no evidence of hepatic fibrosis. Her 2D-Echocardiogram and renal artery Doppler were normal. Ophthalmological evaluation showed bilateral diabetic cataracts without evidence of diabetic retinopathy. A liver biopsy was done, and histopathology showed enlarged hepatocytes with pale cytoplasm and glycogen in hepatocytes with periodic acid–Schiff (PAS) staining (Figs. 1, 2). Based on the clinical profile of growth failure, hepatomegaly, poor glycemic control, and supportive investigations of liver biopsy and FibroScan, a diagnosis of Mauriac syndrome (glycogenic hepatopathy) was made. Considering the clinical presentation, Cushing syndrome was considered a differential diagnosis and evaluated with morning 8 am cortisol of 40.20 (4.82–19.5). However, the histopathology of the liver showed glycogen deposition with no signs of fibrosis; raised cortisol was attributed to poorly controlled hyperglycemia, altering the circadian rhythm of cortisol. The child was initiated on a structured basal–bolus insulin regimen using insulin glargine and insulin aspart, with a total daily dose of approximately 1.25 U/kg/day. Intensive diabetes education, carbohydrate counting, hypoglycemia management, and injection site rotation were reinforced. Vitamin D and calcium supplementation were initiated, and antihypertensive therapy was started with close monitoring. At the 15-day follow-up, the child showed a reduction in abdominal distension, a decrease in liver size with liver palpable 2 cm below the right costal margin, and improved adherence to insulin therapy with better glycemic monitoring. We had planned to monitor liver function tests, HbA1c levels, liver ultrasound, growth monitoring and ophthalmic re-examination after at least 1 month of initiation of treatment; however, the child has not followed up after the first follow-up visit.

Discussion

Mauriac syndrome results from chronic insulin deficiency with intermittent hyperglycemia leading to excessive hepatic glycogen accumulation. Hepatomegaly, growth retardation, delayed bone age, and dyslipidemia are hallmark features.[4] Glycogenic hepatopathy must be differentiated from non-alcoholic fatty liver disease (NAFLD), as the former is potentially reversible with strict glycemic control. Early diagnosis and sustained metabolic control can lead

Table 1. Laboratory findings

	16/9/25	19/9/25	22/9/25	24/9/25	5/10/25
Hemoglobin (g/dL)	13.2			12.8	11.9
Total leukocyte count (×1000/µL)	6.5			10.1	7.52
Platelet count (×1000/µL)	488			437	520
Total bilirubin (mg/dL)	0.5			0.6	
Direct bilirubin (mg/dL)	0.2			0.3	
AST (U/L)	216			282	
ALT (U/L)	462			392	
Serum creatinine (mg/dL)	0.3			0.4	
Pre-feed blood glucose (mg/dL)	344	302	286	210	126
Post-feed blood glucose (mg/dL)	565	556	465	387	202
HbA1c (%)	11				
Serum cholesterol (mg/dL)	382				
LDL (mg/dL)	310				
HDL (mg/dL)	49.9				
Triglycerides (mg/dL)	485				
Cortisol (µg/dL)	40.20				

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

to significant clinical improvement and prevent progression to liver fibrosis. The present case highlights the classical clinical spectrum of Mauriac syndrome. The child had long-standing poor glycemic control, evidenced by persistently elevated HbA1c levels, growth retardation with delayed bone age, delayed pubertal development, dyslipidemia, and marked hepatomegaly. The pathophysiology of Mauriac syndrome involves chronic insulin deficiency interspersed with episodes of relative insulin excess, which promotes excessive hepatic glucose uptake and glycogen deposition.[4] This abnormal glycogen accumulation leads to hepatic glycogenosis, manifesting as hepatomegaly and elevation of liver transaminases, as observed in this patient.[5] Growth failure in Mauriac syndrome is multifactorial. Poor metabolic control leads to disruption of the GH–IGF-1 axis, reduced hepatic IGF-1 production, and relative hypercortisolism, all

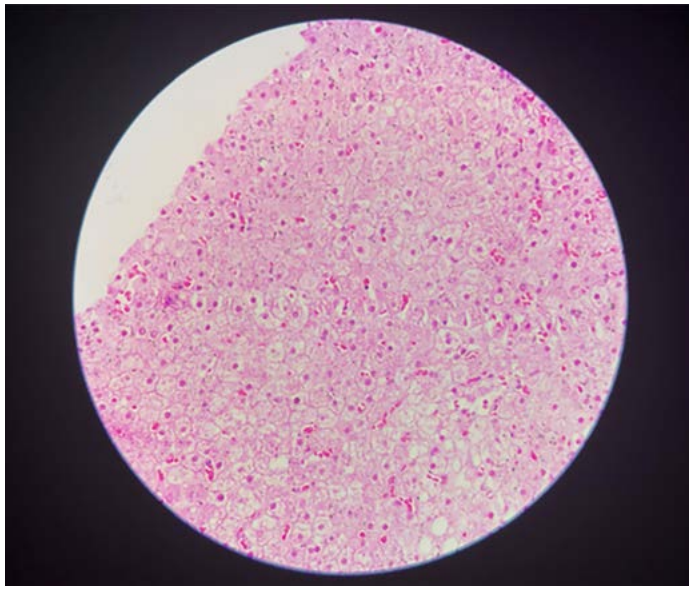


Figure 1. Liver histopathology with PAS staining showing glycogen accumulation in cytoplasm of hepatocytes.

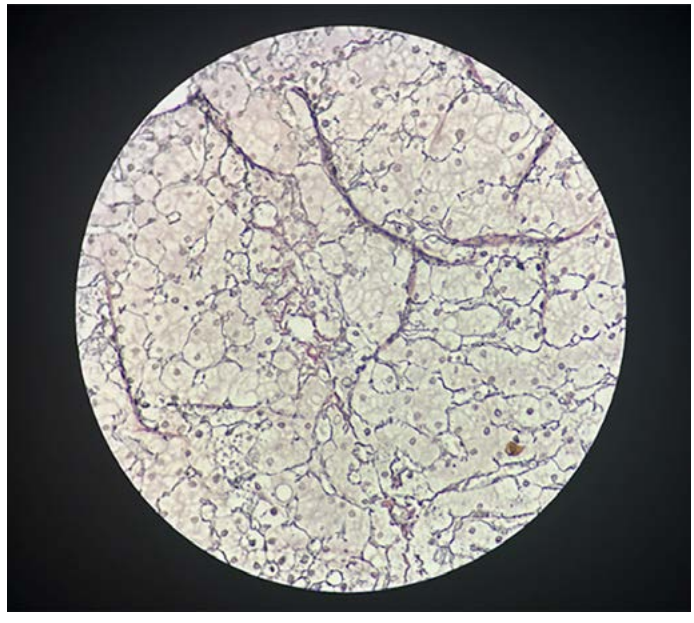


Figure 2. Liver histopathology showing pale swelling of hepatocytes.

of which contribute to impaired linear growth and delayed skeletal maturation.[6] In our case, the child had a significantly low height-for-age Z score and delayed bone age, supporting these mechanisms. In addition, delayed sexual maturation (Tanner stage I) further underscores the impact of prolonged metabolic derangement on pubertal development. Differentiating glycogenic hepatopathy from NAFLD is clinically important, as both conditions may present with hepatomegaly and elevated transaminases in children with T1DM. However, NAFLD is associated with insulin resistance and carries a risk of progression to fibrosis, whereas glycogenic hepatopathy is largely benign and reversible.[7] In this case, the absence of fibrosis on FibroScan, normal synthetic liver function, and liver biopsy findings of PAS-positive glycogen accumulation without significant inflammation or fibrosis confirmed the diagnosis of glycogenic hepatopathy. The presence of diabetic cataract in this child further reflects the chronicity and severity of hyperglycemia. Ocular involvement, though less frequently reported in Mauriac syndrome, emphasizes the systemic impact of prolonged poor glycemic control. Importantly, with initiation of a structured basal–bolus insulin regimen and intensive diabetes education, the child demonstrated clinical improvement, including reduction in hepatomegaly and abdominal distension. This favorable response reinforces existing evidence that strict glycemic control can lead to rapid and sustained reversal of hepatic and growth abnormalities in Mauriac syndrome.[7]

Conclusion

Mauriac syndrome should be considered in children with T1DM presenting with hepatomegaly and growth failure. Early recognition, continuous diabetes education and social support are essential to prevent recurrence. Mauriac syndrome, though rare in the modern era of diabetes management, remains a relevant clinical entity in children with poorly controlled T1DM. This case underscores the importance of considering Mauriac syndrome in children presenting with hepatomegaly, growth failure, delayed puberty, and elevated liver enzymes. Comprehensive diabetes education, regular follow-up, psychosocial support, and reinforcement of treatment adherence are crucial to prevent recurrence and long-term complications. Awareness of this condition among clinicians can facilitate timely intervention and significantly improve clinical outcomes.

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's parent/legal guardian for the publication of this case and accompanying images.

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

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Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

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Peer-review: Externally peer-reviewed.

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LETTER TO THE EDITOR

Response to "Endoscopic ultrasound strain elastography in metabolic dysfunction-associated steatotic liver disease: Evaluation against transient elastography and non-invasive markers"

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To the Editor,

We read with great interest the article recently published by Helal et al.[1] wherein the authors compared endoscopic ultrasound strain elastography with vibration-controlled transient elastography and non-invasive markers such as the controlled attenuation parameter, liver stiffness measurement (LSM), fatty liver index, and fibrosis index based on six parameters (FIB-6) to assess the diagnostic performance of endoscopic ultrasound (EUS) strain elastography parameters in patients with metabolic dysfunction-associated steatotic liver disease (MASLD). The idea of using EUS as a "one-stop-shop" diagnostic modality during indicated upper gastrointestinal endoscopy sessions is both novel and clinically appealing, and the study adds new evidence to the expanding body of literature supporting the role of EUS elastography in assessing liver disease. However, before their conclusions can be widely accepted, we would like to raise several methodological considerations that merit careful examination.

We recognize that this work is novel, but there are a few methodological issues that need to be addressed. Most importantly, the validity of the results is severely limited by the lack of liver biopsy as the reference standard. Circular validation occurs when a new diagnostic tool is validated against various non-invasive markers instead of the histological gold standard. This results in the reported Area Under the Receiver Operating Characteristic Curve (AUROC) values being merely agreement indices rather than actual measurements of diagnostic accuracy.[2] In addition, the FIB-6, developed and validated by co-author Shiha, was used as the main reference standard for fibrosis assessment. We believe this represents a potential source of circularity worth noting for readers, and would encourage the authors to explicitly address this relationship in the conflict-of-interest disclosure in future correspondence or revisions.[3] Furthermore, the strain ratio AUROC against LSM for this group was only 0.677, slightly above chance, with a borderline p=0.048 that would not withstand correction for multiple comparisons. Only 14 patients were eligible for the advanced fibrosis subgroup analysis.[4]

In addition to the aforementioned issues, we would like to raise the possibility of selection bias related to the study's enrollment process. Of the 742 MASLD patients initially interviewed, only 150 were indicated for upper GI endoscopy; of these, 75 (50%) proceeded to EUS, whereas 75 were excluded for four distinct reasons, including 45 (30% of those indicated) who declined participation, alongside 17 excluded for other chronic liver disease, 6 for anesthesia-related high risk, and 7 for large or risky varices or severe portal hypertensive gastropathy. To our reading, the published flowchart does not report a comparison of baseline characteristics between those who declined and those who proceeded to EUS. Given that EUS involves sedation and carries inherent procedural risk, this may merit further consideration, as patients who consented to participate could plausibly differ from those who declined in terms of disease severity, comorbidity burden, or risk tolerance.[5] Without sufficient explanation or dropout analysis, this level of attrition could possibly compromise the study's internal validity. As recommended by the Strengthening The Reporting Of Observational Studies In Epidemiology guidelines for observational studies, which encourage authors to record reasons for non-participation in order to enable readers to evaluate the representativeness of the final study cohort more thoroughly, we kindly request that future iterations of this work take into account reporting baseline characteristics of non-participating patients at each stage of enrolment.[6]

In conclusion, we acknowledge the significant diagnostic utility of the authors' creative "one-stop-shop" idea and strongly appreciate their pioneering efforts in examining EUS strain elastography as a

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unique diagnostic tool in MASLD. However, considering the lack of histological confirmation, the possible conflict of interest in reference standard selection, the underpowered subgroup analyses, and the cohort's restricted generalizability, we kindly advise that the current findings be interpreted cautiously. The true diagnostic potential of EUS strain elastography in MASLD will be further illuminated by future larger, multicenter, biopsy-validated studies from this group. We genuinely hope that these insights are received in the constructive spirit in which they are intended.

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REPLY TO THE LETTER TO THE EDITOR

Reply to Khan and Shoro: Endoscopic ultrasound strain elastography in metabolic dysfunction-associated steatotic liver disease: Evaluation against transient elastography and non-invasive markers

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3: Egyptian Liver and Research Institute and Hospital (ELRIAH), Sherbin, Mansoura, Egypt

We thank Khan and Shoro for their constructive critique,[1] and we hope this expert scientific argument will add value to the original manuscript.[2] Three main points were addressed in the letter:

Absence of Liver Biopsy as the Gold Standard Reference

The standards for reporting of diagnostic accuracy studies (STARD) guidelines (2015)[3] are the primary guidelines for diagnostic accuracy research. STARD accepts the use of a non-gold reference standard or a less accurate reference test.[3] It adds that researchers may choose different tests for clinical, practical, or ethical reasons, provided that they explain why.[3] STARD also requires mentioning any limitations that may affect the results.[3] We followed these statements in our study. We used a non-invasive, non-gold-standard test to minimize invasiveness during the initial evaluation of endoscopic ultrasound (EUS) strain elastography parameters in patients with metabolic dysfunction-associated steatotic liver disease (MASLD), as noted in our manuscript.[2] In addition, our limitations section clearly notes the absence of a liver biopsy and recommends biopsy-based studies for validation.[2] In fact, we later began a biopsy-based study to confirm these findings.

In addition, many studies have tested EUS elastography against non-invasive methods. For example, Schulman et al.[4] compared an EUS elastography-based liver fibrosis (FIB) index with abdominal imaging to diagnose steatosis, FIB, or normal tissue. Robles-Medranda et al.[5] compared EUS elastography with vibration-controlled transient elastography (VCTE) for detecting portal hypertension in chronic liver disease. AbiMansour et al.[6] evaluated EUS shear wave elastography in relation to clinically significant portal hypertension and magnetic resonance elastography.

Finally, circular validation occurs when an argument uses its own conclusions as evidence.[7] This is not the case in our study, as the diagnostic value of EUS elastography has not been proven by a test that depends on it.[2]

FIB Reference Tests in Our Study

Shiha et al. (Shiha is a co-author of the current study) developed FIB-6 (Fibrosis-6, or Fibrosis Index Based on 6 factors), which has been validated against liver biopsy in three distinct international multicenter studies, including a total of 10,313 patients.[8–10] In addition, Kahramanoglu Aksoy et al. conducted an independent biopsy-based study and showed that FIB-6 is superior to FIB-4.[11] Simas et al.[12] conducted a real-world, independent evaluation of FIB-6 against VCTE and found that it outperforms FIB-4 and the Aspartate Aminotransferase-to-Platelet Ratio Index. These two later studies are independent of the current study's authors. Overall, FIB-6 is a well-established, internationally validated, biopsy-proven, real-world-tested tool for assessing liver fibrosis. In addition, it is now the standard non-invasive test for fibrosis at our center.

Our results showed that liver strain ratio (SR) (Area Under the Receiver Operating Characteristic curve [AUROC]=0.707, and p=0.002) and liver strain histogram (SH) Mode% (AUROC=0.725, p<0.001) could diagnose significant fibrosis (stage ≥F2) when referenced by FIB-6 (FIB-6 ≥2.003).[2] On the other hand, we acknowledge that the advanced fibrosis analysis against VCTE included only 14 patients, with an AUROC of 0.677 (p=0.048) and should therefore be interpreted cautiously.[2]

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Not Providing the Data of the Non-Included Patients

To assess potential risk of bias, STARD recommends sharing the study flow chart with the actual number of patients at each step (as done in our study), rather than reporting data for all patients at each step.[3] Moreover, patients not included in the study did not consent to participate in the research or to share their data.

We acknowledge that non-participation among patients eligible for endoscopy may introduce selection bias and limit generalizability. However, the MASLD clinic at our center conducts a screening program for MASLD in our locality, and many patients are not bothered by their symptoms and are unwilling to proceed to subsequent steps, such as endoscopy. In our limitations section, we recommend further assessment with broader and more diverse populations to improve the "generalizability" of the outcomes.[2]

Conclusion

We reiterate our findings: EUS strain elastography parameters "may help" identify steatosis and FIB in patients with MASLD. However, further studies are needed to validate them against "liver biopsy" and to help "generalize" the findings of the current study.[2]

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

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

Use of Artificial Intelligence: Artificial intelligence was not used in the preparation of the article.

Peer-review: Externally peer-reviewed.

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RETRACTION NOTICE

Retraction Notice: Safety and hemostatic effect of *Achillea millefolium L.* in localized bleeding

The article entitled "**Safety and Hemostatic Effect of *Achillea millefolium L.* in Localized Bleeding**" is being retracted due to its inadvertent duplicate publication in *Hepatology Forum*.

The original and valid version of the article was published in *Hepatology Forum*, Volume 5, Issue 1 (2024), and is available under PMID: 38283274 and DOI: **10.14744/hf.2022.2022.0041**. This original publication remains valid and unaffected.

The duplicate version was subsequently published in *Hepatology Forum*, Volume 6, Issue 1 (2025), under PMID: 40255953 and DOI: **10.14744/hf.2022.2022.0041b**. This subsequently published version is hereby retracted to eliminate the duplicate entry from the scholarly record.

This retraction results solely from an inadvertent error in the journal's publication process and does not reflect any concerns regarding the scientific validity or integrity of the article or the conduct of its authors.

The editorial office of *Hepatology Forum* sincerely apologizes to the authors, readers, and scientific community for this error.

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