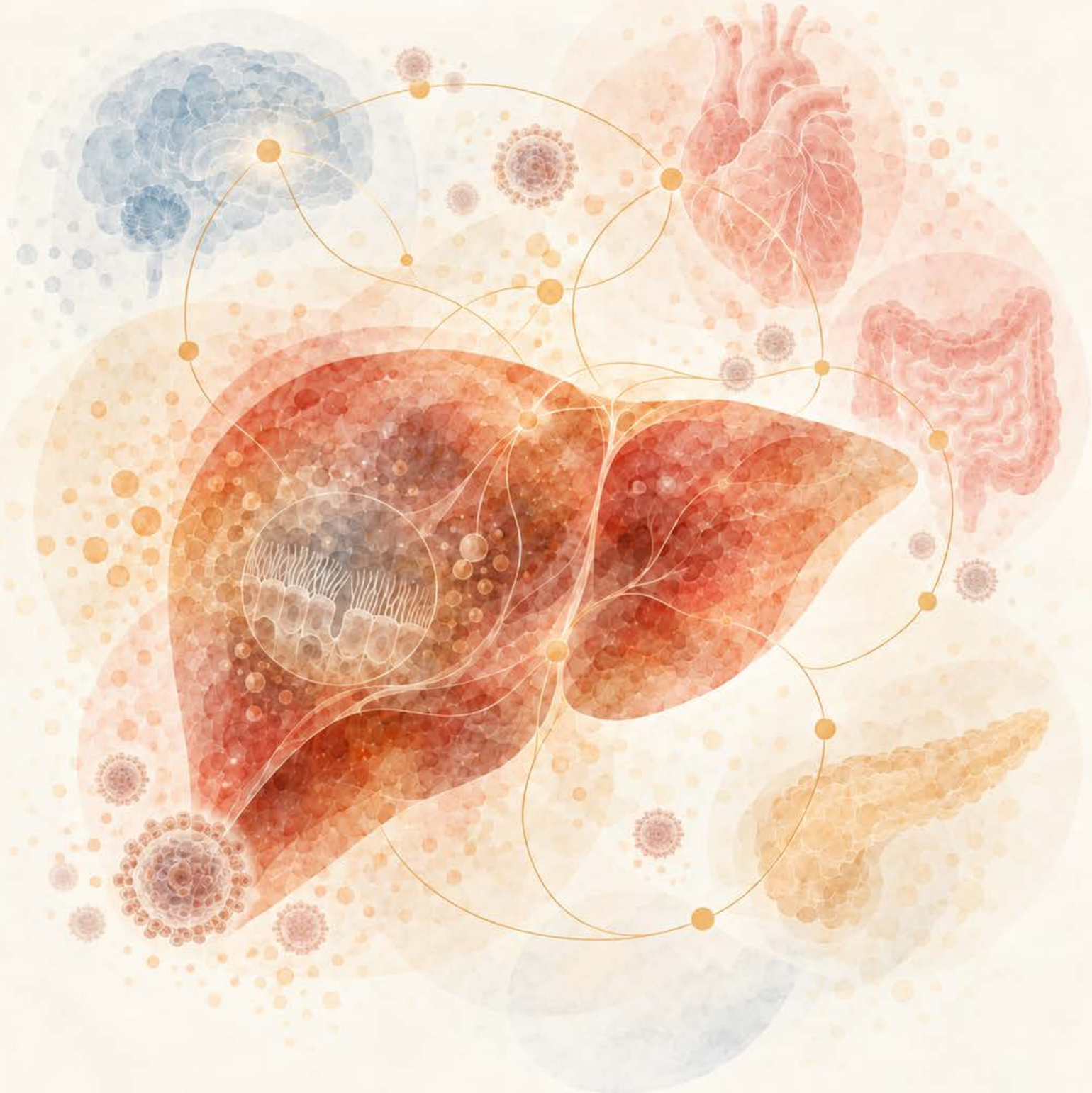
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# HEPATOLOGY FORUM



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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<br>52.5 (26–77) | 49.3±11.6<br>50.0 (26–77) | 52.8±15.4<br>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<br>18 (4–746) | 29.7±28.6<br>18 (4–121) | 85.0±201.3<br>16 (5–746) | 0.538 |
| Serum AST (U/L) | 30.1±56.8<br>18 (7–422) | 21.2±11.3<br>18 (8–66) | 58.2±112.6<br>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<br>172 (90–248) | 177.6±45.6<br>184 (94–248) | 143.3±40.5<br>143 (90–232) | **0.033** |
| HDL (mg/dL) | 41.4±14.2<br>38 (10.5–80) | 44.1±14.3<br>40 (10.5–80) | 32.6±9.9<br>31 (21–53) | **0.005** |
| LDL (mg/dL) | 103.4±38.6<br>101 (19.4–177) | 108.9±38.5<br>107 (19.4–177) | 85.9±35.0<br>79 (40–153) | 0.085 |
| Triglyceride (mg/dL) | 158.6±70.2<br>147 (58–356) | 159.5±76.8<br>142.5 (58–356) | 155.73±44.9<br>156 (88–233) | 0.811 |
| Serum creatinine (mg/dL) | 3.1±2.6<br>1.6 (0.8–10.1) | 2±1.5<br>1.5 (0.8–7) | 6.6±2.4<br>6.5 (3.1–10.1) | **<0.001** |
| Serum phosphorus (mg/dL) | 3.8±1.5<br>3.5 (1.9–7.9) | 3.3±0.9<br>3.3 (1.9–6.0) | 5.7±1.7<br>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.

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

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## References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2025;83(2):502-583.
2. Sneller L, Lin C, Price A, Kottilil S, Chua JV. RNA interference therapeutics for chronic hepatitis B: progress, challenges, and future prospects. Microorganisms 2024;12(3):599. [CrossRef]
3. Üçbilek E, Yıldırım AE, Ellik Z, Turan İ, Haktanıyan B, Orucu B, et al. Changing trends in the etiology of cirrhosis in Türkiye: a multicenter nationwide study. Turk J Gastroenterol 2024;35(10):772-777. [CrossRef]
4. Kilic G, Guvenir T, Bodakci E, Ellik ZM, Gokcan H, Idilman R. The impact of long-term potent antiviral therapy on the natural course of disease in patients with hepatitis B virus-related cirrhosis. Hepatol Forum 2025;6(4):141-145. [CrossRef]
5. Guzelbulut F, Karaogullarindan U, Akkiz H, Altintas E, Demirtas CO, Bahadir O, et al. Characteristics of patients with hepatocellular carcinoma: A multicenter study. Hepatol Forum 2022;3(3):71-76. [CrossRef]
6. Lin S, Huang W, Liao Z, Ma H, Wu W, Lin M, et al. Comparison of lipid profile alterations in chronic hepatitis B patients receiving tenofovir alafenamide or tenofovir disoproxil fumarate. Sci Rep 2024;14(1):27369. [CrossRef]
7. Lim J, Choi WM, Shim JH, Lee D, Kim KM, Lim YS, et al. Efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate in treatment-naïve chronic hepatitis B. Liver Int 2022;42(7):1517-1527. [CrossRef]
8. Dilber F, Durak S, Unsal Y, Demir M, Yildirim AE, Ellik ZM, et al. Efficacy and tolerability of tenofovir alafenamide fumarate prophylaxis in HBV-infected individuals receiving chemo/immunosuppressive therapy. Hepatol Forum 2026;7(1):26-31. [CrossRef]
9. Chan HLY, Buti M, Lim YS, Agarwal K, Marcellin P, Brunetto M, et al. Long-term treatment with tenofovir alafenamide for chronic hepatitis B results in high rates of viral suppression and favorable renal and bone safety. Am J Gastroenterol 2024;119(3):486-496. [CrossRef]
10. Tizzani M, Caviglia GP, Frasson A, Degasperi E, Viganò M, Borghi M, et al. A multicenter analysis on efficacy and safety of Tenofovir alafenamide (TAF) in a wide cohort of patients with chronic hepatitis B (CHB). Dig Liver Dis 2025;57(Suppl 1):S72-S73. [CrossRef]
11. Massih SA, Atta MG, Thio CL, Tornheim JA, Fuchs EJ, Bakshi RP, et al. Pharmacokinetics of tenofovir alafenamide, emtricitabine, and dolutegravir in a patient on peritoneal dialysis. AIDS Res Ther 2024;21(1):34. [CrossRef]
12. Janssen HLA, Lim YS, Lampertico P, Heo J, Chen CY, Fournier C, et al. Switching to tenofovir alafenamide in patients with virologically suppressed chronic hepatitis B and renal or hepatic impairment: final week 96 results from an open-label, multicentre, phase 2 study. Lancet Gastroenterol Hepatol 2024;9(8):718-733. [CrossRef]
13. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67(4):1560-1599. [CrossRef]
14. Farag MS, Fung S, Tam E, Doucette K, Wong A, Ramji A, et al. Effectiveness and Renal Safety of Tenofovir Alafenamide Fumarate among Chronic Hepatitis B Patients: Real-World Study. J Viral Hepat 2021;28(6):942-950. [CrossRef]
15. Liu JK, Vutien P, Huang DQ, Ishigami M, Landis CS, Nguyen MH; REAL-B Liver Transplant Study Group. Renal outcomes with tenofovir alafenamide in liver transplant recipients. Clin Gastroenterol Hepatol 2023;21(2):538-540.e4. [CrossRef]
16. Wong GL, Lemoine M. The 2024 updated WHO guidelines for the prevention and management of chronic hepatitis B: Main changes and potential implications for the next major liver society clinical practice guidelines. J Hepatol 2025;82(5):918-925. [CrossRef]
17. Jeong J, Shin JW, Jung SW, Park EJ, Park NH. Tenofovir alafenamide treatment may not worsen the lipid profile of chronic hepatitis B patients: A propensity score-matched analysis. Clin Mol Hepatol 2022;28(2):254-264. [CrossRef]
18. Zhao W, Liu Y, Zhang M, Cui Z, Qu Z, Li Y, et al. Lipid safety of tenofovir alafenamide during 96-week treatment in treatment-naive chronic hepatitis B patients. Front Med (Lausanne) 2024;11:1399665. [CrossRef]
19. Fung SK, Pan CQ, Wong GL, Seto WK, Ahn SH, Chen CY, et al. Atherosclerotic cardiovascular disease risk profile of patients with chronic hepatitis B treated with tenofovir alafenamide or tenofovir disoproxil fumarate for 96 weeks. Aliment Pharmacol Ther 2024;59(2):217-229. [CrossRef]
20. Opałka B, Żołnierczuk M, Grabowska M. Immunosuppressive agents-effects on the cardiovascular system and selected metabolic aspects: a review. J Clin Med 2023;12(21):6935. [CrossRef]

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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:** CMI and MCMI did not differ significantly between inactive HBV carriers and HBV-negative controls in a small sample, which does not establish equivalence.
- **Key Finding:** In long-term nucleos(t)ide-treated CHB, CMI was associated with CAP-defined hepatic steatosis but not with elevated liver stiffness.
- Waist circumference showed the highest discrimination for elevated liver stiffness (AUC 0.75) and exceeded FIB-4 and APRI on formal DeLong testing.
- **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

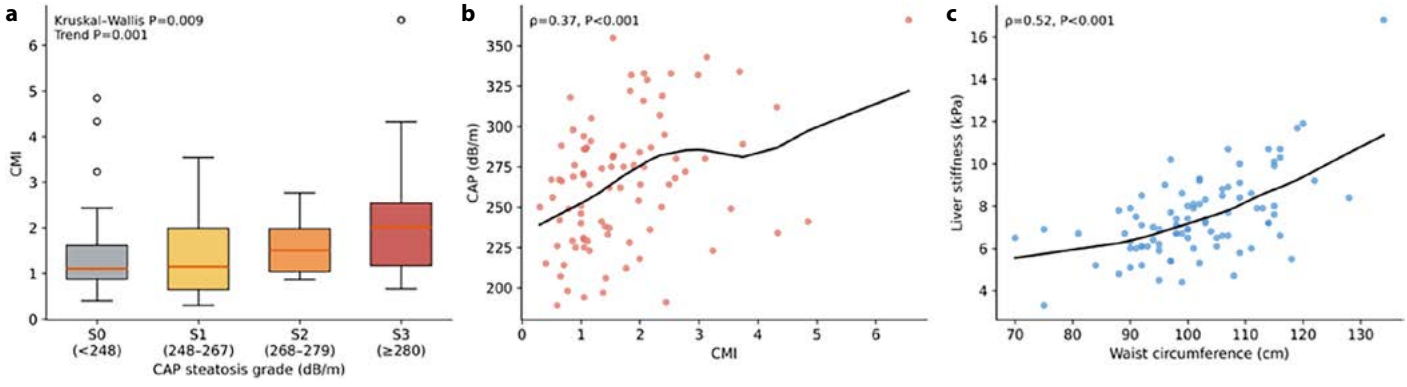



**Figure 1.** Cardiometabolic index (CMI) and anthropometry in relation to hepatic steatosis and liver stiffness in the chronic hepatitis B cohort. **(a)** CMI across controlled attenuation parameter (CAP) steatosis grades defined according to Karlas et al.[19] (S0 below 248 dB/m, S1 248–267 dB/m, S2 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.

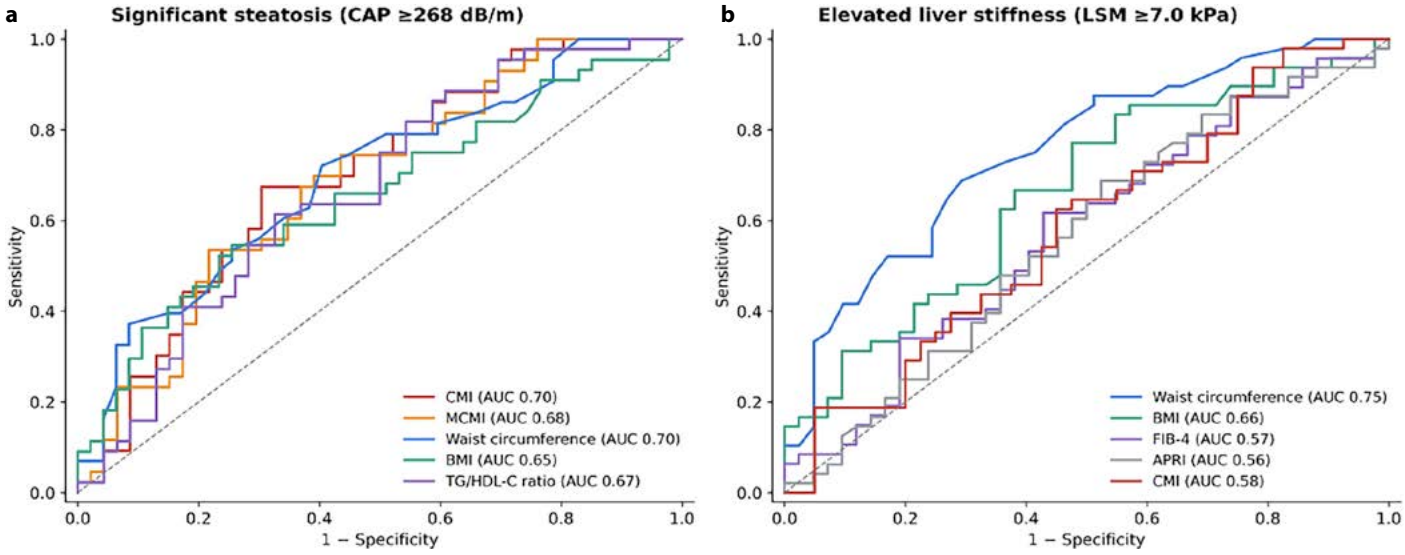



**Figure 2.** Receiver-operating-characteristic curves in the chronic hepatitis B cohort. **(a)** Significant hepatic steatosis, defined as controlled attenuation parameter 268 dB/m or higher. **(b)** Elevated liver stiffness, defined as a liver stiffness measurement of 7.0 kPa or higher. Areas under 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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## References

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2025;83(2):502-583. [CrossRef]
2. Rinella ME, Sookoian S. From NAFLD to MASLD: updated naming and diagnosis criteria for fatty liver disease. J Lipid Res 2024;65(1):100485. [CrossRef]
3. Miao L, Targher G, Byrne CD, Cao YY, Zheng MH. Current status and future trends of the global burden of MASLD. Trends Endocrinol Metab 2024;35(8):697-707. [CrossRef]
4. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol 2024;81(3):492-542. [CrossRef]
5. Zhang S, Mak LY, Yuen MF, Seto WK. Mechanisms of hepatocellular carcinoma and cirrhosis development in concurrent steatotic liver disease and chronic hepatitis B. Clin Mol Hepatol 2025;31(Suppl):S182-S195. [CrossRef]
6. Li MP, Luo KZ. The outcomes and mechanisms of chronic hepatitis B complicated by metabolic dysfunction-associated steatotic liver disease. Hepatobiliary Pancreat Dis Int 2025;24(5):476-483. [CrossRef]
7. Shen F, Mi YQ, Xu L, Liu YG, Wang XY, Pan Q, et al. Moderate to severe hepatic steatosis leads to overestimation of liver stiffness measurement in chronic hepatitis B patients without significant fibrosis. Aliment Pharmacol Ther 2019;50(1):93-102. [CrossRef]
8. Con D, Tu S, Clayton-Chubb D, Lubel JS, Nicoll AJ, Sawhney R, et al. Effect of concurrent metabolic dysfunction-associated steatotic liver disease on serial non-invasive fibrosis markers in chronic hepatitis B. Dig Dis Sci 2024;69(4):1496-1506. [CrossRef]
9. Wakabayashi I, Daimon T. The "cardiometabolic index" as a new marker determined by adiposity and blood lipids for discrimination of diabetes mellitus. Clin Chim Acta 2015;438:274-278. [CrossRef]
10. Torres-Orozco AK, De León LG, Ortiz-Rodríguez B, Candia-Luján R. Wakabayashi & Daimon cardiometabolic index as an indicator to assess risk in adults. A systematic review. Aten Primaria 2024;56(5):102846. [CrossRef]
11. Fan Z, Yang C, Zhao X, Zhang J. Association of cardiometabolic markers with hepatic steatosis and liver fibrosis in population without obesity and diabetes. Sci Rep 2025;15(1):15695. [CrossRef]
12. Yang Y, Zeng C, Jin Z, Huang Y, Liu H. Cardiometabolic index as a predictor of mortality in metabolic dysfunction-associated steatotic liver disease. BMC Gastroenterol 2025;25(1):537. [CrossRef]
13. Azarboo A, Fallahtafti P, Jalali S, Khanmohammadi S, Eslami M, Pourghazi F, et al. The association between cardiometabolic index (CMI) and metabolic dysfunction-associated steatotic liver disease (MASLD): a systematic review and meta-analysis. Diabetol Metab Syndr 2025;17(1):364. [CrossRef]
14. Nathan DM, Kuenen J, Borg R, Zheng H, Schoenfeld D, Heine RJ, et al. Translating the A1C assay into estimated average glucose values. Diabetes Care 2008;31(8):1473-1478. [CrossRef]
15. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord 2008;6(4):299-304. [CrossRef]

16. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38(2):518-526. [CrossRef]
17. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43(6):1317-1325. [CrossRef]
18. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol 2021;75(3):659-689. [CrossRef]
19. Karlas T, Petroff D, Sasso M, Fan JG, Mi YQ, de Lédinghen V, et al. Individual patient data meta-analysis of controlled attenuation parameter (CAP) technology for assessing steatosis. J Hepatol 2017;66(5):1022-1030. [CrossRef]
20. Chon YE, Choi EH, Song KJ, Park JY, Kim DY, Han KH, et al. Performance of transient elastography for the staging of liver fibrosis in patients with chronic hepatitis B: a meta-analysis. PLoS One 2012;7(9):e44930. [CrossRef]
21. Targher G, Byrne CD, Tilg H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications. Gut 2024;73(4):691-702. [CrossRef]
22. Myers RP, Pomier-Layrargues G, Kirsch R, Pollett A, Duarte-Rojo A, Wong D, et al. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. Hepatology 2012;55(1):199-208. [CrossRef]
23. Zhang X, Wong GL, Wong VW. Application of transient elastography in nonalcoholic fatty liver disease. Clin Mol Hepatol 2020;26(2):128-141. [CrossRef]
24. Chen Z, Huang Y, Zhang Y, Zhou D, Yang Y, Zhang S, et al. Impact of hepatic steatosis on liver stiffness measurement by vibration-controlled transient elastography and its diagnostic performance for identifying liver fibrosis in patients with chronic hepatitis B. Insights Imaging 2024;15(1):283. [CrossRef]
25. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. Gastroenterology 2019;156(5):1264-1281.e4. [CrossRef]
26. Wong VW, Adams LA, de Lédinghen V, Wong GL, Sookoian S. Noninvasive biomarkers in NAFLD and NASH - current progress and future promise. Nat Rev Gastroenterol Hepatol 2018;15(8):461-478. [CrossRef]

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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.

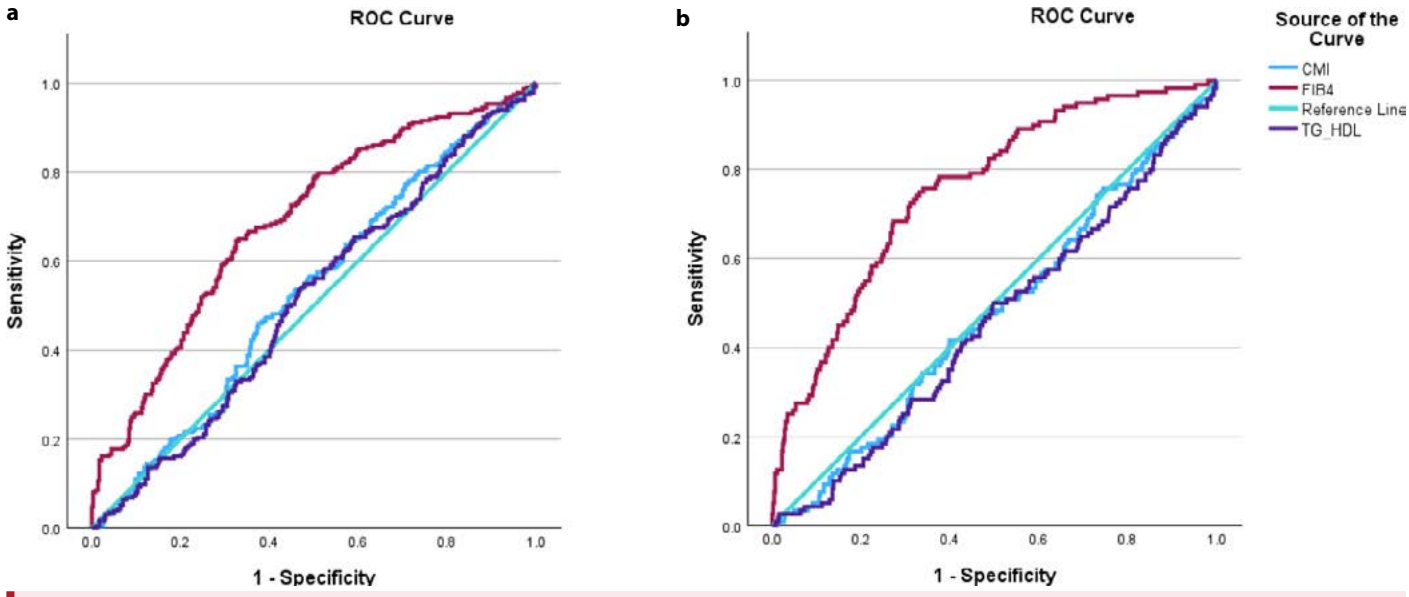



**Figure 1.** Receiver operating characteristic curves for the discrimination of histological fibrosis severity. **(a)** cardiometabolic index (CMI), triglyceride/high-density lipoprotein (TG/HDL) ratio, and fibrosis-4 index (FIB-4) for significant fibrosis; **(b)** CMI, TG/HDL ratio, and FIB-4 for advanced 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.

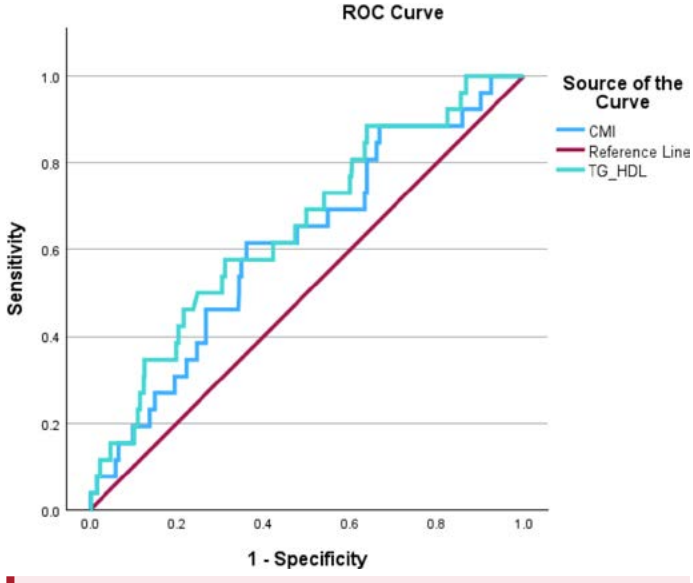



**Figure 2.** Receiver operating characteristic curves for the discrimination of cirrhosis using cardiometabolic index and the triglyceride/high density lipoprotein ratio. Both markers showed an inverse direction of discrimination, with lower values associated with cirrhosis (n=617).

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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## References

1. Miao L, Targher G, Byrne CD, Cao YY, Zheng MH. Current status and future trends of the global burden of MASLD. Trends Endocrinol Metab 2024;35(8):697-707. [CrossRef]
2. Yilmaz Y, Yilmaz N, Ates F, Karakaya F, Gokcan H, Kaya E, et al. The prevalence of metabolic-associated fatty liver disease in the Turkish population: A multicenter study. Hepatol Forum 2021;2(2):37-42. [CrossRef]
3. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149(2):389-397.e10. [CrossRef]

4. Yılmaz Y, Kanı HT, Demirtaş CÖ, Kaya E, Sapmaz AF, Qutranji L, et al. Growing burden of nonalcoholic fatty liver disease in Turkey: A single-center experience. Turk J Gastroenterol 2019;30(10):892-898. [CrossRef]
5. Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005;41(6):1313-1321. [CrossRef]
6. Bedossa P; FLIP Pathology Consortium. Utility and appropriateness of the fatty liver inhibition of progression (FLIP) algorithm and steatosis, activity, and fibrosis (SAF) score in the evaluation of biopsies of nonalcoholic fatty liver disease. Hepatology 2014;60(2):565-575. [CrossRef]
7. Rockey DC, Caldwell SH, Goodman ZD, Nelson RC, Smith AD; American Association for the Study of Liver Diseases. Liver biopsy. Hepatology 2009;49(3):1017-1044. [CrossRef]
8. Kaya E, Bakir A, Kani HT, Demirtas CO, Keklikkiran C, Yilmaz Y. Simple noninvasive scores are clinically useful to exclude, not predict, advanced fibrosis: a study in turkish patients with biopsy-proven nonalcoholic fatty liver disease. Gut Liver 2020;14(4):486-491. [CrossRef]
9. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79(6):1542-1556. [CrossRef]
10. Yilmaz Y, Adali G, Ergenc I, Kaya E, Gokce DT, Keklikkiran C, et al. TASL practice guidance for the diagnosis and management of metabolic dysfunction-associated steatotic liver disease (MASLD). Hepatol Forum 2026;7(3):177-214. [CrossRef]
11. Thallapureddy K, Twitchell D, Ott K, Pedicone LD, Owo C, Kumar N, et al. The accuracy of FibroScan, FIB-4, and nonalcoholic fatty liver disease fibrosis score in predicting biopsy-defined fibrosis and steatosis across all fibrosis stages in patients with metabolic dysfunction associated steatotic liver disease. Medicine (Baltimore) 2025;104(17):e42016. [CrossRef]
12. Ciftel S, Çiftel S, Baykan AR, Cerrah S, Çiftel E, Mercantepe F. Cardiometabolic risk in non-diabetic metabolic dysfunction-associated steatotic liver disease (MAFLD) patients: insights from the triglyceride-glucose, plasma atherogenic, and cardiometabolic index. Arch Med Sci 2024;21(2):401-408. [CrossRef]
13. Yang Y, Zeng C, Jin Z, Huang Y, Liu H. Cardiometabolic Index as a predictor of mortality in metabolic Dysfunction-Associated Steatotic Liver Disease. BMC Gastroenterol 2025;25(1):537. [CrossRef]
14. Yan L, Hu X, Wu S, Cui C, Zhao S. Association between the cardiometabolic index and NAFLD and fibrosis. Sci Rep 2024;14(1):13194. [CrossRef]
15. Wakabayashi I, Daimon T. The "cardiometabolic index" as a new marker determined by adiposity and blood lipids for discrimination of diabetes mellitus. Clin Chim Acta 2015;438:274-278. [CrossRef]
16. Zou J, Xiong H, Zhang H, Hu C, Lu S, Zou Y. Association between the cardiometabolic index and non-alcoholic fatty liver disease: insights from a general population. BMC Gastroenterol 2022;22(1):20. [CrossRef]
17. Azarboo A, Fallahtafti P, Jalali S, Khanmohammadi S, Eslami M, Pourghazi F, et al. The association between cardiometabolic index (CMI) and metabolic dysfunction-associated steatotic liver disease (MASLD): a systematic review and meta-analysis. Diabetol Metab Syndr 2025;17(1):364. [CrossRef]
18. Guo Y, Su W, Tao L, Zhang G, Wang K. The association between modified cardiometabolic index with non-alcoholic fatty liver disease and liver fibrosis: a cross-sectional study. BMC Gastroenterol 2025;25(1):265. [CrossRef]
19. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med 2018;24(7):908-922. [CrossRef]
20. Daniels SJ, Leeming DJ, Eslam M, Hashem AM, Nielsen MJ, Krag A, et al. ADAPT: An Algorithm Incorporating PRO-C3 Accurately Identifies Patients With NAFLD and Advanced Fibrosis. Hepatology 2019;69(3):1075-1086. [CrossRef]
21. Kjaergaard M, Lindvig KP, Thorhauge KH, Andersen P, Hansen JK, Kastrup N, et al. Using the ELF test, FIB-4 and NAFLD fibrosis score to screen the population for liver disease. J Hepatol 2023;79(2):277-286. [CrossRef]
22. Loomba R, Wolfson T, Ang B, Hooker J, Behling C, Peterson M, et al. Magnetic resonance elastography predicts advanced fibrosis in patients with nonalcoholic fatty liver disease: a prospective study. Hepatology 2014;60(6):1920-1928. [CrossRef]

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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 occurred in 11.0% of patients after nucleos(t)ide analogue discontinuation, whereas no seroclearance was observed during continued treatment.
- **Key Finding:** Clinical relapse occurred in 39.7% of patients after treatment discontinuation, with 72% of relapses occurring within the first 3 months.
- None of the patients who achieved HBsAg seroclearance experienced clinical relapse, and 75% developed anti-HBs.
- **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

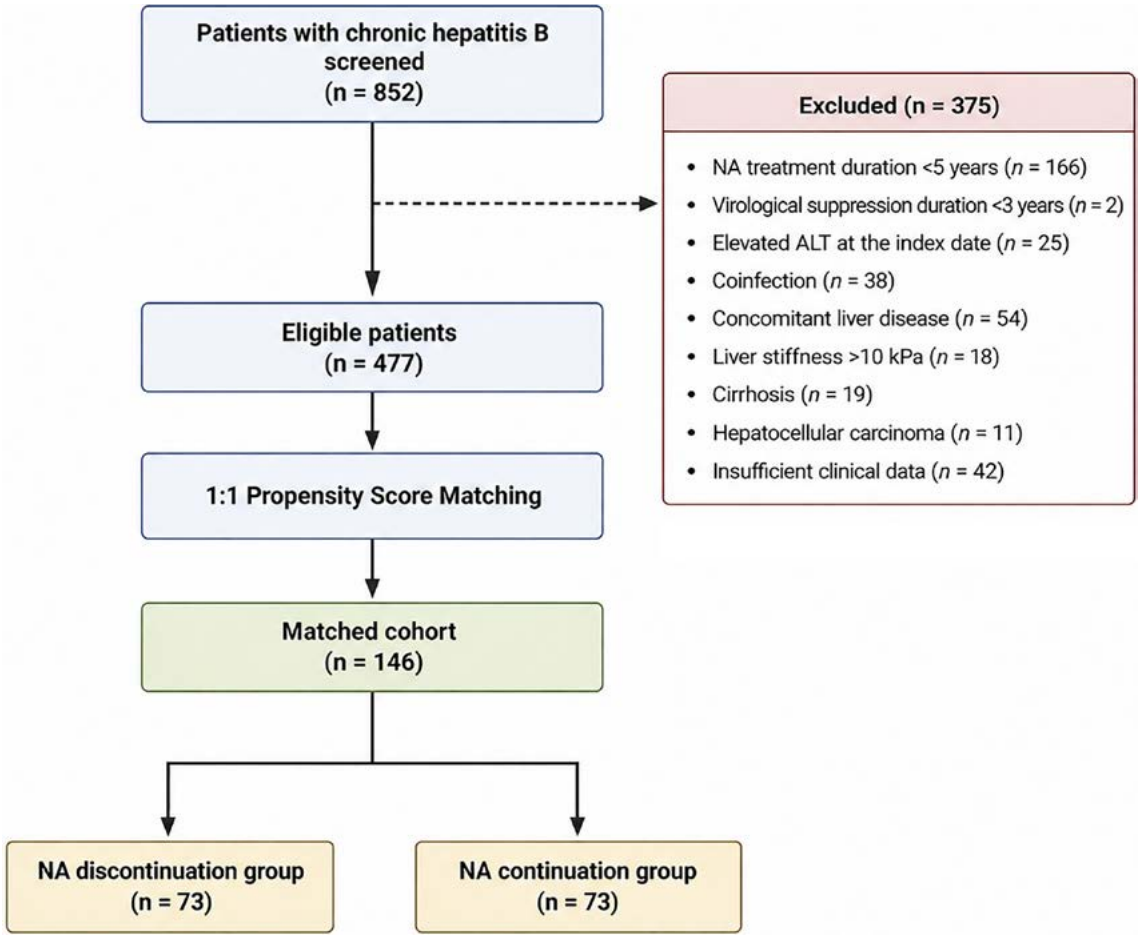



**Figure 1.** Flowchart illustrating patient selection and propensity score matching.

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<br>105 TDF<br>14 other | 12 ETV<br>50 TDF<br>11 other | 15 ETV<br>55 TDF<br>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-

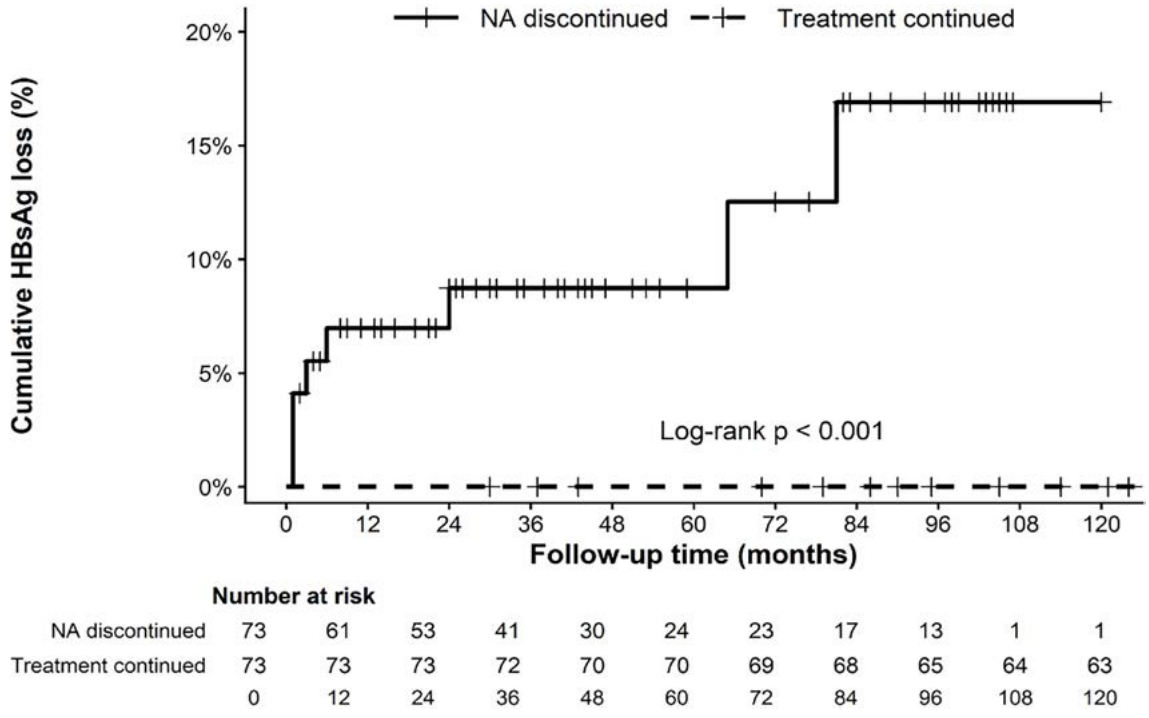



**Figure 2.** Kaplan–Meier curves illustrating the cumulative probability of HBsAg seroclearance in the nucleos(t)ide analogue discontinuation and continuation groups.

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 ($\times 10^3/\mu L$) | 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) | 0.647 |
| Significant fibrosis (stage ≥2) (%) | 20 | 36.5 | 1.000 |

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 |

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

**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.

the 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 discontinuation 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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## References

1. World Health Organization. Hepatitis B [Internet]. Geneva; 2024 [cited 2025 Oct 21]. Available from: https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
2. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol 2018;3(6):383-403. [CrossRef]
3. Idilman R, Aydogan M, Oruncu MB, Kartal A, Elhan AH, Ellik Z, et al. Natural history of cirrhosis: changing trends in etiology over the years. Dig Dis 2021;39(4):358-365. [CrossRef]
4. Üçbilek E, Yıldırım AE, Ellik Z, Turan İ, Haktanıyan B, Orucu B, et al. Changing trends in the etiology of cirrhosis in türkiye: a multicenter nationwide study. Turk J Gastroenterol 2024;35(10):772-777. [CrossRef]
5. Guzelbulut F, Karaogullarindan U, Akkiz H, Altintas E, Demirtas CO, Bahadir O, et al. Characteristics of patients with hepatocellular carcinoma: A multicenter study. Hepatol Forum 2022;3(3):71-76. [CrossRef]
6. Tozun N, Ozdogan O, Cakaloglu Y, Idilman R, Karasu Z, Akarca U, et al. Seroprevalence of hepatitis B and C virus infections and risk factors in Turkey: a fieldwork TURHEP study. Clin Microbiol Infect 2015;21(11):1020-1026. [CrossRef]
7. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67(2):370-398. [CrossRef]
8. van Bömmel F, Berg T. Risks and benefits of discontinuation of nucleos(t)ide analogue treatment: a treatment concept for patients with HBeAg-negative chronic hepatitis B. Hepatol Commun 2021;5(10):1632-1648. [CrossRef]
9. Marcellin P, Gane EJ, Flisiak R, Trinh HN, Petersen J, Gurel S, et al. Long term treatment with tenofovir disoproxil fumarate for chronic hepatitis b

infection is safe and well tolerated and associated with durable virologic response with no detectable resistance: 8 year results from two phase 3 trials: 229. Hepatology 2014;60:313A-314A.

10. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2025;83(2):502-583.
11. Maung ST, Decharatanachart P, Chaiteerakij R. Hepatitis B surface antigen seroclearance rate after stopping nucleos(t)ide analogues in chronic hepatitis B-a systematic review and meta-analysis. J Gastroenterol Hepatol 2025;40(5):1079-1104. [CrossRef]
12. van Bömmel F, Stein K, Heyne R, Petersen J, Buggisch P, Berg C, et al. A multicenter randomized-controlled trial of nucleos(t)ide analogue cessation in HBeAg-negative chronic hepatitis B. J Hepatol 2023;78(5):926-936. [CrossRef]
13. Berg T, Simon KG, Mauss S, Schott E, Heyne R, Klass DM, et al. Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients - FINITE study. J Hepatol 2017;67(5):918-924. [CrossRef]
14. Papatheodoridi M, Papachristou E, Moschidis Z, Hadziyannis E, Rigopoulou E, Zachou K, et al. Significance of serum HBV RNA in non-cirrhotic HBeAg-negative chronic hepatitis B patients who discontinue effective antiviral therapy. J Viral Hepat 2022;29(11):948-957. [CrossRef]
15. Papatheodoridis G, Vlachogiannakos I, Cholongitas E, Wursthorn K, Thomadakis C, Touloumi G, et al. Discontinuation of oral antivirals in chronic hepatitis B: A systematic review. Hepatology 2016;63(5):1481-1492. [CrossRef]
16. Hirode G, Choi HSJ, Chen CH, Su TH, Seto WK, Van Hees S, et al. Off-therapy response after nucleos(t)ide analogue withdrawal in patients with chronic hepatitis B: an international, multicenter, multiethnic cohort (RETRACT-B Study). Gastroenterology 2022;162(3):757-771.e4. [CrossRef]
17. Kiremitçi S, Koçhan K, Seven G, Biberci Keskin E, Okay G, Akkoyunlu Y, et al. Results of nucleos(t)ide analog treatment discontinuation in hepatitis b e-antigen-negative chronic hepatitis B: NUCSTOP Study. Turk J Gastroenterol 2024;35(1):17-26. [CrossRef]
18. Höner Zu Siederdissen C, Rinker F, Maasoumy B, Wiegand SB, Filmann N, Falk CS, et al. Viral and host responses after stopping long-term nucleos(t)ide analogue therapy in HBeAg-negative chronic hepatitis B. J Infect Dis 2016;214(10):1492-1497. [CrossRef]
19. Hadziyannis SJ, Sevastianos V, Rapti I, Vassilopoulos D, Hadziyannis E. Sustained responses and loss of HBsAg in HBeAg-negative patients with chronic hepatitis B who stop long-term treatment with adefovir. Gastroenterology 2012;143(3):629-636.e1. [CrossRef]
20. Bodakci E, Kiremitci S, Ellik ZM, Koc O, Gumussoy M, Yilmaz V, et al. Hepatic steatosis is associated with HBsAg seroclearance in patients with chronic hepatitis B virus infection but it is also associated with disease progression. Hepatol Forum 2026;7(1):14-20. [CrossRef]
21. Rinker F, Zimmer CL, Höner Zu Siederdissen C, Manns MP, Kraft ARM, Wedemeyer H, et al. Hepatitis B virus-specific T cell responses after stopping nucleos(t)ide analogue therapy in HBeAg-negative chronic hepatitis B. J Hepatol 2018;69(3):584-593. [CrossRef]
22. Xia Y, Stadler D, Lucifora J, Reisinger F, Webb D, Hösel M, et al. Interferon-γ and Tumor Necrosis Factor-α Produced by T Cells Reduce the HBV Persistence Form, cccDNA, Without Cytolysis. Gastroenterology 2016;150(1):194-205. [CrossRef]
23. Boni C, Fisicaro P, Valdatta C, Amadei B, Di Vincenzo P, Giuberti T, et al. Characterization of hepatitis B virus (HBV)-specific T-cell dysfunction in chronic HBV infection. J Virol 2007;81(8):4215-4225. [CrossRef]
24. Boni C, Laccabue D, Lampertico P, Giuberti T, Viganò M, Schivazappa S, et al. Restored function of HBV-specific T cells after long-term effective therapy with nucleos(t)ide analogues. Gastroenterology 2012;143(4):963-973.e9. [CrossRef]
25. Boni C, Penna A, Bertoletti A, Lamonaca V, Rapti I, Missale G, et al. Transient restoration of anti-viral T cell responses induced by lamivudine therapy in chronic hepatitis B. J Hepatol 2003;39(4):595-605. [CrossRef]

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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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## References

1. Uyanıkoğlu A. The role of steatohepatitis in cirrhosis etiology. J Acad Gastroenterol 2020;19(1):17-20. [Turkish] [CrossRef]
2. Abbas Z, Siddiqui AR. Management of hepatitis B in developing countries. World J Hepatol 2011;3(12):292-299. [CrossRef]
3. Zhou WC, Zhang QB, Qiao L. Pathogenesis of liver cirrhosis. World J Gastroenterol 2014;20(23):7312-7324. [CrossRef]
4. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10(1):1-98. [CrossRef]
5. Peng S, Plank LD, McCall JL, Gillanders LK, McIlroy K, Gane EJ. Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: a comprehensive study. Am J Clin Nutr 2007;85(5):1257-1266. [CrossRef]
6. Tilg H, Wilmer A, Vogel W, Herold M, Nolchen B, Judmaier G, et al. Serum levels of cytokines in chronic liver diseases. Gastroenterology 1992;103(1):264-274. [CrossRef]

7. Müller MJ, Böttcher J, Selberg O, Weselmann S, Böker KH, Schwarze M, et al. Hypermetabolism in clinically stable patients with liver cirrhosis. Am J Clin Nutr 1999;69(6):1194-1201. [CrossRef]
8. Sidiq T. Nutrient requirements of patients with liver cirrhosis. Curr Trends Biomed Eng Biosci 2017;4(4):73-75. [CrossRef]
9. Lindor KD, Bowlus CL, Boyer J, Levy C, Mayo M. Primary biliary cholangitis: 2018 practice guidance from the AASLD. Hepatology 2019;69(1):394-419. [CrossRef]
10. Weismann K, Christensen E, Dreyer V. Zinc supplementation in alcoholic cirrhosis: a double-blind clinical trial. Acta Med Scand 1979;205(5):361-366. [CrossRef]
11. Grüngreiff K, Reinhold D, Wedemeyer H. The role of zinc in liver cirrhosis. Ann Hepatol 2016;15(1):7-16. [CrossRef]
12. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 1973;60(8):646-649. [CrossRef]
13. Munoz N, Bernstein M. Nutrition Assessment: Clinical and Research Applications. Massachusetts, USA: Jones & Bartlett Publishers; 2018. ISBN: 978-1284127669
14. Amaral TF, Santos A, Guerra RS, Sousa AS, Álvares L, Valdiviesso R, et al. Nutritional strategies facing an older demographic: The nutrition UP 65 study protocol. JMIR Res Protoc 2016;5(3):e184. [CrossRef]
15. Kondrup J, Rasmussen HH, Hamberg O, Stanga Z; Ad Hoc ESPEN Working Group. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr. 2003;22(3):321-336. [CrossRef]
16. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. Clin Nutr. 2003;22(4):415-421. [CrossRef]
17. Kim S, Haines PS, Siega-Riz AM, Popkin BM. The Diet Quality Index-International (DQI-I) provides an effective tool for cross-national comparison of diet quality as illustrated by China and the United States. J Nutr. 2003;133(11):3476-3484. [CrossRef]
18. European Association for the Study of the Liver (EASL). EASL Clinical Practice Guidelines on nutrition in chronic liver disease. J Hepatol 2019;70(1):172-193. [CrossRef]
19. Saueressig C, Alves BC, Luft VC, Anastácio LR, Santos BC, Ferreira LG, et al. Mid-arm muscle circumference cutoff points in patients with cirrhosis: low muscle mass related to malnutrition predicts mortality. Nutrition 2024:112471. [CrossRef]
20. Saueressig C, Luft VC, Dall'Alba V. Measurement of mid-arm circumference as a starting point for nutritional assessment in decompensated cirrhosis: a prospective cohort study. J Hum Nutr Diet 2023;36(1):116-125. [CrossRef]
21. Sharma P, Rauf A, Matin A, Agarwal R, Tyagi P, Arora A. Handgrip strength as an important bedside tool to assess malnutrition in patients with liver disease. J Clin Exp Hepatol 2017;7(1):16-22. [CrossRef]
22. Hayashi F, Momoki C, Yuikawa M, Simotani Y, Kawamura E, Hagihara A, et al. Nutritional status in relation to lifestyle in patients with compensated viral cirrhosis. World J Gastroenterol. 2012;18(40):5759-5767. [CrossRef]
23. Mendez-Guerrero O, Carranza-Carrasco A, Chi-Cervera LA, Torre A, Navarro-Alvarez N. Optimizing nutrition in hepatic cirrhosis: a comprehensive assessment and care approach. World J Gastroenterol 2024;30(10):1313-1325. [CrossRef]
24. Ney M, Abraldes JG, Ma M, Belland D, Harvey A, Robbins S, Den Heyer V, Tandon P. Insufficient protein intake is associated with increased mortality in 630 patients with cirrhosis awaiting liver transplantation. Nutr Clin Pract 2015;30(4):530-536. [CrossRef]
25. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, Abdelmalek MF, Caldwell S, Barb D, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. Hepatology 2023;77(5):1797-1835. [CrossRef]
26. Najibi N, Jahromi MK, Teymoori F, Farhadnejad H, Salehi-Sahlabadi A, Mirmiran P. International diet quality index and revised diet quality index relationship with NAFLD. BMC Gastroenterol 2023;23(1):441. [CrossRef]
27. Chan R, Wong VW, Chu WC, Wong GL, Li LS, Leung J, et al. Diet-quality scores and prevalence of nonalcoholic fatty liver disease: A population study using proton-magnetic resonance spectroscopy. PLoS One 2015;10(9):e0139310. [CrossRef]
28. Paik J, Henry L, Younossi Y, Ong J, Alqahtani S, Younussi Z. The global burden of liver cancer (LC) and chronic liver diseases (CLD) is driven by non-alcoholic steatohepatitis (NASH) and alcohol liver disease (ALD). J Hepatol 2022;77(Suppl 1):S5-S7. [CrossRef]

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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]

## Conclusion

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.

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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## References

1. De Brito T, Silva AMGD, Abreu PAE. Pathology and pathogenesis of human leptospirosis: a commented review. Rev Inst Med Trop Sao Paulo 2018;60:e23. [CrossRef]
2. Bradley EA, Lockaby G. Leptospirosis and the environment: A review and future directions. Pathogens. 2023;12(9):1167. [CrossRef]
3. Karpagam KB, Ganesh B. Leptospirosis: a neglected tropical zoonotic infection of public health importance-an updated review. Eur J Clin Microbiol Infect Dis 2020;39(5):835-846. [CrossRef]
4. Camous L, Pommier JD, Tressières B, Martino F, Picardeau M, Loraux C, et al. Organ involvement related to death in critically ill patients with leptospirosis: unsupervised analysis in a French West Indies ICU. Crit Care Explor. 2024;6(7):e1126. [CrossRef]
5. Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89(6):806-815. [CrossRef]
6. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care 2013;17(1):204. [CrossRef]
7. Ooteman MC, Vago AR, Koury MC. Evaluation of MAT, IgM ELISA and PCR methods for the diagnosis of human leptospirosis. J Microbiol Methods 2006;65(2):247-257. [CrossRef]
8. Taylor AJ, Paris DH, Newton PN. A systematic review of the mortality from untreated leptospirosis. PLoS Negl Trop Dis 2015;9(6):e0003866. [CrossRef]
9. De Brito T, Machado MM, Montans SD, Hoshino S, Freymüller E. Liver biopsy in human leptospirosis: a light and electron microscopy study. Virchows Arch Pathol Anat Physiol Klin Med 1967;342(1):61-69. [CrossRef]
10. Brito de T, Penna DO, Hoshino S, Pereira VG, Caldas AC, Rothstein W. Cholestasis in human leptospirosis: a clinical, histochemical, biochemical and electron microscopy study based on liver biopsies. Beitr Pathol Anat 1970;140(3):345-361.
11. Miyahara S, Saito M, Kanemaru T, Villanueva SY, Gloriani NG, Yoshida S. Destruction of the hepatocyte junction by intercellular invasion of Leptospira causes jaundice in a hamster model of Weil's disease. Int J Exp Pathol 2014;95(4):271-281. [CrossRef]
12. Alves VA, Gayotto LC, De Brito T, Santos RT, Wakamatsu A, Vianna MR, et al. Leptospiral antigens in the liver of experimentally infected guinea pig and their relation to the morphogenesis of liver damage. Exp Toxicol Pathol 1992;44(7):425-434. [CrossRef]
13. Dutta S, Islam M. A case of leptospirosis presenting with thrombocytopenia, acute liver failure and acute renal failure. Cureus 2025;17(8):e90834. [CrossRef]
14. Carvalho CR, Bethlem EP. Pulmonary complications of leptospirosis. Clin Chest Med 2002;23(2):469-478. [CrossRef]
15. Amin MA, Nahin S, Bonna AS, Kabir Rozars MF, Hossain Hawlader MD. Leptospirosis and COVID-19 co-infection case in Bangladesh. Heliyon 2022;8(11):e11828. [CrossRef]
16. Ruwanpathirana P, Rambukwella R, Perera N, Priyankara D. Severe leptospirosis in the intensive care unit: single centre prospective cohort study from Sri Lanka. BMC Infect Dis 2026;26(1):265. [CrossRef]
17. Chou LF, Yang HY, Hung CC, Tian YC, Hsu SH, Yang CW. Leptospirosis kidney disease: Evolution from acute to chronic kidney disease. Biomed J 2023;46(4):100595. [CrossRef]
18. Allyn J, Miailhe AF, Delmas B, Marti L, Allou N, Jabot J, et al. Severe leptospirosis in tropical and non-tropical areas: A comparison of two French, multicentre, retrospective cohorts. PLoS Negl Trop Dis 2024;18(4):e0012084. [CrossRef]
19. Esen S, Sunbul M, Leblebicioglu H, Eroglu C, Turan D. Impact of clinical and laboratory findings on prognosis in leptospirosis. Swiss Med Wkly 2004;134(23-24):347-352. [CrossRef]

20. Turhan V, Polat E, Murat Atasoyu E, Ozmen N, Kucukardali Y, Cavuslu S. Leptospirosis in Istanbul, Turkey: a wide spectrum in clinical course and complications. Scand J Infect Dis 2006;38(10):845-852. [CrossRef]
21. Ioannou P, Pendondgis M, Kampanieri E, Koukias S, Gorgomyti M, Tryfinopoulou K, et al. A retrospective cohort study of leptospirosis in Crete, Greece. Trop Med Infect Dis 2025;10(8):209. [CrossRef]
22. Tse KC, Yip PS, Hui KM, Li FK, Yuen KY, Lai KN, et al. Potential benefit of plasma exchange in treatment of severe icteric leptospirosis complicated by acute renal failure. Clin Diagn Lab Immunol 2002;9(2):482-484. [CrossRef]
23. Ullah R, Al Harakeh K, Hussain F, Bazilah Mehmood Rufai S, Khan W. The role of plasmapheresis in severe leptospirosis refractory to standard therapy: A case report and a comprehensive literature review. Cureus 2024;16(7):e63682. [CrossRef]
24. Trivedi SV, Vasava AH, Bhatia LC, Patel TC, Patel NK, Patel NT. Plasma exchange with immunosuppression in pulmonary alveolar haemorrhage due to leptospirosis. Indian J Med Res 2010;131:429-433.

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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 85$^{th}$ and 95$^{th}$ percentiles for their age and sex, and obese if it was at or above the 95$^{th}$ 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).

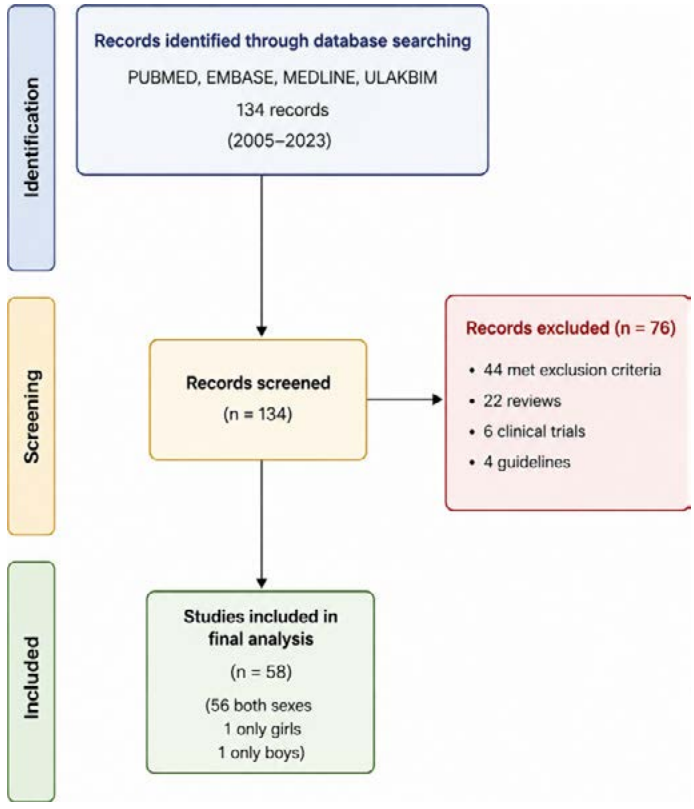



**Figure 1.** Literature search strategy.

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.

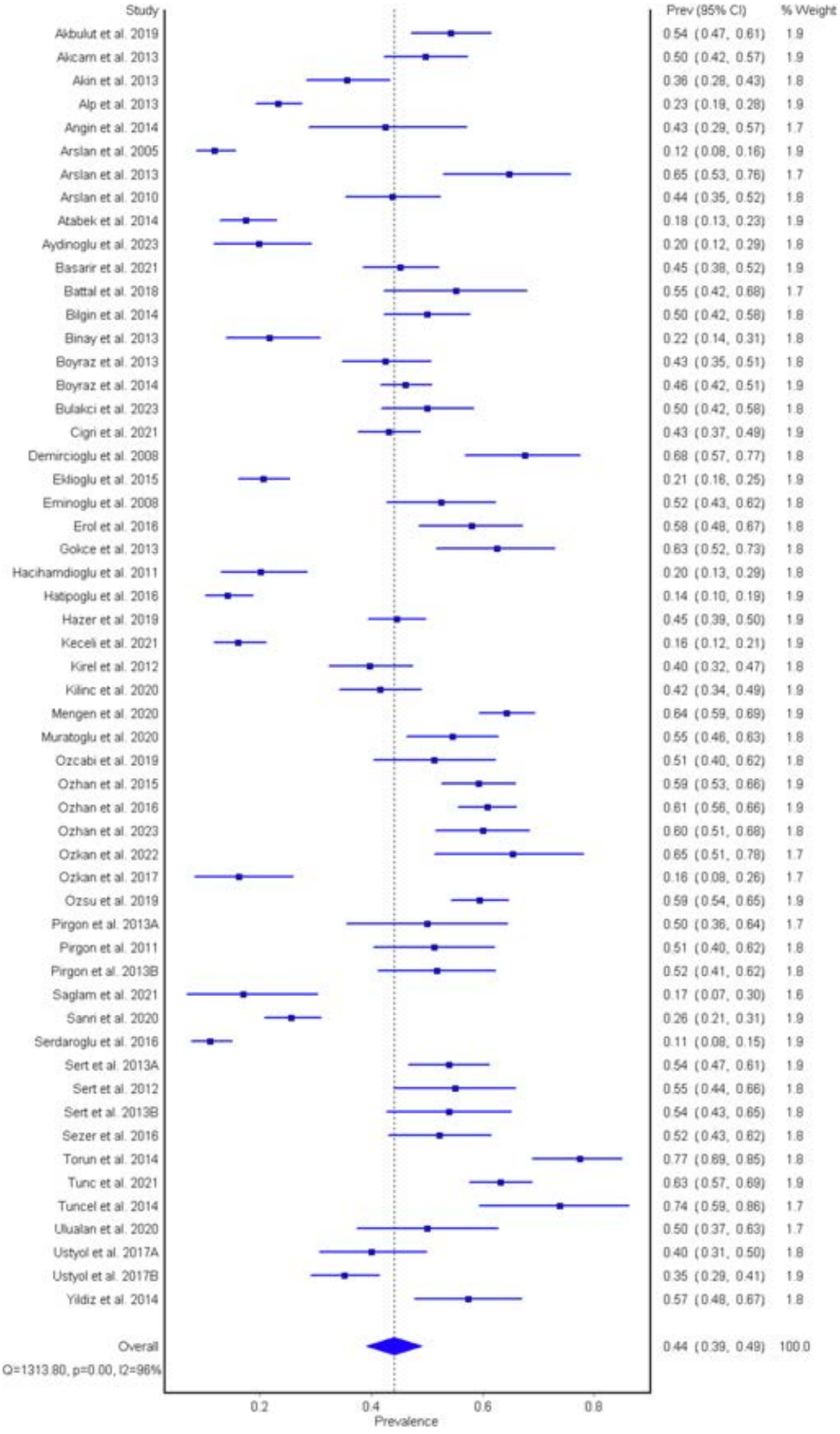
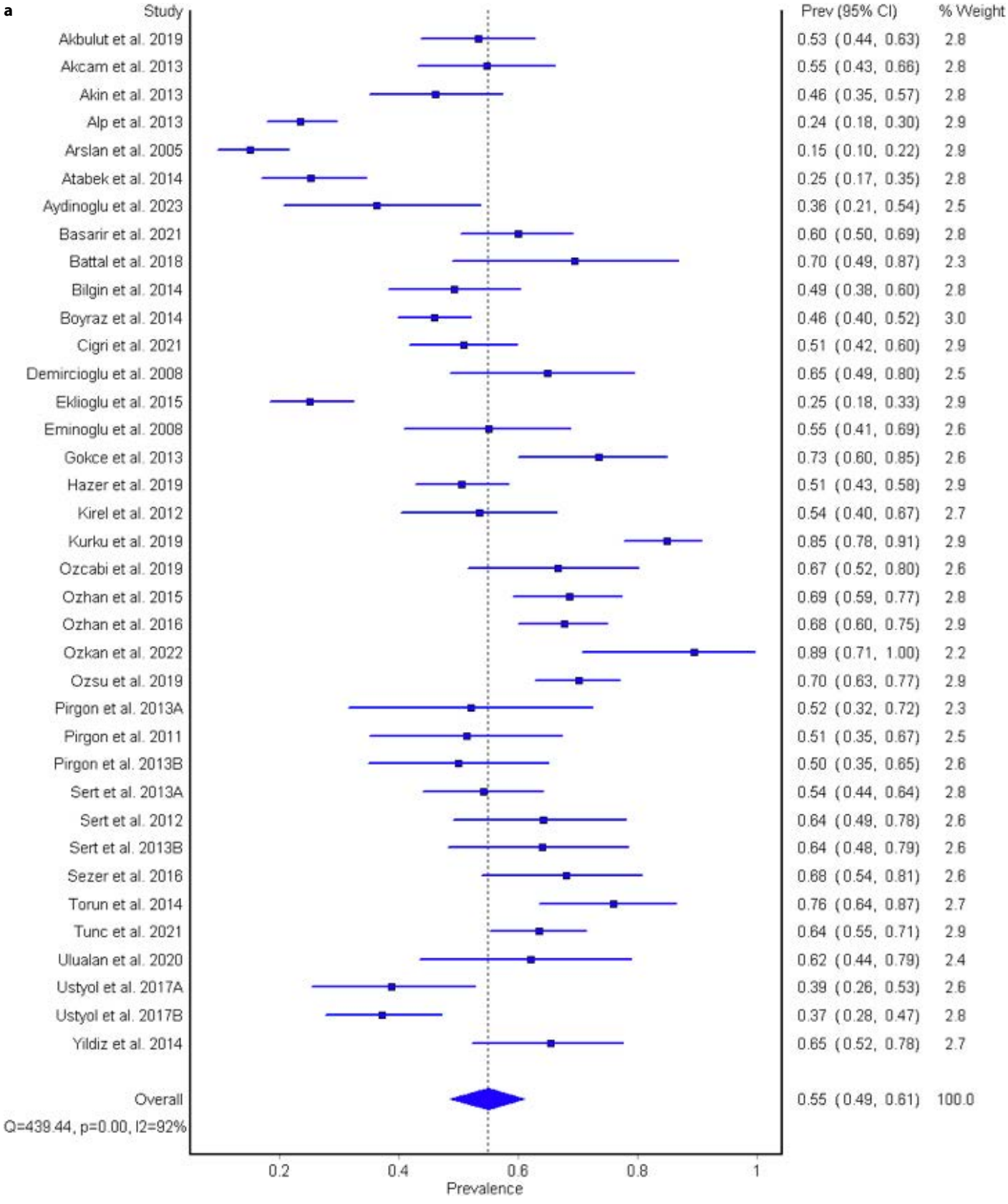



**Figure 2.** The pooled prevalence of pediatric metabolic dysfunction-associated steatotic liver disease across all studies.


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

Cont →

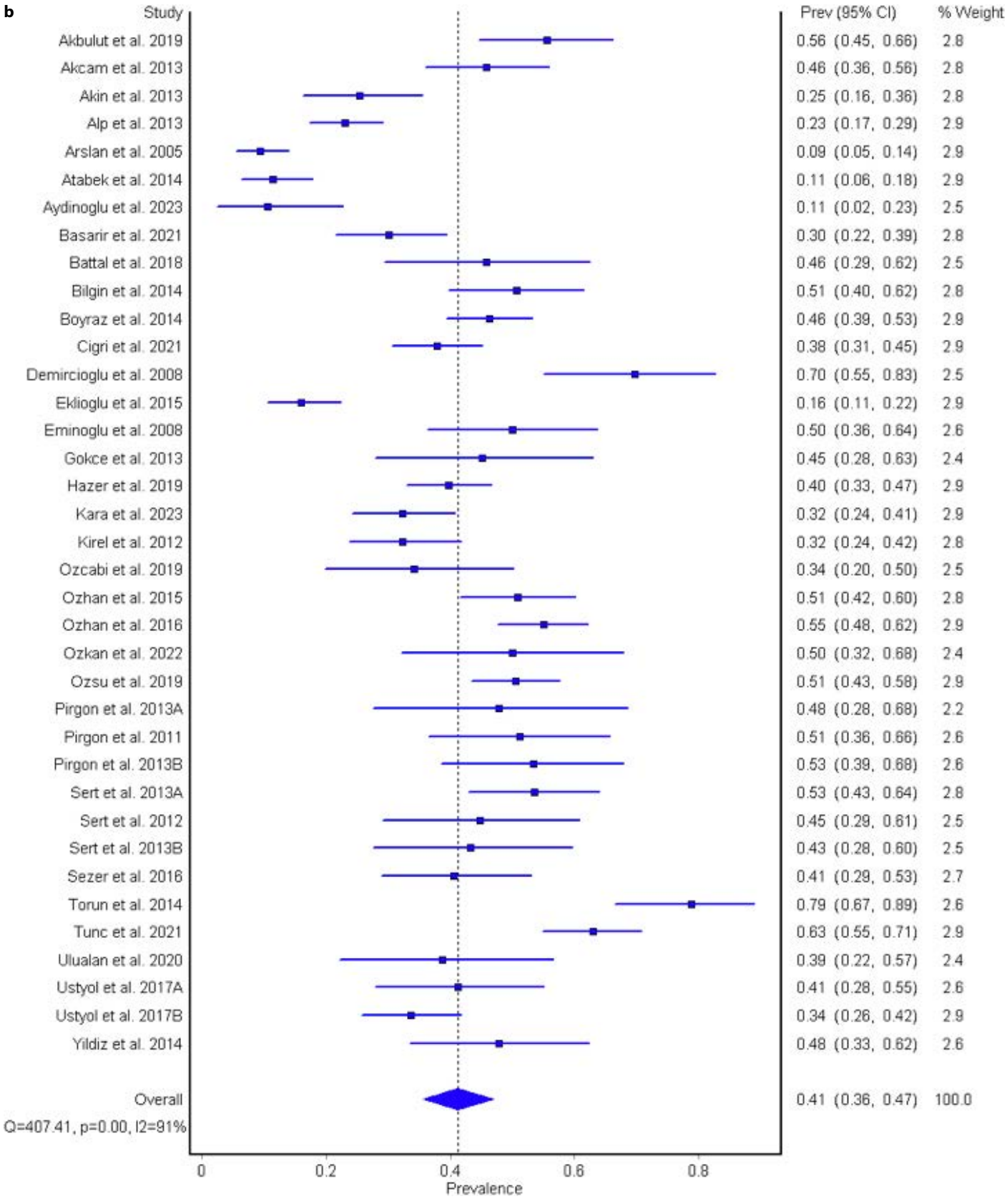
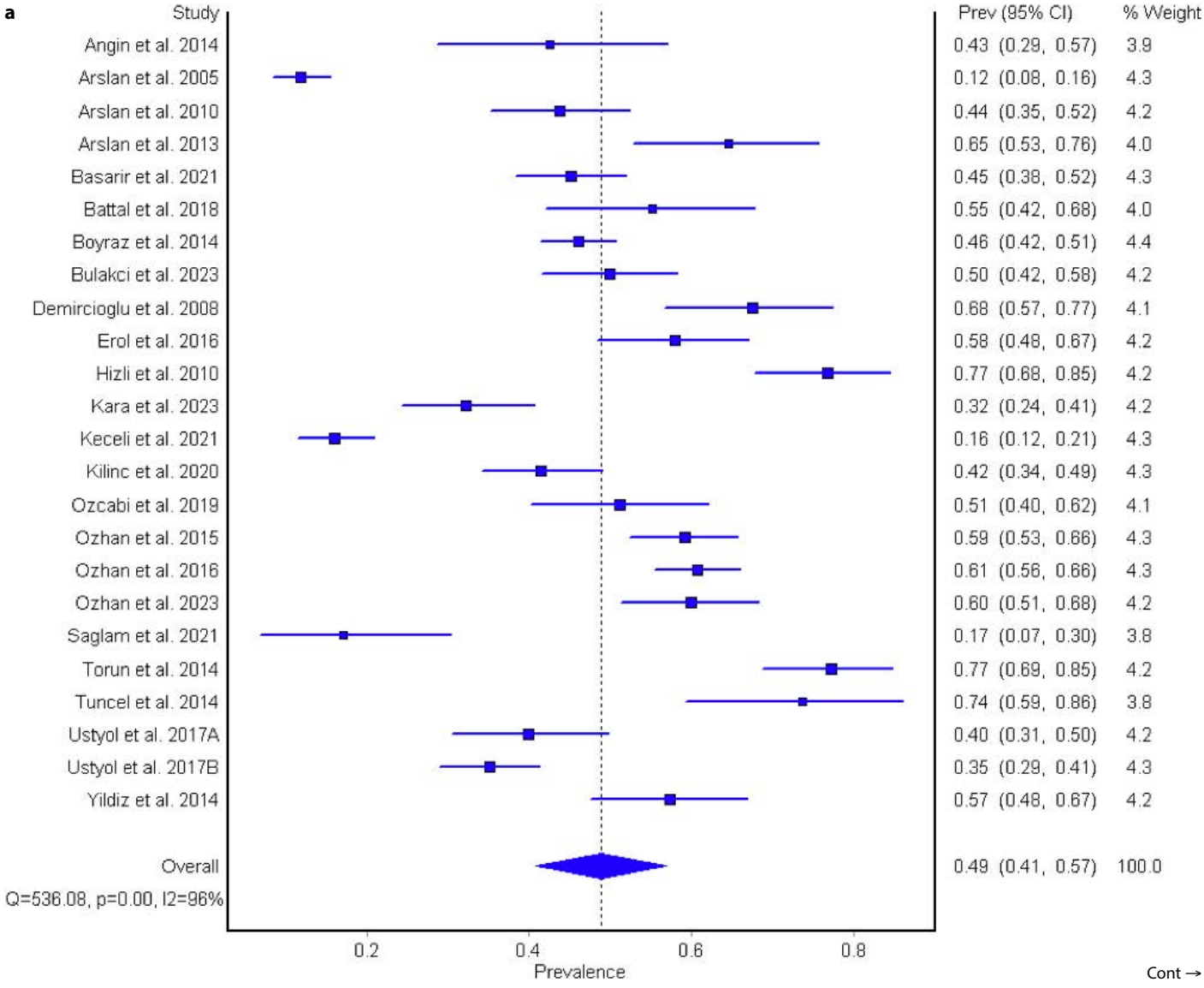



**Figure 3. (a)** Prevalence of pediatric metabolic dysfunction-associated steatotic liver disease (MASLD) among boys; **(b)** prevalence of pediatric MASLD among girls.




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]

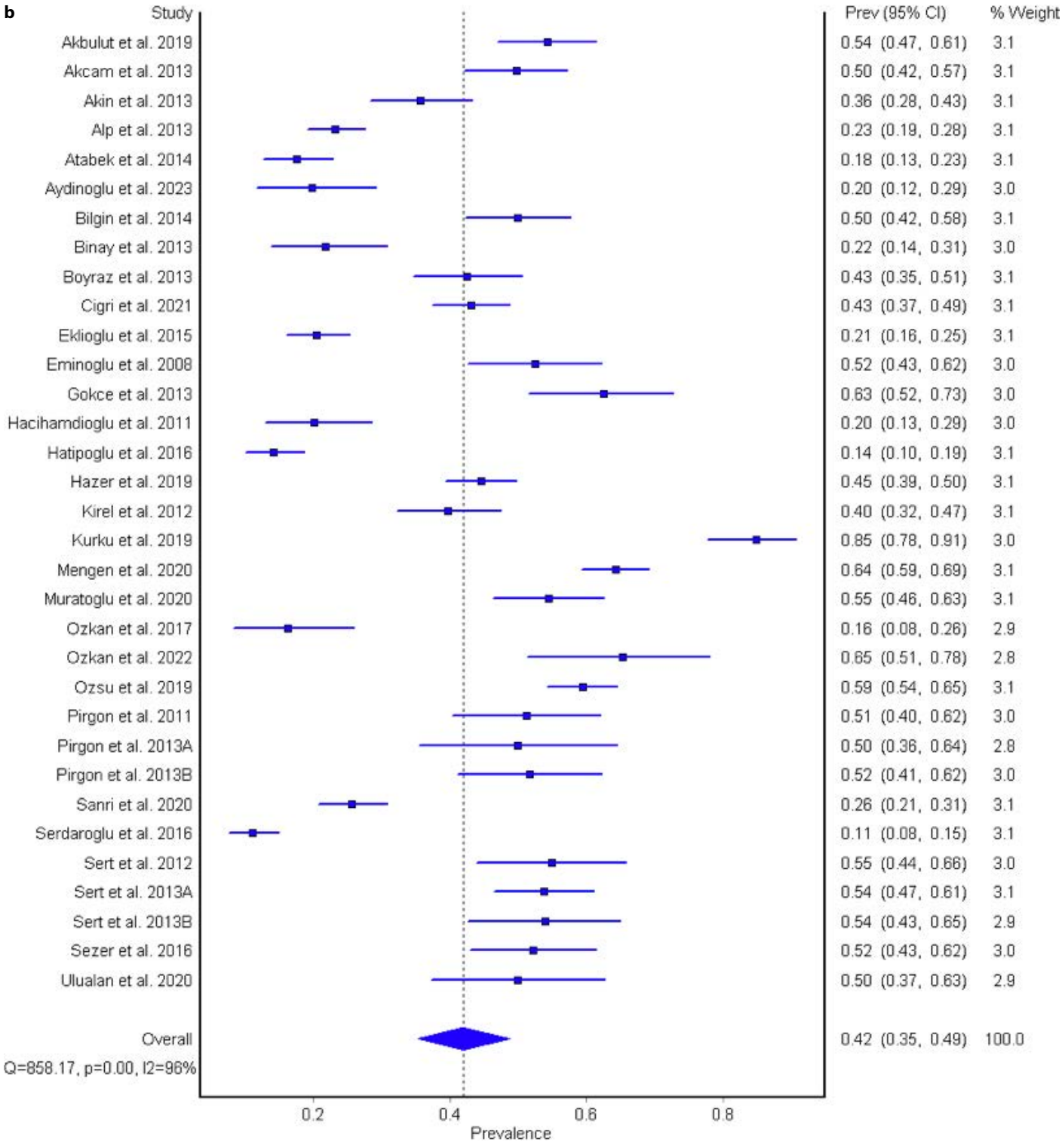



**Figure 4. (a)** Prevalence of pediatric MASLD in the Marmara and Aegean regions; **(b)** Prevalence of pediatric MASLD in the Black Sea, Mediterranean and Central Anatolia regions.

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.

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

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**Author Contributions:** Concept: CK, MT, YY; Design: EK, CK, MT, YY; Supervision: YY; Materials: CK, MT, YY; Data Collection and/or Processing: CK, MT; Analysis and/or Interpretation: EK, CK, MT, YY; Literature Review: EK, YY; Writing: EK, YY; Critical Review: EK, CK, MT, YY.

**Peer-review:** Externally peer-reviewed.

## References

1. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology 2023;77(4):1335-1347. [CrossRef]
2. Ogden CL, Carroll MD, Lawman HG, Fryar CD, Kruszon-Moran D, Kit BK, et al. Trends in obesity prevalence among children and adolescents in the United States, 1988-1994 Through 2013-2014. JAMA 2016;315(21):2292-2299. [CrossRef]
3. Anderson EL, Howe LD, Jones HE, Higgins JPT, Lawlor DA, Fraser A. The prevalence of non-alcoholic fatty liver disease in children and adolescents: A Systematic review and meta-analysis. PLoS One 2015;10(10):e0140908. [CrossRef]
4. Hartmann P, Mouzaki M, Hassan S, Kehar M, Mysore KR, Mauney E, et al. Call to action - pediatric MASLD requires immediate attention to curb health crisis. Hepatology 2025;82(5):1341-1351. [CrossRef]
5. Souza M, Khalil SM, de Oliveira FD. Meta-analysis: Histological severity of biopsy-proven metabolic dysfunction-associated steatotic liver disease in pediatric patients. J Pediatr Gastroenterol Nutr 2025;81(3):663-673. [CrossRef]
6. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. [CrossRef]
7. Younossi ZM, Paik JM, Stepanova M, Ong J, Alqahtani S, Henry L. Clinical profiles and mortality rates are similar for metabolic dysfunction-associated steatotic liver disease and non-alcoholic fatty liver disease. J Hepatol 2024;80(5):694-701. [CrossRef]
8. Ozsu E, Yazıcıoğlu B. Obese boys with low concentrations of high-density lipoprotein cholesterol are at greater risk of hepatosteatosis. Hormones (Athens) 2019;18(4):477-484. [CrossRef]
9. Atabek ME, Selver Eklioglu B, Akyürek N. Which metabolic syndrome criteria best predict non-alcoholic fatty liver disease in children? Eat Weight Disord 2014;19(4):495-501. [CrossRef]
10. Akbulut UE, Emeksiz HC, Citli S, Cebi AH, Korkmaz HAA, Baki G. IL-17A, MCP-1, CCR-2, and ABCA1 polymorphisms in children with non-alcoholic fatty liver disease. J Pediatr (Rio J) 2019;95(3):350-357. [CrossRef]
11. Akcam M, Boyaci A, Pirgon O, Koroglu M, Dundar BN. Importance of the liver ultrasound scores in pubertal obese children with nonalcoholic fatty liver disease. Clin Imaging 2013;37(3):504-508. [CrossRef]
12. Akın L, Kurtoglu S, Yikilmaz A, Kendirci M, Elmalı F, Mazicioglu M. Fatty liver is a good indicator of subclinical atherosclerosis risk in obese children and adolescents regardless of liver enzyme elevation. Acta Paediatr 2013;102(3):e107-e113. [CrossRef]
13. Alp H, Karaarslan S, Selver Eklioğlu B, Atabek ME, Altın H, Baysal T. Association between nonalcoholic fatty liver disease and cardiovascular risk in obese children and adolescents. Can J Cardiol 2013;29(9):1118-1125. [CrossRef]
14. Aydinoğlu A, Atar M, Aydin H, Pirgon Ö. The effect of fatty liver disease on portal vein flow in obese adolescents. Med J SDU 2023;30(3):294-300. [CrossRef]
15. Arslan N, Büyükgebiz B, Oztürk Y, Cakmakçi H. Fatty liver in obese children: prevalence and correlation with anthropometric measurements and hyperlipidemia. Turk J Pediatr 2005;47(1):23-27.

16. Basarir G, Ozcabi B, Aksu Sayman O, Ozturkmen Akay H, Yildiz FM. Evaluation of clinical, endocrine and metabolic findings in obese children with and without hepatosteatosis. J Pediatr Endocrinol Metab 2021;34(9):1081-1087. [CrossRef]
17. Battal F, Türkön H, Aylanç N, Aylanç H, Yıldırım Ş, Kaymaz N, et al. Investigation of blood betatrophin levels in obese children with non-alcoholic fatty liver disease. Pediatr Gastroenterol Hepatol Nutr 2018;21(2):111-117. [CrossRef]
18. Bilgin H, Pirgon Ö. Thyroid function in obese children with non-alcoholic fatty liver disease. J Clin Res Pediatr Endocrinol 2014;6(3):152-157. [CrossRef]
19. Boyraz M, Hatipoğlu N, Sarı E, Akçay A, Taşkın N, Ulucan K, et al. Non-alcoholic fatty liver disease in obese children and the relationship between metabolic syndrome criteria. Obes Res Clin Pract 2014;8(4):e356-e363. [CrossRef]
20. Cigri E, Inan FC, Er E, Yildiz E. The relationship between lipid profile and non-alcoholic fatty liver disease in children and adolescents with obesity. J Coll Physicians Surg Pak 2022;32(5):591-595. [CrossRef]
21. Demircioğlu F, Koçyiğit A, Arslan N, Cakmakçi H, Hizli S, Sedat AT. Intima-media thickness of carotid artery and susceptibility to atherosclerosis in obese children with nonalcoholic fatty liver disease. J Pediatr Gastroenterol Nutr 2008;47(1):68-75. [CrossRef]
22. Eklioğlu BS, Atabek ME, Akyürek N, Alp H. Assessment of cardiovascular parameters in obese children and adolescents with non-alcoholic fatty liver disease. J Clin Res Pediatr Endocrinol 2015;7(3):222-227. [CrossRef]
23. Eminoğlu TF, Camurdan OM, Oktar SO, Bideci A, Dalgiç B. Factors related to non-alcoholic fatty liver disease in obese children. Turk J Gastroenterol 2008;19(2):85-91.
24. Gökçe S, Atbinici Z, Aycan Z, Cınar HG, Zorlu P. The relationship between pediatric nonalcoholic fatty liver disease and cardiovascular risk factors and increased risk of atherosclerosis in obese children. Pediatr Cardiol 2013;34(2):308-315. [CrossRef]
25. Hazer İ, Kabukçu HO, Yağcı M, Ertürk Z, Yıldırım GK, Kirel B. The association of lipid metabolism and non-alcoholic fatty liver disease in children with obesity. Turk Pediatri Ars 2020;55(3):263-269.
26. Kara O, Arsoy HA, Keskin M. Relationship between nonalcoholic fatty liver disease and hyperandrogenemia in adolescents with polycystic ovary syndrome. Clin Exp Pediatr 2023;66(9):395-402. [CrossRef]
27. Kirel B, Simsek E, Toker RT, Colak E. Nonalcoholic fatty liver diseases in obese children and adolescents. Turk Arch Ped 2012;47(3):174-180.
28. Kurku H, Atar M, Pirgon Ö, Büyükinan M, Erdem SS, Deniz İ, et al. Pubertal status and gonadal functions in obese boys with fatty liver. Metab Syndr Relat Disord 2019;17(2):102-107. [CrossRef]
29. Özcabı B, Demirhan S, Akyol M, Öztürkmen Akay H, Güven A. Lipid accumulation product is a predictor of nonalcoholic fatty liver disease in childhood obesity. Korean J Pediatr 2019;62(12):450-455. [CrossRef]
30. Ozhan B, Ersoy B, Kiremitci S, Ozkol M, Taneli F. Insulin sensitivity indices: fasting versus glucose-stimulated indices in pediatric non-alcoholic fatty liver disease. Eur Rev Med Pharmacol Sci 2015;19(18):3450-3458.
31. Özhan B, Ersoy B, Özkol M, Kiremitci S, Ergin A. Waist to height ratio: a simple screening tool for nonalcoholic fatty liver disease in obese children. Turk J Pediatr 2016;58(5):518-523. [CrossRef]
32. Özkan EA, Sadigov A, Öztürk O. Evaluation of serum omentin-1, vaspin, leptin, adiponectin levels in obese/overweight children and their relationship with non-alcoholic fatty liver disease. Clin Nutr Res 2022;11(3):194-203. [CrossRef]
33. Pirgon Ö, Bilgin H, Çekmez F, Kurku H, Dündar BN. Association between insulin resistance and oxidative stress parameters in obese adolescents with non-alcoholic fatty liver disease. J Clin Res Pediatr Endocrinol 2013;5(1):33-39. [CrossRef]
34. Pirgon O, Bilgin H, Tolu I, Odabas D. Correlation of insulin sensitivity with bone mineral status in obese adolescents with nonalcoholic fatty liver disease. Clin Endocrinol (Oxf) 2011;75(2):189-195. [CrossRef]
35. Pirgon O, Cekmez F, Bilgin H, Eren E, Dundar B. Low 25-hydroxyvitamin D level is associated with insulin sensitivity in obese adolescents with non-alcoholic fatty liver disease. Obes Res Clin Pract 2013;7(4):e275-e283. [CrossRef]
36. Sert A, Aypar E, Pirgon O, Yilmaz H, Odabas D, Tolu I. Left ventricular function by echocardiography, tissue Doppler imaging, and carotid intima-media thickness in obese adolescents with nonalcoholic fatty liver disease. Am J Cardiol 2013;112(3):436-443. [CrossRef]
37. Sert A, Pirgon O, Aypar E, Yilmaz H, Odabas D. Relationship between left ventricular mass and carotid intima media thickness in obese adolescents with non-alcoholic fatty liver disease. J Pediatr Endocrinol Metab 2012;25(9-10):927-934. [CrossRef]
38. Sert A, Pirgon O, Aypar E, Yılmaz H, Dündar B. Relationship between aspartate aminotransferase-to-platelet ratio index and carotid intima-media thickness in obese adolescents with non-alcoholic fatty liver disease. J Clin Res Pediatr Endocrinol 2013;5(3):182-188. [CrossRef]
39. Sezer OB, Buluş D, Hızlı Ş, Andıran N, Yılmaz D, Ramadan SU. Low 25-hydroxyvitamin D level is not an independent risk factor for hepatosteatosis in obese children. J Pediatr Endocrinol Metab 2016;29(7):783-788. [CrossRef]
40. Torun E, Özgen IT, Gökçe S, Aydın S, Cesur Y. Thyroid hormone levels in obese children and adolescents with non-alcoholic fatty liver disease. J Clin Res Pediatr Endocrinol 2014;6(1):34-39. [CrossRef]
41. Tunç S. Evaluation of risk factors associated with fatty liver disease in obese children and adolescents: a single center experience. Van Med J 2021;28(2):171-177. [CrossRef]
42. Ulualan G, Kiraz ZK, Kırel B. Relation of serum irisin levels to obesity and non-alcoholic fatty liver disease. Turk J Pediatr 2022;64(2):246-254. [CrossRef]
43. Ustyol A, Aycan Ustyol E, Gurdol F, Kokali F, Bekpınar S. P-selectin, endocan, and some adhesion molecules in obese children and adolescents with non-alcoholic fatty liver disease. Scand J Clin Lab Invest 2017;77(3):205-209. [CrossRef]
44. Ustyol A, Kokali F, Selçuk Duru N, Elevli M. Association of serum triglyceride-to-high-density lipoprotein cholesterol ratio with insulin resistance and non-alcoholic fatty liver disease in children and adolescents. Med Bull Haseki 2017;55(4):286-291. [CrossRef]
45. Yildiz I, Erol OB, Toprak S, Cantez MS, Omer B, Kilic A, et al. Role of vitamin D in children with hepatosteatosis. J Pediatr Gastroenterol Nutr 2014;59(1):106-111. [CrossRef]
46. Kılınç S, Demirbaş T, Atay E, Ceran Ö, Atay Z. Elevated 1-h post-load plasma glucose levels in normal glucose tolerance children with obesity is associated with early carotid atherosclerosis. Obes Res Clin Pract 2020;14(2):136-141. [CrossRef]
47. Keçeli Başaran M, Çiçek T. Causes of hypertransaminasemia in children, single-center experience. Family Pract Palliat Care 2021;6(1):56-61. [CrossRef]
48. Angın Y, Arslan N, Kuralay F. Leptin-to-adiponectin ratio in obese adolescents with nonalcoholic fatty liver disease. Turk J Pediatr 2014;56(3):259-266.

49. Arslan N, Makay B, Hızlı Ş, Koçyiğit A, Demircioğlu F, Tuncel AS, et al. Assessment of atherosclerosis in obese adolescents: positive correlation of mean platelet volume and carotid intima media thickness. J Paediatr Child Health 2013;49(11):963-968. [CrossRef]
50. Arslan N, Makay B. Mean platelet volume in obese adolescents with nonalcoholic fatty liver disease. J Pediatr Endocrinol Metab 2010;23(8):807-813. [CrossRef]
51. Binay C, Kirel B. Prevalence of metabolic syndrome in obese children who presented at our endocrinology clinic. Turkish J Pediatr Dis 2013;7(2):79-85. [CrossRef]
52. Boyraz M, Cekmez F, Karaoglu A, Cinaz P, Durak M, Bideci A. Serum adiponectin, leptin, resistin and RBP4 levels in obese and metabolic syndrome children with nonalcoholic fatty liver disease. Biomark Med 2013;7(5):737-745. [CrossRef]
53. Bulakci M, Ercan CC, Karapinar E, Aksakal MZT, Aliyev S, Bicen F, et al. Quantitative evaluation of hepatic steatosis using attenuation imaging in a pediatric population: a prospective study. Pediatr Radiol 2023;53(8):1629-1639. Erratum in: Pediatr Radiol 2023;53(8):1730. [CrossRef]
54. Erol M, Bostan Gayret O, Tekin Nacaroglu H, Yigit O, Zengi O, Salih Akkurt M, et al. Association of osteoprotegerin with obesity, insulin resistance and non-alcoholic fatty liver disease in children. Iran Red Crescent Med J 2016;18(11):e41873. [CrossRef]
55. Hacihamdioğlu B, Okutan V, Yozgat Y, Yildirim D, Kocaoğlu M, Lenk MK, et al. Abdominal obesity is an independent risk factor for increased carotid intima-media thickness in obese children. Turk J Pediatr 2011;53(1):48-54.
56. Hatipoğlu N, Doğan S, Mazıcıoğlu MM, Kurtoğlu S. Relationship between neck circumference and non-alcoholic fatty liver disease in childhood obesity. J Clin Res Pediatr Endocrinol 2016;8(1):32-39. [CrossRef]
57. Hizli S, Koçyigit A, Arslan N, Tuncel SA, Demircioglu F, Cakmakçi H, et al. Hepatic artery resistance in children with obesity and fatty liver. Indian J Pediatr 2010;77(4):407-411. [CrossRef]
58. Mengen E. The relation of vitamin d levels to insulin resistance and hepatosteatosis in obese children. Turk J Pediatr Dis 2020;14(1):36-41. [Turkish] [CrossRef]
59. Muratoğlu Şahin N, Arasli Yilmaz A, Aycan Z. Is the 1st hour plasma glucose level in ogtt an important parameter in children with normal glucose tolerance? Turkiye Klinikleri J Med Sci 2020;40(1):1-9. [CrossRef]
60. Özhan B, Bilgihan E, Çetin O, Ağladioğlu K. The relations of vitamin D receptor gene polymorphisms with risk of obesity, metabolic syndrome, hepatosteatosis in Turkish children. Pamukkale Med J 2023;16(2):274-280. [CrossRef]
61. Özkan MB, Bilgici MC, Eren E, Caltepe G, Yilmaz G, Kara C, et al. Role of point shear wave elastography in the determination of the severity of fibrosis in pediatric liver diseases with pathologic correlations. J Ultrasound Med 2017;36(11):2337-2344. [CrossRef]
62. Sağlam NÖ, Aksoy S, Kazancı SY, Palabıyık F, Hatipoğlu SS, İnci E. The performance of shear wave elastography on evaluating liver changes in obese and overweight children. Turk J Pediatr 2021;63(4):575-583. [CrossRef]
63. Sanri A, Tuna Kirsaçlioğlu C, Sanri E, Şayli TR. Etiological evaluation of the elevated transaminases in children. Cumhuriyet Med J 2020;42(1):56-64. [CrossRef]
64. Serdaroğlu F, Koca T, Dereci S, Akçam M. The etiology of hypertransaminasemia in Turkish children. Bosn J Basic Med Sci 2016;16(2):151-156. [CrossRef]
65. Tuncel SA, Koçyiğit A, Demircioğlu F, Hızlı Ş, Çakmakçı H. Assessment of hepatic artery flow volume changes due to hepatosteatosis on pediatric obese patients. Pamukkale Med J 2014;2(1):131-136. [CrossRef]
66. Yilmaz Y, Yilmaz N, Ates F, Karakaya F, Gokcan H, Kaya E, et al; Turkish Association for the Study of the Liver (TASL); Fatty Liver Diseases Special Interest Groups. The prevalence of metabolic-associated fatty liver disease in the Turkish population: A multicenter study. Hepatol Forum 2021;2(2):37-42. [CrossRef]
67. Sezgin O, Akpınar H, Özer B, Törüner M, Bal K, Bor S. The Abdominal ultrasonography results of cappadocia cohort study of Türkiye reveals high prevalence of fatty liver. Turk J Gastroenterol 2023;34(6):652-664. [CrossRef]
68. Kaya E, Demir D, Alahdab YO, Yilmaz Y. Prevalence of hepatic steatosis in apparently healthy medical students: a transient elastography study on the basis of a controlled attenuation parameter. Eur J Gastroenterol Hepatol 2016;28(11):1264-1267. [CrossRef]
69. Okur G, Karacaer Z. The prevalence of non-alcoholic fatty liver disease in healthy young persons. North Clin Istanb 2016;3(2):111-117. [CrossRef]
70. Avcu A, Kaya E, Yilmaz Y. Feasibility of fibroscan in assessment of hepatic steatosis and fibrosis in obese patients: report from a general internal medicine clinic. Turk J Gastroenterol 2021;32(5):466-472. [CrossRef]
71. Yüksel F, Türkkan D, Yüksel I, Kara S, Celik N, Samdancı E. Fatty liver disease in an autopsy series of children and adolescents. Hippokratia 2012;16(1):61-65.
72. Jebeile H, Kelly AS, O'Malley G, Baur LA. Obesity in children and adolescents: epidemiology, causes, assessment, and management. Lancet Diabetes Endocrinol 2022;10(5):351-365. [CrossRef]
73. Feldstein AE, Charatcharoenwitthaya P, Treeprasertsuk S, Benson JT, Enders FB, Angulo P. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. Gut 2009;58(11):1538-1544. [CrossRef]
74. Cioffi C, Welsh J, Cleeton R, Caltharp S, Romero R, Wulkan M, et al. Natural history of NAFLD diagnosed in childhood: A single-center study. Children 2017;4:34. [CrossRef]
75. Brumbaugh DE, Tearse P, Cree-Green M, Fenton LZ, Brown M, Scherzinger A, et al. Intrahepatic fat is increased in the neonatal offspring of obese women with gestational diabetes. J Pediatr 2013;162(5):930-936.e1. [CrossRef]
76. Geserick M, Vogel M, Gausche R, Lipek T, Spielau U, Keller E, et al. Acceleration of BMI in early childhood and risk of sustained obesity. N Engl J Med 2018;379(14):1303-1312. [CrossRef]
77. Ball GDC, Merdad R, Birken CS, Cohen TR, Goodman B, Hadjiyannakis S, et al. Managing obesity in children: a clinical practice guideline. CMAJ 2025;197(14):E372-E389. [CrossRef]
78. Vos MB, Abrams SH, Barlow SE, Caprio S, Daniels SR, Kohli R, et al. NASPGHAN Clinical Practice Guideline for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Disease in Children: Recommendations from the Expert Committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN). J Pediatr Gastroenterol Nutr 2017;64(2):319-334. [CrossRef]
79. Allen AM, Lazarus JV, Alkhouri N, Noureddin M, Wong VW, Tsochatzis EA, et al. Global patterns of utilization of noninvasive tests for the clinical management of metabolic dysfunction-associated steatotic liver disease. Hepatol Commun 2025;9(5):e0678. [CrossRef]
80. Eren F, Kaya E, Yilmaz Y. Accuracy of Fibrosis-4 index and non-alcoholic

fatty liver disease fibrosis scores in metabolic (dysfunction) associated fatty liver disease according to body mass index: failure in the prediction of advanced fibrosis in lean and morbidly obese individuals. Eur J Gastroenterol Hepatol 2022;34(1):98-103. [CrossRef]

81. Kaya E, Bakir A, Eren F, Yilmaz Y. The utility of noninvasive scores in non-alcoholic fatty liver disease patients with normal and elevated serum transaminases. Hepatol Forum 2020;1(1):8-13. [CrossRef]
82. Alkayyali T, Qutranji L, Kaya E, Bakir A, Yilmaz Y. Clinical utility of noninvasive scores in assessing advanced hepatic fibrosis in patients with type 2 diabetes mellitus: a study in biopsy-proven non-alcoholic fatty liver disease. Acta Diabetol 2020;57(5):613-618. [CrossRef]
83. Panganiban J, Kehar M, Ibrahim SH, Hartmann P, Sood S, Hassan S, et al. Metabolic dysfunction-associated steatotic liver disease (MASLD) in children with obesity: An Obesity Medicine Association (OMA) and expert joint perspective 2025. Obes Pillars 2025;14:100164. [CrossRef]
84. Degertekin B, Tozun N, Demir F, Soylemez G, Yapali S, Bozkurt U, et al. Determination of the upper limits of normal serum alanine aminotransferase (ALT) level in healthy Turkish population. Hepatol Forum 2020;1(2):44-47. [CrossRef]
85. Sun M, Sun H. Recent prevalence and trends of obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) among US adolescents: 1999 to 2020. Pediatr Obes 2025;20(5):e70003. [CrossRef]
86. Harrison SA, Bedossa P, Guy CD, Schattenberg JM, Loomba R, Taub R, et al; MAESTRO-NASH Investigators. A Phase 3, Randomized, Controlled Trial of Resmetirom in NASH with Liver Fibrosis. N Engl J Med 2024;390(6):497-509. [CrossRef]
87. Le P, Kaya E, Phan A, Yilmaz Y, Alkhouri N. Resmetirom-eligible population among US adults: An estimation analysis based on NHANES 2017-March 2020. Hepatol Commun 2025;9(7):e0755. [CrossRef]
88. Sanyal AJ, Newsome PN, Kliers I, Østergaard LH, Long MT, Kjær MS, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. N Engl J Med 2025;392(21):2089-2099. [CrossRef]
89. Fox CK, Barrientos-Pérez M, Bomberg EM, Dcruz J, Gies I, Harder-Lauridsen NM, et al. Liraglutide for Children 6 to <12 Years of Age with Obesity - A Randomized Trial. N Engl J Med 2025;392(6):555-565. [CrossRef]
90. Kelly AS, Auerbach P, Barrientos-Perez M, Gies I, Hale PM, Marcus C, et al. A randomized, controlled trial of liraglutide for adolescents with obesity. N Engl J Med 2020;382(22):2117-2128. [CrossRef]

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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).

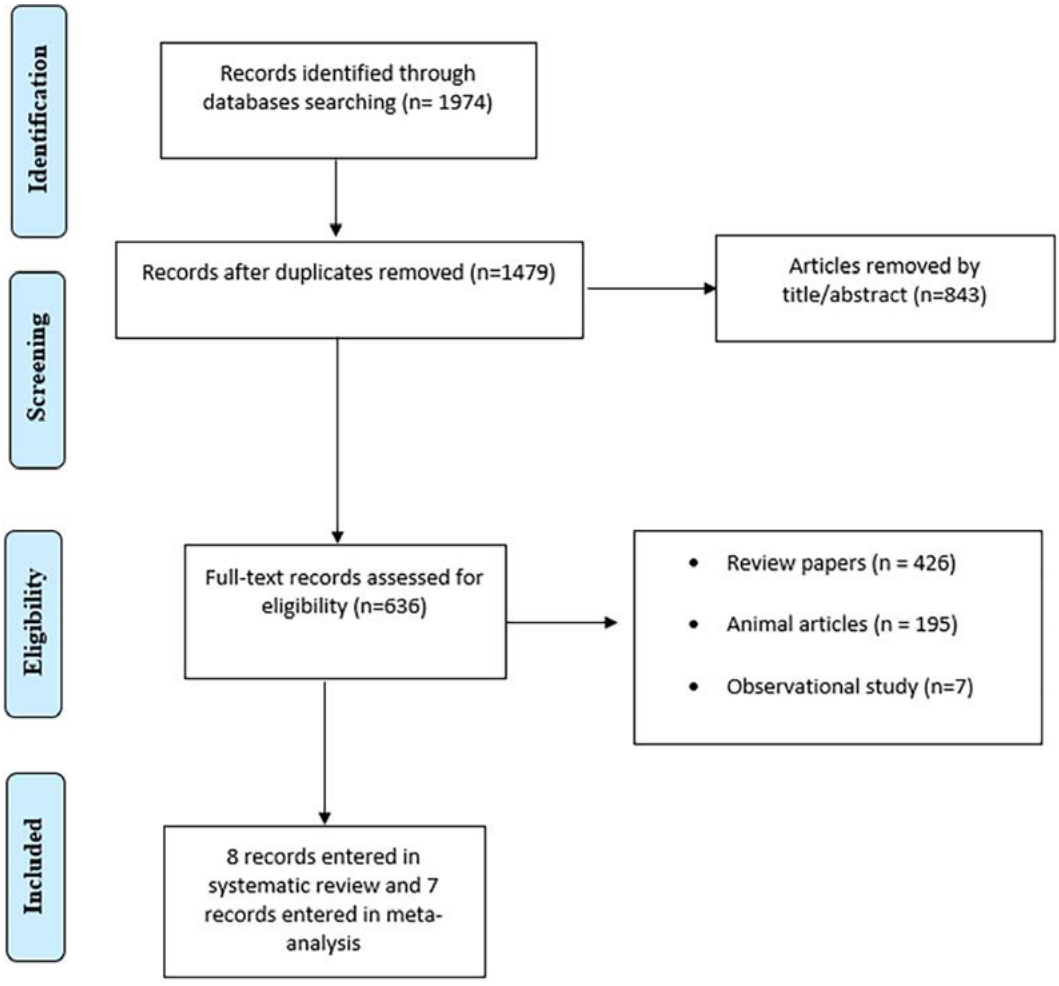



**Figure 1.** Flow diagram of the literature selection process.

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;

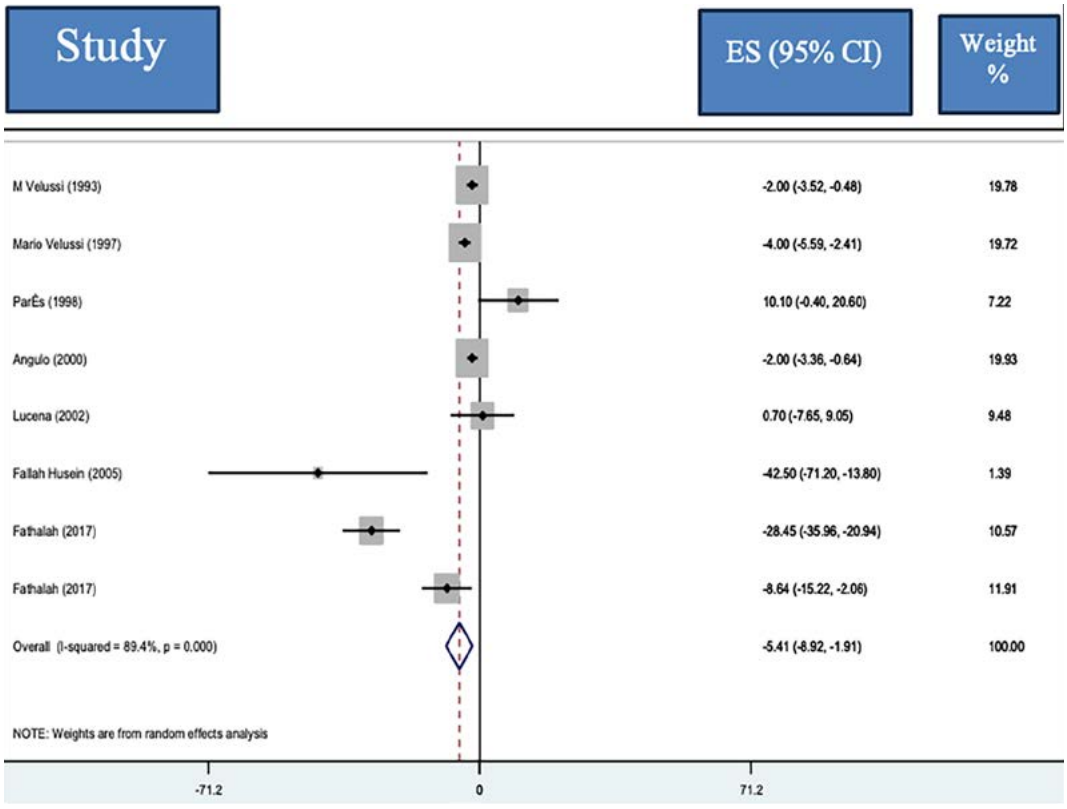



**Figure 2.** The effect of silymarin on aspartate aminotransferase in cirrhotic patients.

$I^2$=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).

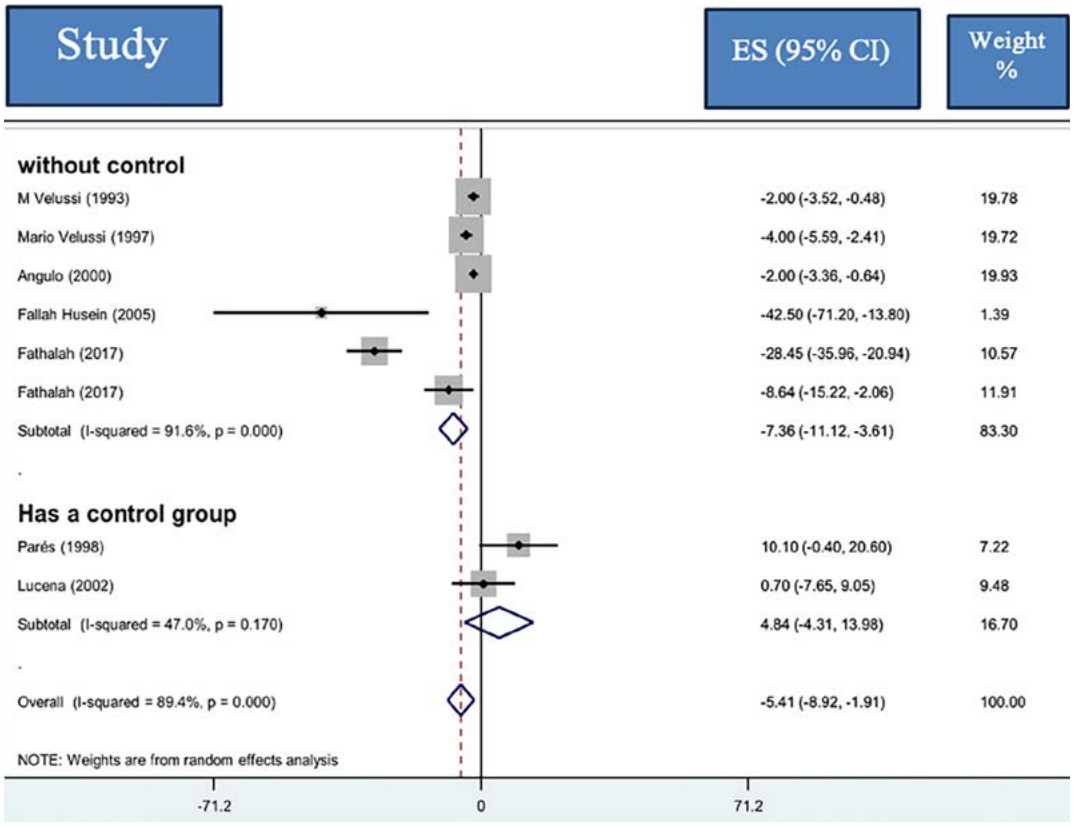



**Figure 3.** The effect of silymarin on aspartate aminotransferase in cirrhotic patients. Subgroup analysis based on having or not having a control group.

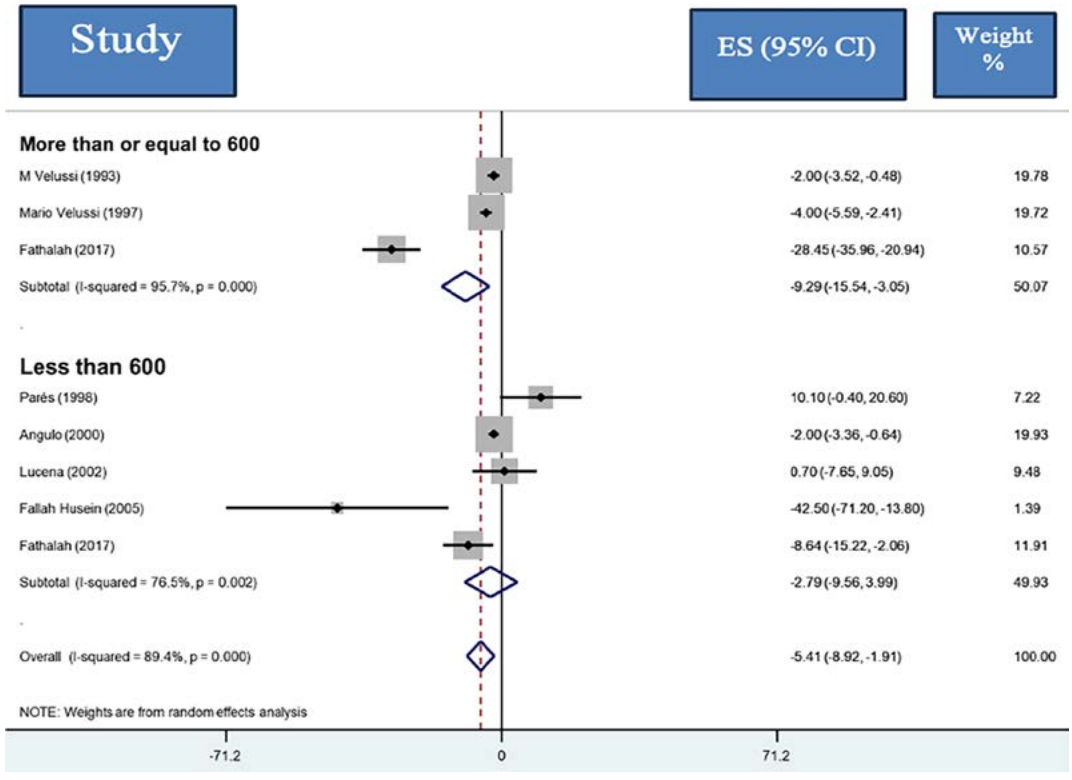



**Figure 4.** The effect of silymarin on aspartate aminotransferase in cirrhotic patients. Subgroup analysis based on dose (<600 mg/day or ≥600 mg/day).

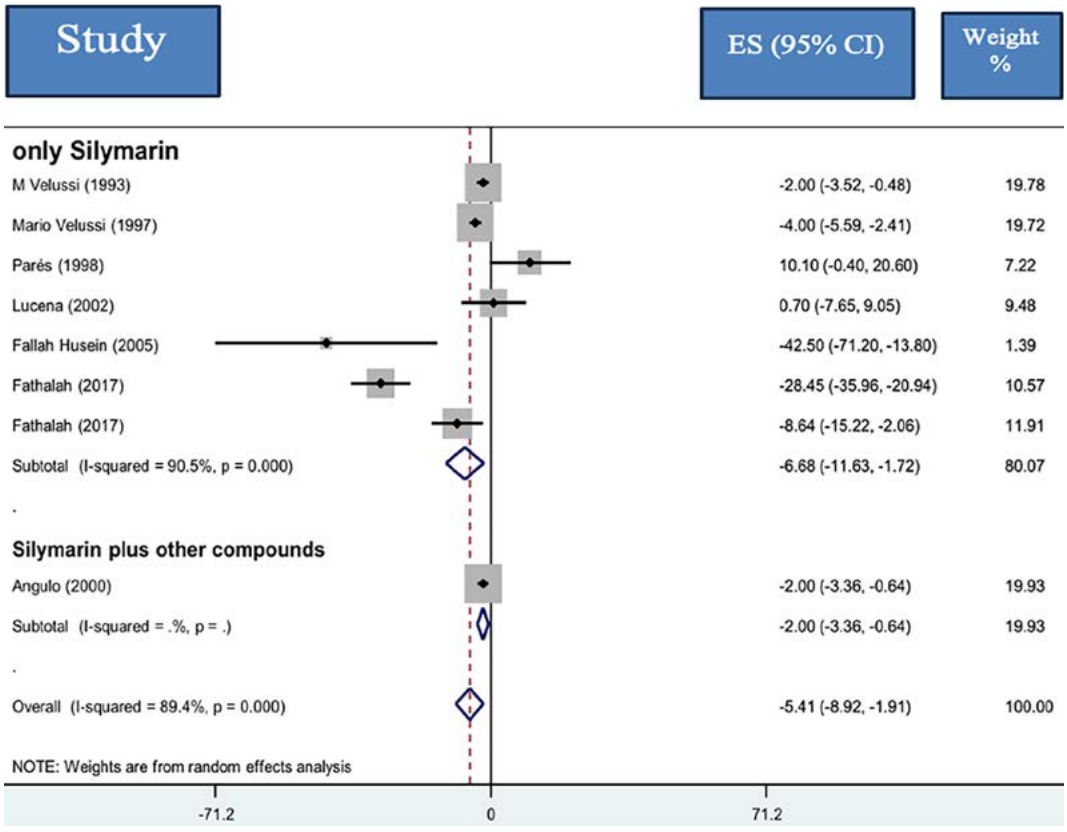



**Figure 5.** The effect of silymarin on aspartate aminotransferase in cirrhotic patients. Subgroup analysis based on intervention with silymarin or silymarin plus other compounds.

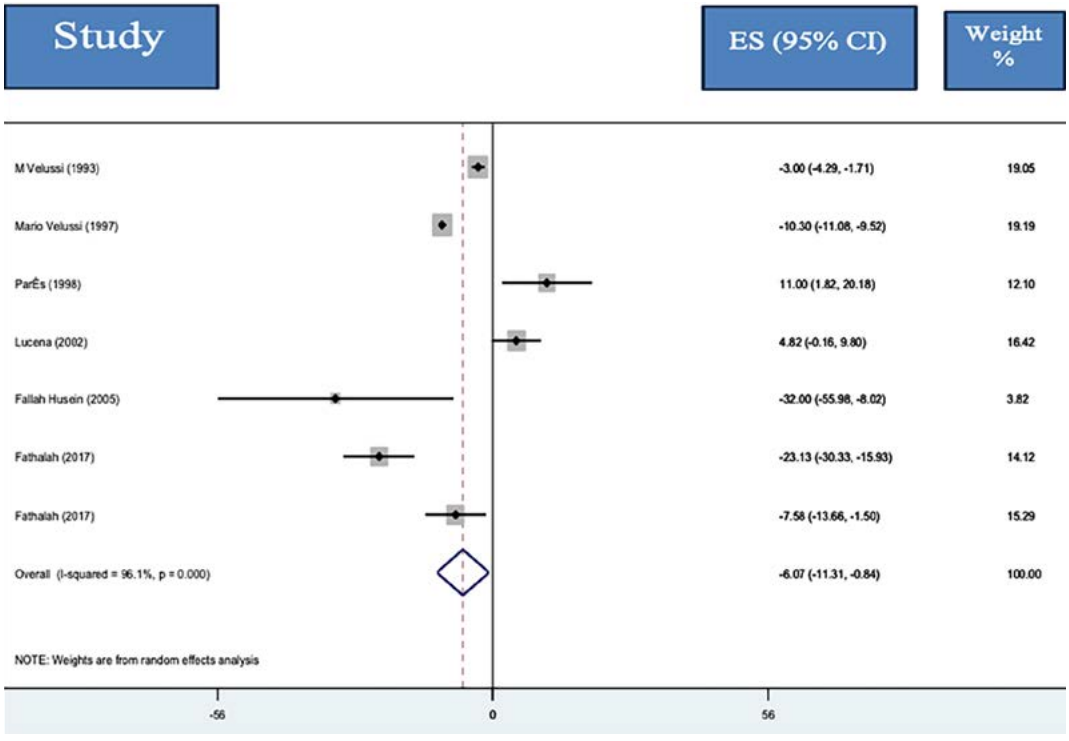



**Figure 6.** The effect of silymarin on alanine aminotransferase in cirrhotic patients.

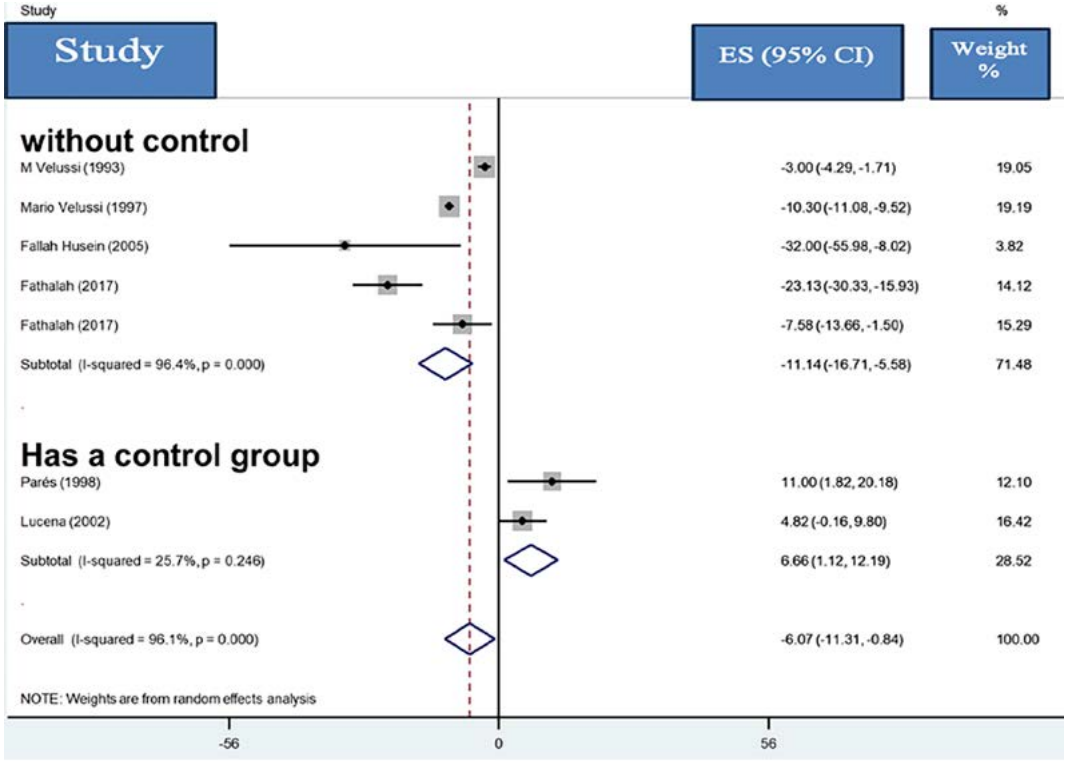



**Figure 7.** The effect of silymarin on alanine aminotransferase in cirrhotic patients. Subgroup analysis based on having or not having a control group.

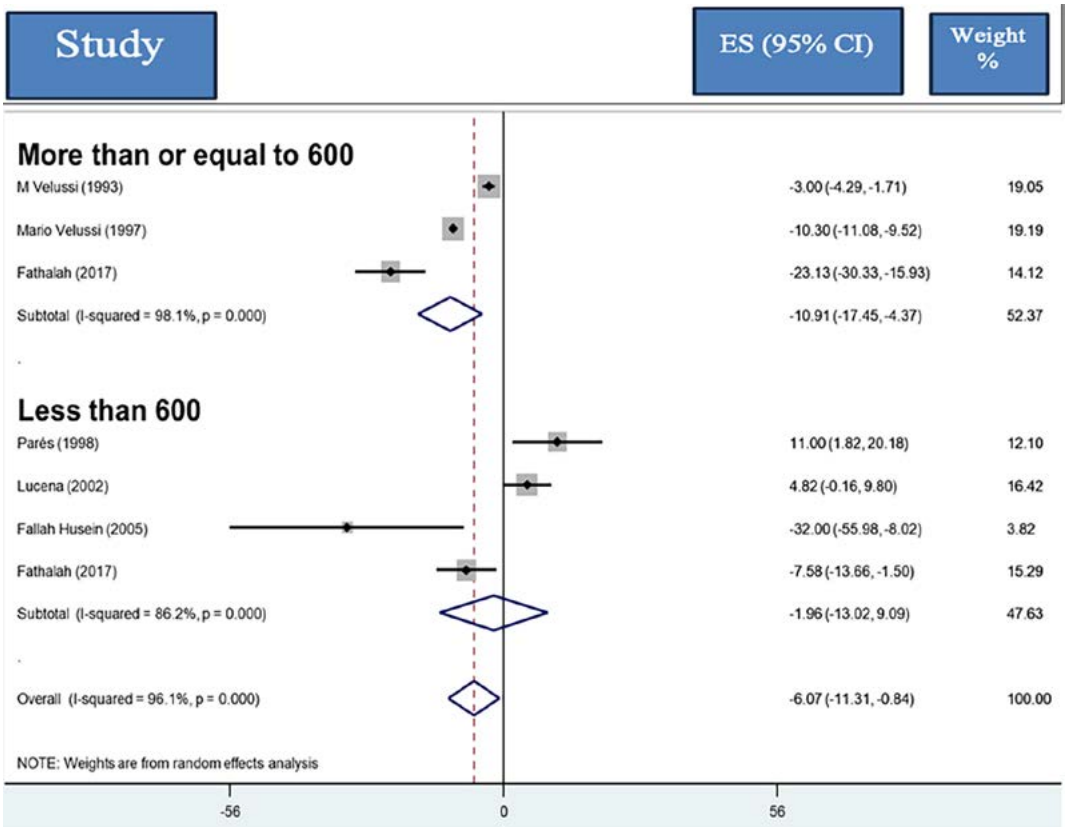



**Figure 8.** The effect of silymarin on alanine aminotransferase in cirrhotic patients. Subgroup analysis based on dose (<600 mg/day or ≥600 mg/day).

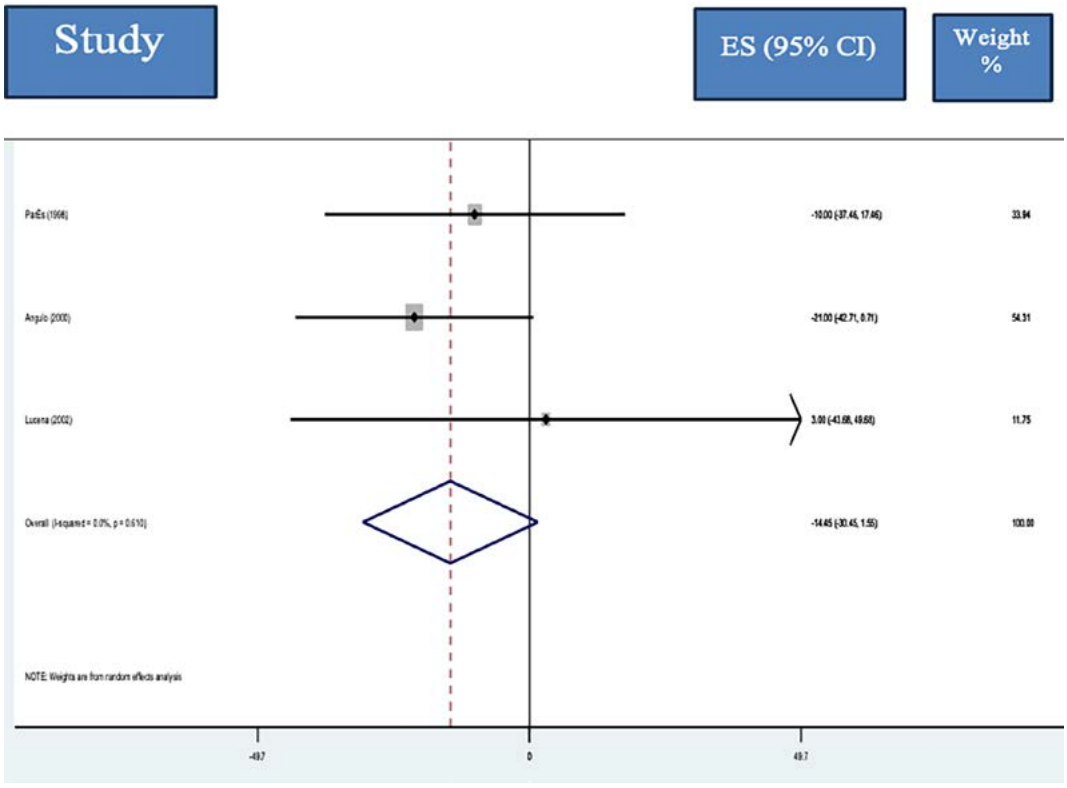



**Figure 9.** The effect of silymarin on alkaline phosphatase in cirrhotic patients.

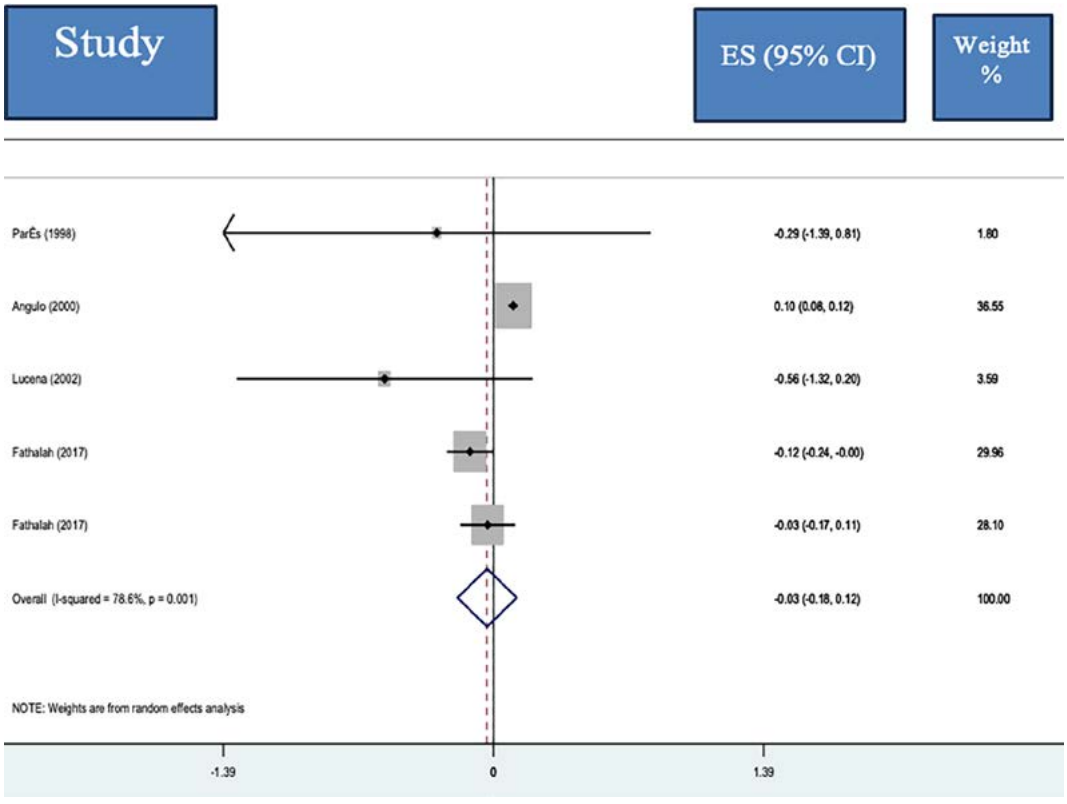



**Figure 10.** The effect of silymarin on bilirubin in cirrhotic patients.

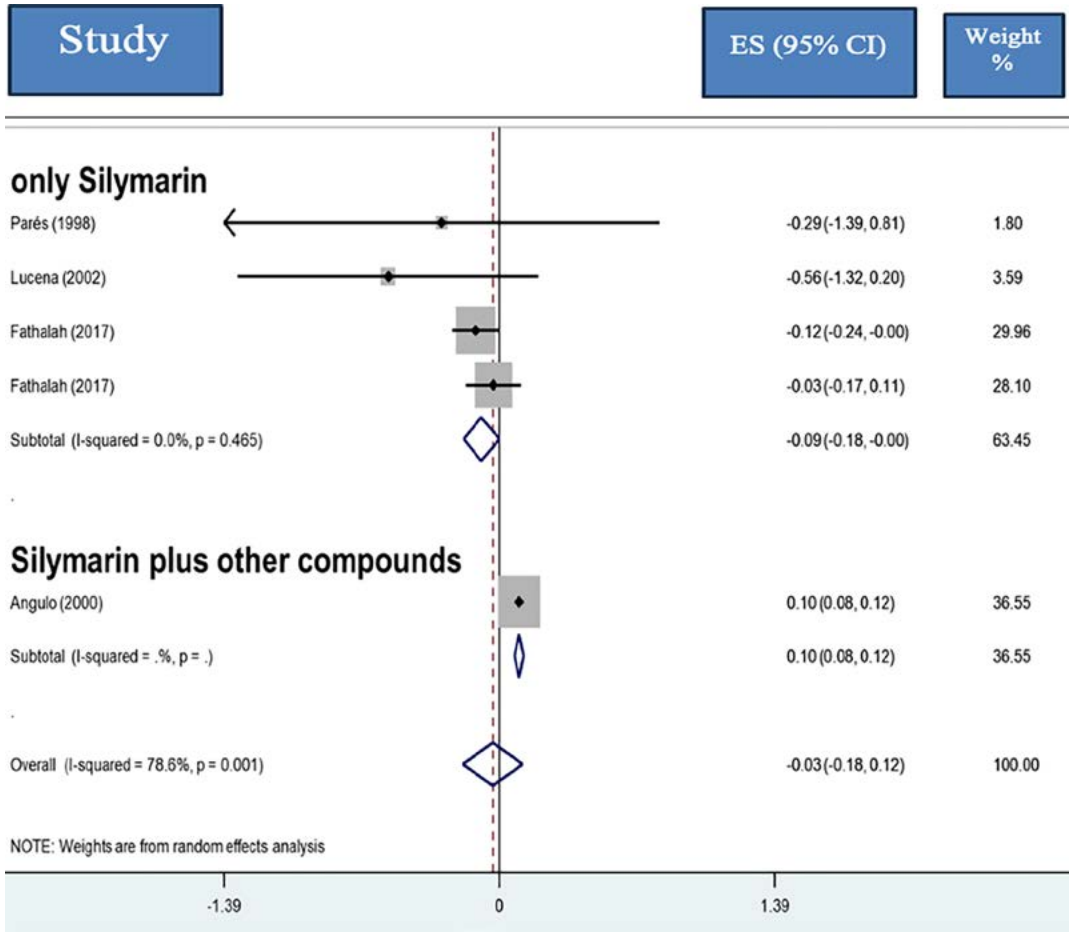



**Figure 11.** The effect of silymarin on bilirubin in cirrhotic patients. Subgroup analysis based on intervention with silymarin or silymarin plus other compounds.

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

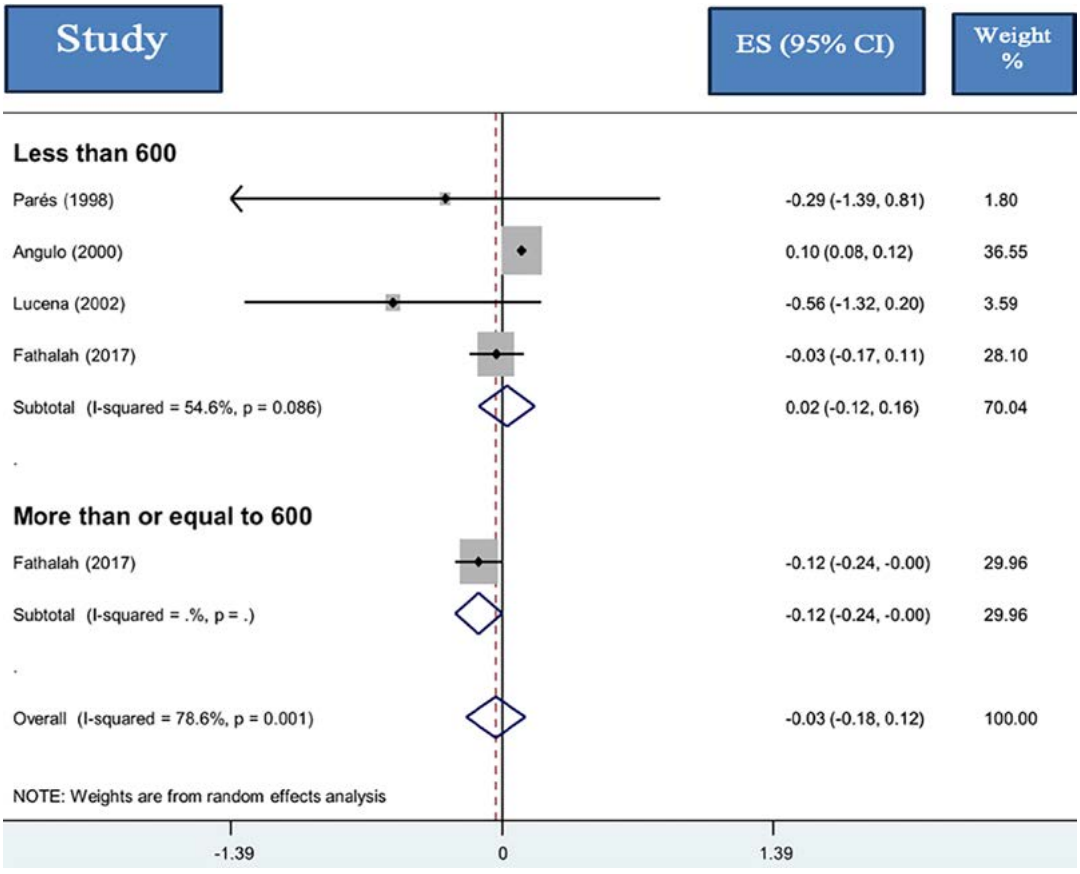



**Figure 12.** The effect of silymarin on Bilirubin in cirrhotic patients. Subgroup analysis based on dose (<600 mg/day or ≥600 mg/day).

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

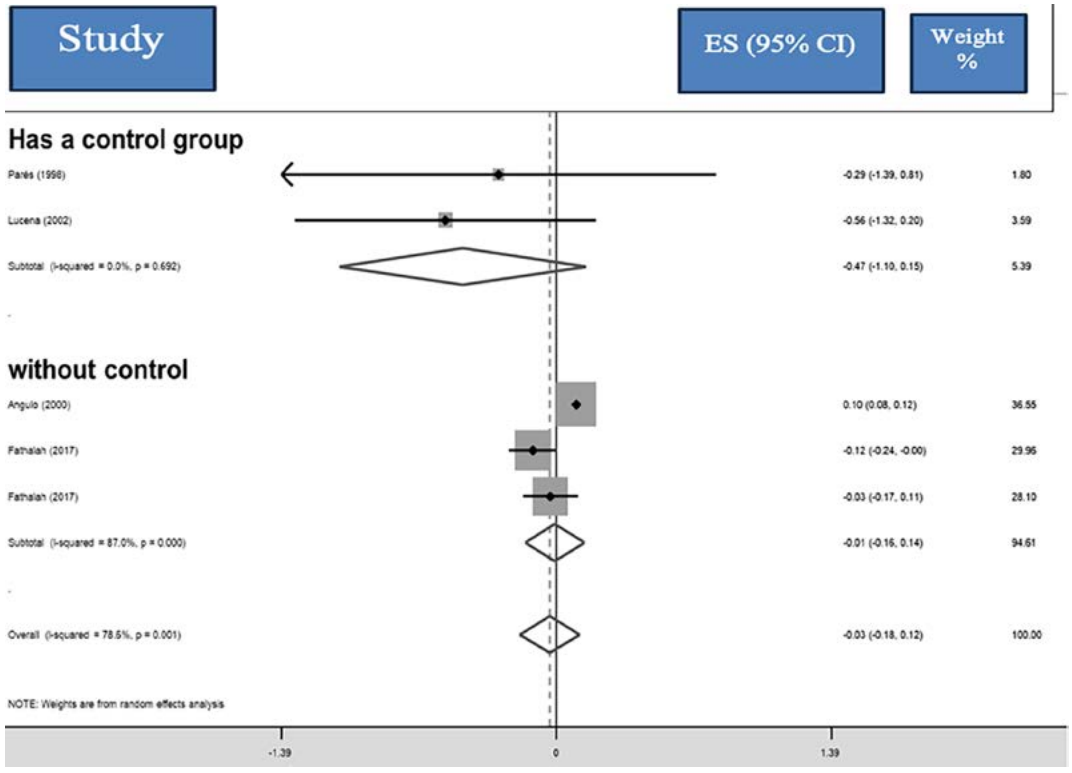



**Figure 13.** The effect of silymarin on Bilirubin in cirrhotic patients. Subgroup analysis based on having or not having a control group.

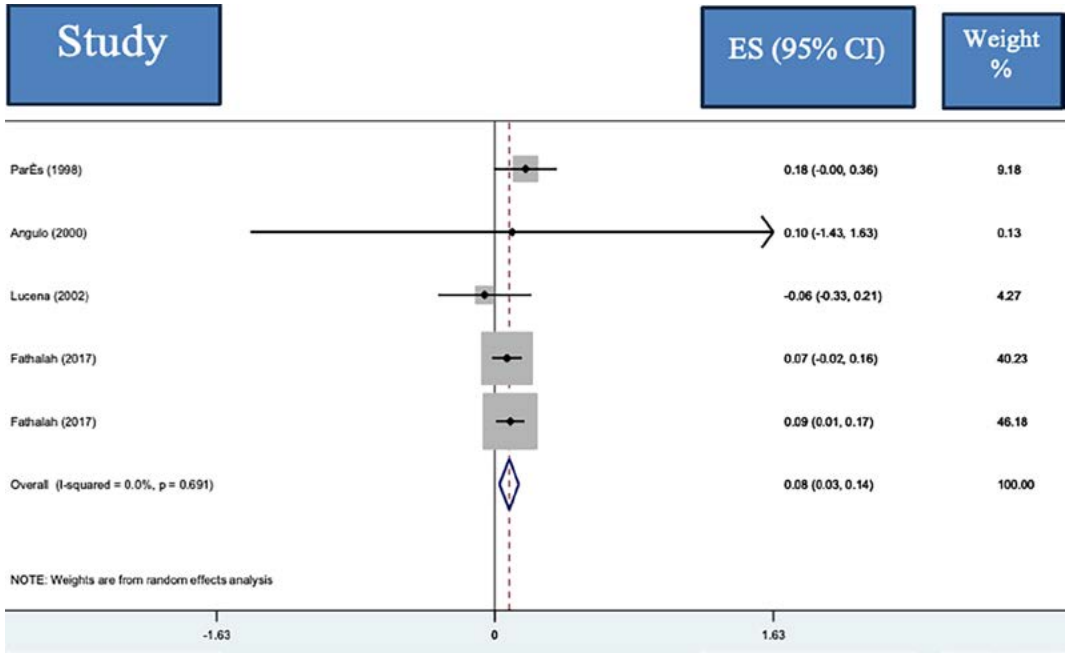



**Figure 14.** The effect of silymarin on the albumin in cirrhotic patients.

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

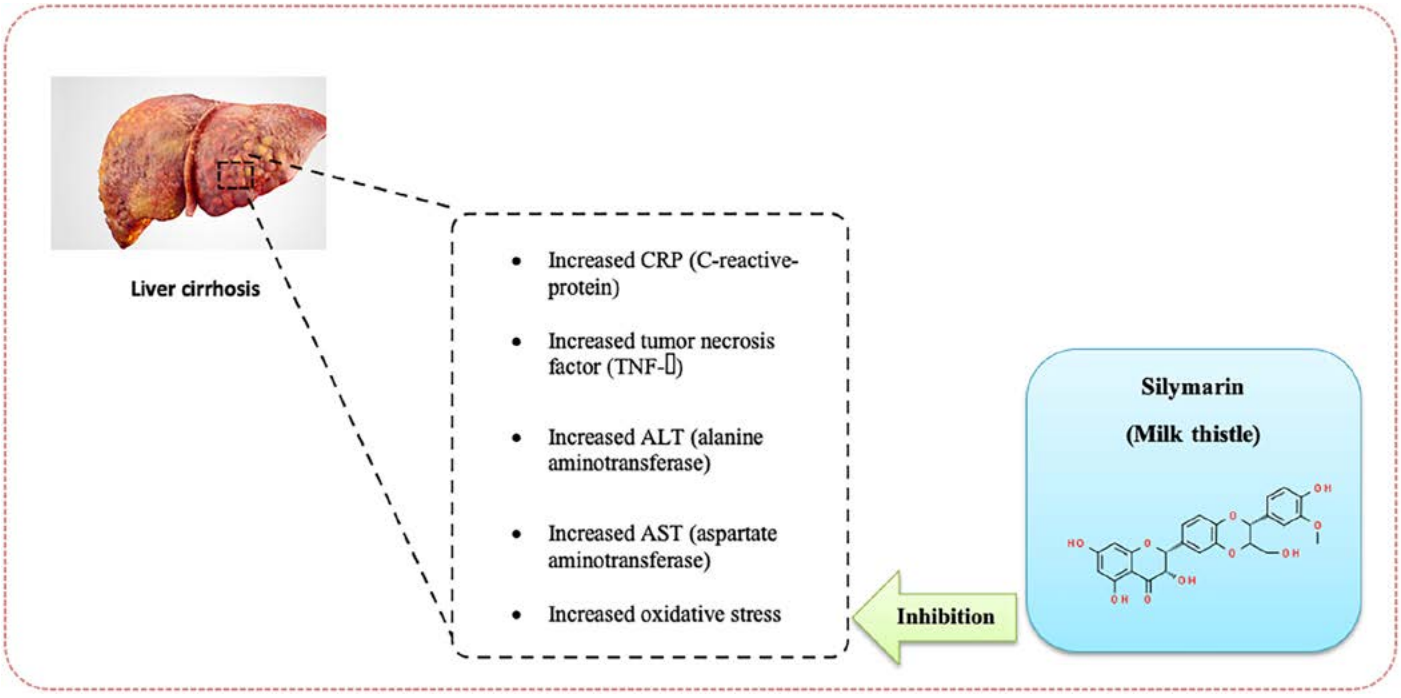



**Figure 15.** Possible mechanism of silymarin (milk thistle) on liver cirrhosis.

(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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**Peer-review:** Externally peer-reviewed.

## References

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet 2014;383(9930):1749-1761. [CrossRef]
2. Scaglione S, Kliethermes S, Cao G, Shoham D, Durazo R, Luke A, et al. The Epidemiology of Cirrhosis in the United States: A Population-based Study. J Clin Gastroenterol 2015;49(8):690-696. [CrossRef]
3. Wiegand J, Berg T. The etiology, diagnosis and prevention of liver cirrhosis: part 1 of a series on liver cirrhosis. Dtsch Arztebl Int 2013;110(6):85-91. [CrossRef]
4. Tang K-T, Dufour J-F, Chen P-H, Hernaez R, Hutfless S. Antitumour necrosis factor-α agents and development of new-onset cirrhosis or non-alcoholic fatty liver disease: a retrospective cohort. BMJ Open Gastroenterol 2020;7(1):e000349. [CrossRef]
5. Lu SC. Dysregulation of glutathione synthesis in liver disease. Liver Res 2020;4(2):64-73. [CrossRef]
6. Lai CY, Cheng SB, Lee TY, Liu HT, Huang SC, Huang YC. Possible synergistic effects of glutathione and c-reactive protein in the progression of liver cirrhosis. Nutrients. 2018 27;10(6):678. [CrossRef]
7. Czeczot H, Scibior D, Skrzycki M, Podsiad M. Glutathione and GSH-dependent enzymes in patients with liver cirrhosis and hepatocellular carcinoma. Acta Biochim Pol 2006;53(1):237-242. [CrossRef]
8. Vairappan B. Endothelial dysfunction in cirrhosis: Role of inflammation and oxidative stress. World J Hepatol 2015;7(3):443-459. [CrossRef]
9. Görg B, Qvartskhava N, Bidmon HJ, Palomero-Gallagher N, Kircheis G, Zilles K, Häussinger D. Oxidative stress markers in the brain of patients with cirrhosis and hepatic encephalopathy. Hepatology 2010;52(1):256-265. [CrossRef]
10. Natarajan SK, Thomas S, Ramamoorthy P, Basivireddy J, Pulimood AB, Ramachandran A, et al. Oxidative stress in the development of liver cirrhosis: a comparison of two different experimental models. J Gastroenterol Hepatol 2006;21(6):947-957. [CrossRef]
11. Zhou L, Wang S-B, Chen S-G, Qu Q, Rui J-A. Prognostic Value of ALT, AST, and AAR in Hepatocellular Carcinoma with B-Type Hepatitis-Associated Cirrhosis after Radical Hepatectomy. Clin Lab 2018;64(10):1739-1747. [CrossRef]
12. Ioannou GN, Green P, Lowy E, Mun EJ, Berry K. Differences in hepatocellular carcinoma risk, predictors and trends over time according to etiology of cirrhosis. PLoS One 2018;13(9):e0204412. [CrossRef]
13. Yoshiji H, Nagoshi S, Akahane T, Asaoka Y, Ueno Y, Ogawa K, et al. Evidence-based clinical practice guidelines for Liver Cirrhosis 2020. J Gastroenterol 2021;56(7):593-619. [CrossRef]
14. Smith A, Baumgartner K, Bositis C. Cirrhosis: Diagnosis and Management. Am Fam Physician 2019;100(12):759-770.
15. Chinese Society of Hepatology, Chinese Medical Association; Xu X, Duan Z, Ding H, Li W, Jia J, Wei L, et al. Chinese guidelines on the management of ascites and its related complications in cirrhosis. Hepatol Int 2019;13(1):1-21. [CrossRef]
16. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69(2):406-460. [CrossRef]
17. Ivashkin VT, Mayevskaya MV, Pavlov CS, Fedosyina YA, Bessonova YN, Pirogova IY, Garbuzenko DV. Treatment of liver cirrhosis complications: Clinical guidelines of the Russian Scientific Liver Society and Russian gastroenterological association. Russian J Gastroenterol Hepatol Coloproctol 2016;26(4):71-102. [CrossRef]
18. Ge PS, Runyon BA. Treatment of patients with cirrhosis. N Engl J Med 2016;375(8):767-777. [CrossRef]
19. Saller R, Meier R, Brignoli R. The use of silymarin in the treatment of liver diseases. Drugs 2001;61(14):2035-2063. [CrossRef]
20. Valková V, Ďúranová H, Bilčíková J, Habán M. Milk thistle (Silybum marianum): a valuable medicinal plant with several therapeutic purposes. J Microbiol Biotechnol and Food Sci 2021;9(4):836-843. [CrossRef]
21. Adetuyi BO, Omolabi FK, Olajide PA, Oloke JK. Pharmacological, biochemical and therapeutic potential of milk thistle (silymarin): a review. World News Nat Sci 2021;37:75-91.
22. Gillesen A, Schmidt HHJ. Silymarin as supportive treatment in liver diseases: A narrative review. Adv Ther 2020;37(4):1279-1301. [CrossRef]

23. Federico A, Dallio M, Loguercio C. Silymarin/silybin and chronic liver disease: a marriage of many years. Molecules 2017;22(2):191. [CrossRef]
24. Zaidi SNF, Mahboob T. Prevention of liver cirrhosis by Silymarin. Pak J Pharm Sci. 2017;30(4):1203-1211.
25. Ferenci P. Silymarin in the treatment of liver diseases: What is the clinical evidence? Clin Liver Dis (Hoboken) 2016;7(1):8-10. [CrossRef]
26. Kim SH, Oh DS, Oh JY, Son TG, Yuk DY, Jung YS. silymarin prevents restraint stress-induced acute liver injury by ameliorating oxidative stress and reducing inflammatory response. Molecules 2016;21(4):443. [CrossRef]
27. Abenavoli L, Izzo AA, Milić N, Cicala C, Santini A, Capasso R. Milk thistle (Silybum marianum): A concise overview on its chemistry, pharmacological, and nutraceutical uses in liver diseases. Phytother Res 2018;32(11):2202-2213. [CrossRef]
28. Bahmani M, Shirzad H, Rafieian S, Rafieian-Kopaei M. Silybum marianum: beyond hepatoprotection. J Evid Based Complementary Altern Med 2015;20(4):292-301. [CrossRef]
29. Soleimani V, Delghandi PS, Moallem SA, Karimi G. Safety and toxicity of silymarin, the major constituent of milk thistle extract: An updated review. Phytother Res 2019;33(6):1627-1638. [CrossRef]
30. Fehér J, Lengyel G. Silymarin in the prevention and treatment of liver diseases and primary liver cancer. Curr Pharm Biotechnol 2012;13(1):210-217. [CrossRef]
31. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Syst Rev 2021;10(1):89. [CrossRef]
32. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions. New York: John Wiley & Sons; 2019. [CrossRef]
33. Begg CB. Publication bias. The Handbook of Research Synthesis. New York: Russell Sage Foundation; 1994. p. 299-409.
34. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315(7109):629-634. [CrossRef]
35. Deeks JJ, Higgins JP, Altman DG. Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al (editors). Cochrane Handbook for Systematic Reviews of Interventions. New York: Wiley Online Library; 2019. p. 241-284. [CrossRef]
36. Ferenci P, Dragosics B, Dittrich H, Frank H, Benda L, Lochs H, et al. Randomized controlled trial of silymarin treatment in patients with cirrhosis of the liver. Hepatology 1989;9(1):105-113. [CrossRef]
37. Velussi M, Cernigoi A, Viezzoli L, Dapas F, Caffau C, Zilli M. Silymarin reduces hyperinsulinemia, malondialdehyde levels, and daily insulin need in cirrhotic diabetic patients. Curr Ther Res 1993;53(5):533-545. [CrossRef]
38. Velussi M, Cernigoi AM, De Monte A, Dapas F, Caffau C, Zilli M. Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients. J Hepatol 1997;26(4):871-879. [CrossRef]
39. Parés A, Planas R, Torres M, Caballería J, Viver JM, Acero D, et al. Effects of silymarin in alcoholic patients with cirrhosis of the liver: results of a controlled, double-blind, randomized and multicenter trial. J Hepatol 1998;28(4):615-621. [CrossRef]
40. Angulo P, Patel T, Jorgensen RA, Therneau TM, Lindor KD. Silymarin in the treatment of patients with primary biliary cirrhosis with a suboptimal response to ursodeoxycholic acid. Hepatology 2000;32(5):897-900. [CrossRef]
41. Lucena MI, Andrade RJ, de la Cruz JP, Rodriguez-Mendizabal M, Blanco E, Sánchez de la Cuesta F. Effects of silymarin MZ-80 on oxidative stress in patients with alcoholic cirrhosis. Results of a randomized, double-blind, placebo-controlled clinical study. Int J Clin Pharmacol Ther 2002;40(1):2-8. [CrossRef]
42. Fallah Huseini H, Alavian S, Toliat T, Jamshidi A, Heshmat R, Naghdi Badi H, et al. The efficacy of herbal medicine Khar Maryam (Silybum marianum (L.) Gaertn.) on liver cirrhosis in chronic hepatitis B patients. J Med Plants 2005;4(13):1-6.
43. Fathalah WF, Abdel Aziz MA, Abou el Soud NH, El Raziky MES. High dose of silymarin in patients with decompensated liver disease: a randomized controlled trial. J Interferon Cytokine Res 2017;37(11):480-487. [CrossRef]
44. Czaja AJ. Hepatic inflammation and progressive liver fibrosis in chronic liver disease. World J Gastroenterol 2014;20(10):2515-2532. [CrossRef]
45. Forbes SJ, Newsome PN. Liver regeneration - mechanisms and models to clinical application. Nat Rev Gastroenterol Hepatol 2016;13(8):473-485. [CrossRef]
46. Dhande D, Dhok A, Anjankar A, Nagpure S. Silymarin as an antioxidant therapy in chronic liver diseases: A comprehensive review. Cureus 2024;16(8):e67083. [CrossRef]
47. Cacciapuoti F, Scognamiglio A, Palumbo R, Forte R, Cacciapuoti F. Silymarin in non alcoholic fatty liver disease. World J Hepatol 2013;5(3):109-113. [CrossRef]
48. Calderon Martinez E, Herrera D, Mogan S, Hameed Z, Jangda AA, Khan TJ, et al. Impact of silymarin supplements on liver enzyme levels: A systematic review. Cureus 2023;15(10):e47608. [CrossRef]
49. Clichici S, Olteanu D, Nagy A-L, Oros A, Filip A, Mircea PA. Silymarin inhibits the progression of fibrosis in the early stages of liver injury in CCl4-treated rats. J Med Food 2015;18(3):290-298. [CrossRef]
50. Bernardi M, Ricci CS, Zaccherini G. Role of human albumin in the management of complications of liver cirrhosis. J Clin Exp Hepatol 2014;4(4):302-311. [CrossRef]
51. Kalas MA, Chavez L, Leon M, Taweesedt PT, Surani S. Abnormal liver enzymes: A review for clinicians. World J Hepatol 2021;13(11):1688-1698. [CrossRef]
52. Poupon R. Liver alkaline phosphatase: a missing link between choleresis and biliary inflammation. Hepatology 2015;61(6):2080-2090. [CrossRef]
53. Vargas-Mendoza N, Madrigal-Santillán E, Morales-González A, Esquivel-Soto J, Esquivel-Chirino C, García-Luna Y, et al. Hepatoprotective effect of silymarin. World J Hepatol 2014;6(3):144-149. [CrossRef]
54. Kerner A, Avizohar O, Sella R, Bartha P, Zinder O, Markiewicz W, et al. Association between elevated liver enzymes and C-reactive protein: possible hepatic contribution to systemic inflammation in the metabolic syndrome. Arterioscler Thromb Vasc Biol 2005;25(1):193-197. [CrossRef]
55. Yang Y, Nemoto E, Harvey S, Subbotin V, Gandhi C. Increased hepatic platelet activating factor (PAF) and PAF receptors in carbon tetrachloride induced liver cirrhosis. Gut 2004;53(6):877-883. [CrossRef]
56. Zhao Y, Chen Y-Q, Bonacci TM, Bredt DS, Li S, Bensch WR, et al. Identification and characterization of a major liver lysophosphatidylcholine acyltransferase. J Biol Chem 2008;283(13):8258-8265. [CrossRef]
57. Harayama T, Shindou H, Ogasawara R, Suwabe A, Shimizu T. Identification of a novel noninflammatory biosynthetic pathway of platelet-activating factor. J Biol Chem 2008;283(17):11097-11106. [CrossRef]
58. Stanca E, Serviddio G, Bellanti F, Vendemiale G, Siculella L, Giudetti AM. Down-regulation of LPCAT expression increases platelet-activating factor level in cirrhotic rat liver: potential antiinflammatory effect of silybin. Biochim Biophys Acta 2013;1832(12):2019-2026. [CrossRef]

59. Guo Y, Wang S, Wang Y, Zhu T. Silymarin improved diet-induced liver damage and insulin resistance by decreasing inflammation in mice. Pharm Biol 2016;54(12):2995-3000. [CrossRef]
60. Freitag AF, Cardia GF, da Rocha BA, Aguiar RP, Silva-Comar FM, Spironello RA, et al. Hepatoprotective effect of silymarin (Silybum marianum) on hepatotoxicity induced by acetaminophen in spontaneously hypertensive rats. Evid Based Complement Alternat Med 2015;2015:538317. [CrossRef]
61. Gracia-Sancho J, Laviña B, Rodríguez-Vilarrupla A, García-Calderó H, Fernández M, Bosch J, García-Pagán JC. Increased oxidative stress in cirrhotic rat livers: a potential mechanism contributing to reduced nitric oxide bioavailability. Hepatology 2008;47:1248-1256. [CrossRef]
62. Wagner GM, Lubin BH, Chiu DT-Y. Oxidative damage to red blood cells. In Chow CK (editor). Cellular Antioxidant Defense Mechanisms. Boca Raton, Florida: CRC Press; 2019. p. 185-196. [CrossRef]
63. Girón-González JA, Martínez-Sierra C, Rodriguez-Ramos C, Macías MA, Rendón P, Díaz F, et al. Implication of inflammation-related cytokines in the natural history of liver cirrhosis. Liver Int 2004;24(5):437-445. [CrossRef]
64. Arroyo V, Angeli P, Moreau R, Jalan R, Clària J, Trebicka J, et al. The systemic inflammation hypothesis: towards a new paradigm of acute decompensation and multiorgan failure in cirrhosis. J Hepatol 2021;74(3):670-685. [CrossRef]
65. Geetha A, Priya ML, Jeyachristy SA, Surendran R. Level of oxidative stress in the red blood cells of patients with liver cirrhosis. Indian J Med Res 2007;126(3):204-210.
66. Park GJH, Lin BP, Ngu MC, Jones DB, Katelaris PH. Aspartate aminotransferase: alanine aminotransferase ratio in chronic hepatitis C infection: is it a useful predictor of cirrhosis? Journal of gastroenterology and hepatology 2000;15(4):386-390. [CrossRef]
67. Nyblom H, Björnsson E, Simrén M, Aldenborg F, Almer S, Olsson R. The AST/ALT ratio as an indicator of cirrhosis in patients with PBC. Liver Int 2006;26(7):840-845. [CrossRef]
68. Alempijevic T, Krstic M, Jesic R, Jovanovic I, Milutinovic AS, Kovacevic N, et al. Biochemical markers for non-invasive assessment of disease stage in patients with primary biliary cirrhosis. World J Gastroenterol 2009;15(5):591-594. [CrossRef]
69. Bernardi M, Caraceni P. Novel perspectives in the management of decompensated cirrhosis. Nat Rev Gastroenterol Hepatol 2018;15:753-764. [CrossRef]
70. Shaker E, Mahmoud H, Mnaa S. Silymarin, the antioxidant component and Silybum marianum extracts prevent liver damage. Food Chem Toxicol 2010;48(3):803-806 [CrossRef]
71. El-Lakkany NM, Hammam OA, El-Maadawy WH, Badawy AA, Ain-Shoka AA, Ebeid FA. Anti-inflammatory/anti-fibrotic effects of the hepatoprotective silymarin and the schistosomicide praziquantel against Schistosoma mansoni-induced liver fibrosis. Parasit Vectors 2012;5:9. [CrossRef]
72. Camini FC, Costa DC. Silymarin: not just another antioxidant. J Basic Clin Physiol Pharmacol 2020;31(4):/j/jbcpp.2020.31.issue-4/jbcpp-2019-0206/jbcpp-2019-0206.xml. [CrossRef]
73. Abdel-Moneim AM, Al-Kahtani MA, El-Kersh MA, Al-Omair MA. Free radical-scavenging, anti-inflammatory/anti-fibrotic and hepatoprotective actions of taurine and silymarin against CCl4 induced rat liver damage. PLoS One 2015;10(12):e0144509. [CrossRef]
74. Tsai JH, Liu JY, Wu TT, Ho PC, Huang CY, Shyu JC, et al. Effects of silymarin on the resolution of liver fibrosis induced by carbon tetrachloride in rats. J Viral Hepat 2008;15(7):508-514. [CrossRef]
75. Mayer KE, Myers RP, Lee SS. Silymarin treatment of viral hepatitis: a systematic review. J Viral Hepat 2005;12(6):559-567. [CrossRef]
76. de Avelar CR, Pereira EM, de Farias Costa PR, de Jesus RP, de Oliveira LPM. Effect of silymarin on biochemical indicators in patients with liver disease: Systematic review with meta-analysis. World J Gastroenterol 2017;23(27):5004-5017. [CrossRef]
77. Chen IS, Chen YC, Chou CH, Chuang RF, Sheen LY, Chiu CH. Hepatoprotection of silymarin against thioacetamide-induced chronic liver fibrosis. J Sci Food Agric 2012;92(7):1441-1447. [CrossRef]
78. Tighe SP, Akhtar D, Iqbal U, Ahmed A. Chronic liver disease and silymarin: A biochemical and clinical review. J Clin Transl Hepatol 2020;8(4):454-458. [CrossRef]
79. Freedman N, Curto T, Morishima C, Seeff L, Goodman Z, Wright E, Sinha R, et al. Silymarin use and liver disease progression in the hepatitis C antiviral long-term treatment against cirrhosis trial. Aliment Pharmacol Ther 2011;33(1):127-137. [CrossRef]
80. Kalopitas G, Antza C, Doundoulakis I, Siargkas A, Kouroumalis E, Germanidis G, et al. Impact of Silymarin in individuals with nonalcoholic fatty liver disease: A systematic review and meta-analysis. Nutrition 2021;83:111092. [CrossRef]

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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.

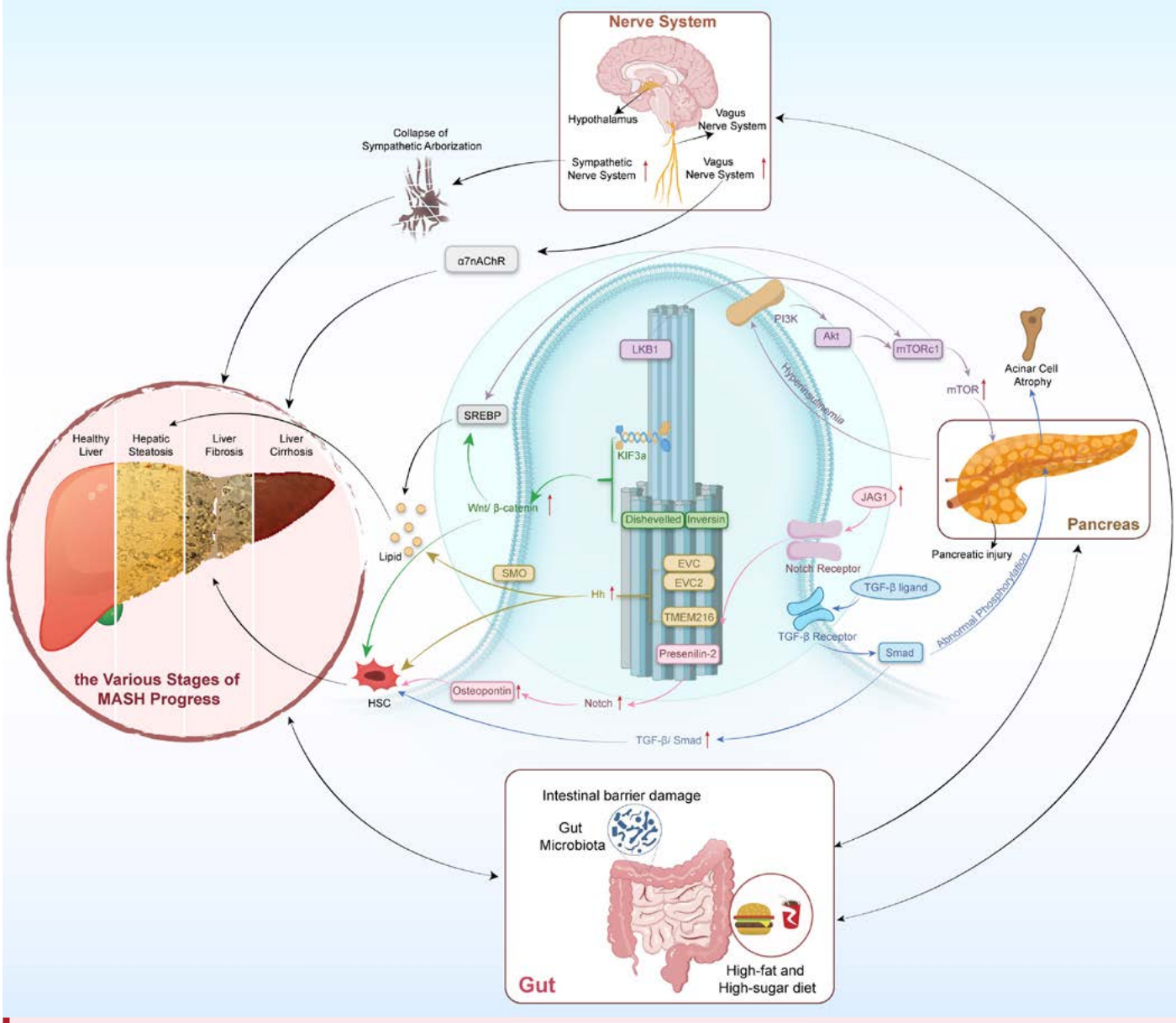



**Figure 1.** The regulatory pathway of the primary cilia in metabolic dysfunction-associated steatohepatitis. This schematic illustrates the pivotal role of PC as a signaling hub connecting the gut, pancreas, brain, and liver in MASH pathogenesis. PC dysfunction disrupts key pathways – including mTOR, 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; LED225 | 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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## References

1. Wong VW, Ekstedt M, Wong GL, Hagström H. Changing epidemiology, global trends and implications for outcomes of NAFLD. J Hepatol 2023;79(3):842-852. [CrossRef]
2. Guo Z, Wu D, Mao R, Yao Z, Wu Q, Lv W. Global burden of MAFLD, MAFLD related cirrhosis and MASH related liver cancer from 1990 to 2021. Sci Rep 2025;15(1):7083. [CrossRef]
3. Mellemkjær A, Kjær MB, Haldrup D, Grønbæk H, Thomsen KL. Management of cardiovascular risk in patients with metabolic dysfunction-associated steatotic liver disease. Eur J Intern Med 2024;122:28-34. [CrossRef]
4. Theodorakis N, Nikolaou M. From Cardiovascular-Kidney-Metabolic Syndrome to Cardiovascular-Renal-Hepatic-Metabolic Syndrome: Proposing an Expanded Framework. Biomolecules 2025;15(2):213. [CrossRef]
5. Kelty TJ, Dashek RJ, Arnold WD, Rector RS. Emerging Links between Nonalcoholic Fatty Liver Disease and Neurodegeneration. Semin Liver Dis 2023;43(1):77-88. [CrossRef]
6. Malicki JJ, Johnson CA. The Cilium: Cellular Antenna and Central Processing Unit. Trends Cell Biol 2017;27(2):126-140. [CrossRef]
7. Bloodgood RA. From central to rudimentary to primary: the history of an underappreciated organelle whose time has come. The primary cilium. Methods Cell Biol 2009;94:3-52. [CrossRef]
8. Ge R, Cao M, Chen M, Liu M, Xie S. Cytoskeletal networks in primary cilia: Current knowledge and perspectives. J Cell Physiol 2022;237(11):3975-3983. [CrossRef]
9. Volta F, Gerdes JM. The role of primary cilia in obesity and diabetes. Ann N Y Acad Sci 2017;1391(1):71-84. [CrossRef]
10. Yoo JJ, Cho EJ, Chung GE, Chang Y, Cho Y, Park SH, et al. Nonalcoholic Fatty Liver Disease Is a Precursor of New-Onset Metabolic Syndrome in Metabolically Healthy Young Adults. J Clin Med 2022;11(4):935. [CrossRef]
11. Baghaei K, Mazhari S, Tokhanbigli S, Parsamanesh G, Alavifard H, Schaafsma D, et al. Therapeutic potential of targeting regulatory mechanisms of hepatic stellate cell activation in liver fibrosis. Drug Discov Today 2022;27(4):1044-1061. [CrossRef]
12. Shamsan E, Almezgagi M, Gamah M, Khan N, Qasem A, Chuanchuan L, et al. The role of PI3k/AKT signaling pathway in attenuating liver fibrosis: a comprehensive review. Front Med 2024;11:1389329. [CrossRef]
13. Nguyen VTT, Brücker L, Volz AK, Baumgärtner JC, Dos Santos Guilherme M, Valeri F, et al. Primary Cilia Structure Is Prolonged in Enteric Neurons of 5xFAD Alzheimer's Disease Model Mice. Int J Mol Sci 2021;22(24):13564. [CrossRef]
14. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79(6):1542-1556. [CrossRef]
15. Steinberg GR, Valvano CM, De Nardo W, Watt MJ. Integrative metabolism in MASLD and MASH: Pathophysiology and emerging mechanisms. J Hepatol 2025;83(2):584-595. [CrossRef]
16. Gofton C, Upendran Y, Zheng MH, George J. MAFLD: How is it different from NAFLD? Clin Mol Hepatol 2023;29(Suppl):S17-S31. [CrossRef]
17. Hydes T, Alam U, Cuthbertson DJ. The impact of macronutrient intake on non-alcoholic fatty liver disease (NAFLD): Too much fat, too much carbohydrate, or just too many calories? Front Nutr 2021;8:640557. [CrossRef]
18. Li Y, Yang P, Ye J, Xu Q, Wu J, Wang Y. Updated mechanisms of MASLD pathogenesis. Lipids Health Dis 2024;23(1):117. [CrossRef]
19. Quek J, Chan KE, Wong ZY, Tan C, Tan B, Lim WH, et al. Global prevalence of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in the overweight and obese population: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2023;8(1):20-30. [CrossRef]
20. Kamm DR, McCommis KS. Hepatic stellate cells in physiology and pathology. J Physiol 2022;600(8):1825-1837. [CrossRef]
21. Amer AE, Ghoneim HA, Abdelaziz RR, Shehatou GSG, Suddek GM. L-carnitine attenuates autophagic flux, apoptosis, and necroptosis in rats with dexamethasone-induced non-alcoholic steatohepatitis. BMC Pharmacol Toxicol 2024;25(1):102. [CrossRef]
22. Simões ICM, Amorim R, Teixeira J, Karkucinska-Wieckowska A, Carvalho A, Pereira SP, et al. The alterations of mitochondrial function during NAFLD progression-an independent effect of mitochondrial ROS production. Int J Mol Sci 2021;22(13):6848. [CrossRef]
23. Masyuk AI, Masyuk TV, Splinter PL, Huang BQ, Stroope AJ, LaRusso NF. Cholangiocyte cilia detect changes in luminal fluid flow and transmit them into intracellular $Ca^{2+}$ and cAMP signaling. Gastroenterology 2006;131(3):911-920. [CrossRef]
24. Masyuk AI, Gradilone SA, Banales JM, Huang BQ, Masyuk TV, Lee SO, et al. Cholangiocyte primary cilia are chemosensory organelles that detect biliary nucleotides via P2Y12 purinergic receptors. Am J Physiol Gastrointest Liver Physiol 2008;295(4):G725-G734. [CrossRef]
25. Torrice A, Cardinale V, Gatto M, Semeraro R, Napoli C, Onori P, et al. Polycystins play a key role in the modulation of cholangiocyte proliferation. Dig Liver Dis 2010;42(5):377-385. [CrossRef]
26. Kaffe E, Fiorotto R, Pellegrino F, Mariotti V, Amenduni M, Cadamuro M, et al. β-Catenin and interleukin-1β-dependent chemokine (C-X-C motif) ligand 10 production drives progression of disease in a mouse model of congenital hepatic fibrosis. Hepatology 2018;67(5):1903-1919. [CrossRef]
27. Quelhas P, Oliveira R, Kieling C, Vieira S, Dos Santos J. Structural Disruption of Cilia and Increased Cytoplasmic Tubulin in Biliary Atresia-An Exploratory Study Focusing on Early Postoperative Prognosis Following Portoenterostomy. Biomedicines 2025;13(1):87. [CrossRef]
28. Chen IY, Whitney-Miller CL, Liao X. Congenital hepatic fibrosis and its mimics: a clinicopathologic study of 19 cases at a single institution. Diagn Pathol 2021;16(1):81. [CrossRef]
29. Lanser HC, Puckett Y. Biliary Duct Hamartoma. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. [CrossRef]
30. Quelhas P, Breton MC, Oliveira RC, Cipriano MA, Teixeira P, Cerski CT, et al. HIF-1alpha-pathway activation in cholangiocytes of patients with biliary atresia: An immunohistochemical/molecular exploratory study. J Pediatr Surg 2023;58(3):587-594. [CrossRef]
31. Foley DP, Fernandez LA, Leverson G, Anderson M, Mezrich J, Sollinger HW, et al. Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcomes from a single center. Ann Surg 2011;253(4):817-825. [CrossRef]
32. O'Neill S, Roebuck A, Khoo E, Wigmore SJ, Harrison EM. A meta-analysis and meta-regression of outcomes including biliary complications in donation after cardiac death liver transplantation. Transpl Int 2014;27(11):1159-

1174. [CrossRef]

33. Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E, Kamath PS. Global burden of liver disease: 2023 update. J Hepatol 2023;79(2):516-537. [CrossRef]
34. Wang S, Livingston MJ, Su Y, Dong Z. Reciprocal regulation of cilia and autophagy via the MTOR and proteasome pathways. Autophagy 2015;11(4):607-616. [CrossRef]
35. Vallianou NG, Kounatidis D, Psallida S, Vythoulkas-Biotis N, Adamou A, Zachariadou T, et al. NAFLD/MASLD and the Gut-Liver Axis: From Pathogenesis to Treatment Options. Metabolites 2024;14(7):366. [CrossRef]
36. Vallianou N, Christodoulatos GS, Karampela I, Tsilingiris D, Magkos F, Stratigou T, et al. Understanding the role of the gut microbiome and microbial metabolites in non-alcoholic fatty liver disease: Current evidence and perspectives. Biomolecules 2021;12(1):56. [CrossRef]
37. Wan YY, Sheng L. Regulation of bile acid receptor activity(☆). Liver Res 2018;2(4):180-185. [CrossRef]
38. Adorini L, Trauner M. FXR agonists in NASH treatment. J Hepatol 2023;79(5):1317-1331. [CrossRef]
39. Tilg H, Adolph TE, Trauner M. Gut-liver axis: Pathophysiological concepts and clinical implications. Cell Metab 2022;34(11):1700-1718. [CrossRef]
40. Scherer T, Sakamoto K, Buettner C. Brain insulin signalling in metabolic homeostasis and disease. Nat Rev Endocrinol 2021;17(8):468-483. [CrossRef]
41. Younossi ZM, Kalligeros M, Henry L. Epidemiology of metabolic dysfunction-associated steatotic liver disease. Clin Mol Hepatol 2025;31(Suppl):S32-S50. [CrossRef]
42. Taylor R. Pathogenesis of type 2 diabetes: tracing the reverse route from cure to cause. Diabetologia 2008;51(10):1781-1789. [CrossRef]
43. Raff EJ, Kakati D, Bloomer JR, Shoreibah M, Rasheed K, Singal AK. Diabetes Mellitus Predicts Occurrence of Cirrhosis and Hepatocellular Cancer in Alcoholic Liver and Non-alcoholic Fatty Liver Diseases. J Clin Transl Hepatol 2015;3(1):9-16. [CrossRef]
44. Brannick B, Dagogo-Jack S. Prediabetes and cardiovascular disease: Pathophysiology and interventions for prevention and risk reduction. endocrinology and metabolism Clinics of North America 2018;47(1):33-50. [CrossRef]
45. Sanyal AJ, Campbell-Sargent C, Mirshahi F, Rizzo WB, Contos MJ, Sterling RK, et al. Nonalcoholic steatohepatitis: association of insulin resistance and mitochondrial abnormalities. Gastroenterology 2001;120(5):1183-1192. [CrossRef]
46. Metz M, Beghini M, Wolf P, Pfleger L, Hackl M, Bastian M, et al. Leptin increases hepatic triglyceride export via a vagal mechanism in humans. Cell Metab 2022;34(11):1719-1731.e5. [CrossRef]
47. Hwang J, Lee S, Okada J, Liu L, Pessin JE, Chua SC, Jr., et al. Liver-innervating vagal sensory neurons are indispensable for the development of hepatic steatosis and anxiety-like behavior in diet-induced obese mice. Nat Commun 2025;16(1):991. [CrossRef]
48. Kimura I, Inoue D, Maeda T, Hara T, Ichimura A, Miyauchi S, et al. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41). Proc Natl Acad Sci U S A 2011;108(19):8030-8035. [CrossRef]
49. Ding Y, Yanagi K, Cheng C, Alaniz RC, Lee K, Jayaraman A. Interactions between gut microbiota and non-alcoholic liver disease: The role of microbiota-derived metabolites. Pharmacol Res 2019;141:521-529. [CrossRef]
50. Hong R, Tan Y, Tian X, Huang Z, Wang J, Ni H, et al. XIAP-mediated degradation of IFT88 disrupts HSC cilia to stimulate HSC activation and liver fibrosis. EMBO Rep 2024;25(3):1055-1074. [CrossRef]
51. Lee CH, Song DK, Park CB, Choi J, Kang GM, Shin SH, et al. Primary cilia mediate early life programming of adiposity through lysosomal regulation in the developing mouse hypothalamus. Nat Commun 2020;11(1):5772. [CrossRef]
52. Etemad A, Tanaka Y, Wang S, Slae M, Sultan M, Elpeleg O, et al. Mutations in the kinesin KIF12 promote MASH in humans and mice by disrupting lipogenic enzyme turnover. Embo j 2025;44(6):1608-1640. [CrossRef]
53. Wu CT, Hilgendorf KI, Bevacqua RJ, Hang Y, Demeter J, Kim SK, et al. Discovery of ciliary G protein-coupled receptors regulating pancreatic islet insulin and glucagon secretion. Genes Dev 2021;35(17-18):1243-1255. [CrossRef]
54. Li B, He YY, Yang ZM. Primary cilia function as hubs for signal transduction. Cell Biosci 2025;15(1):163. [CrossRef]
55. Liu J, Xiao Q, Xiao J, Niu C, Li Y, Zhang X, et al. Wnt/β-catenin signalling: function, biological mechanisms, and therapeutic opportunities. Signal Transduct Target Ther 2022;7(1):3. [CrossRef]
56. Bahitham W, Banoun Y, Aljahdali M, Almuaiqly G, Bahshwan SM, Aljahdali L, et al. "Trust your gut": exploring the connection between gut microbiome dysbiosis and the advancement of Metabolic Associated Steatosis Liver Disease (MASLD)/Metabolic Associated Steatohepatitis (MASH): a systematic review of animal and human studies. Front Nutr 2025;12:1637071. [CrossRef]
57. Cho JH, Li ZA, Zhu L, Muegge BD, Roseman HF, Lee EY, et al. Islet primary cilia motility controls insulin secretion. Sci Adv 2022;8(38):eabq8486. [CrossRef]
58. Müller A, Klena N, Pang S, Garcia LEG, Topcheva O, Aurrecoechea Duran S, et al. Structure, interaction and nervous connectivity of beta cell primary cilia. Nat Commun 2024;15(1):9168. [CrossRef]
59. Barbeito P, Garcia-Gonzalo FR. HTR6 and SSTR3 targeting to primary cilia. Biochem Soc Trans 2021;49(1):79-91. [CrossRef]
60. Hilgendorf KI, Johnson CT, Mezger A, Rice SL, Norris AM, Demeter J, et al. Omega-3 Fatty Acids Activate Ciliary FFAR4 to Control Adipogenesis. Cell 2019;179(6):1289-1305.e21. [CrossRef]
61. Pablos M, Casanueva-Álvarez E, González-Casimiro CM, Merino B, Perdomo G, Cózar-Castellano I. Primary cilia in pancreatic β- and α-Cells: Time to revisit the role of insulin-degrading enzyme. Front Endocrinol (Lausanne) 2022;13:922825. [CrossRef]
62. Ramasubbu K, Devi Rajeswari V. Impairment of insulin signaling pathway PI3K/Akt/mTOR and insulin resistance induced AGEs on diabetes mellitus and neurodegenerative diseases: a perspective review. Mol Cell Biochem 2023;478(6):1307-1324. [CrossRef]
63. Qiu H, Liu J, Wu Q, Ong H, Zhang Y, Huang X, et al. An in vitro study of the impact of IL-17A and IL-22 on ciliogenesis in nasal polyps epithelium via the Hippo-YAP pathway. J Allergy Clin Immunol 2024;154(5):1180-1194. [CrossRef]
64. González-Rodríguez A, Mayoral R, Agra N, Valdecantos MP, Pardo V, Miquilena-Colina ME, et al. Impaired autophagic flux is associated with increased endoplasmic reticulum stress during the development of NAFLD. Cell Death Dis 2014;5(4):e1179. [CrossRef]
65. Wang X, Zhang X, Chu ESH, Chen X, Kang W, Wu F, et al. Defective lysosomal clearance of autophagosomes and its clinical implications in nonalcoholic steatohepatitis. FASEB J 2018;32(1):37-51. [CrossRef]
66. Tang Z, Lin MG, Stowe TR, Chen S, Zhu M, Stearns T, et al. Autophagy promotes primary ciliogenesis by removing OFD1 from centriolar satellites. Nature 2013;502(7470):254-257. [CrossRef]

67. Orhon I, Dupont N, Pampliega O, Cuervo AM, Codogno P. Autophagy and regulation of cilia function and assembly. Cell Death Differ 2015;22(3):389-397. [CrossRef]
68. Boucher J, Softic S, El Ouaamari A, Krumpoch MT, Kleinridders A, Kulkarni RN, et al. Differential Roles of Insulin and IGF-1 Receptors in Adipose Tissue Development and Function. Diabetes 2016;65(8):2201-2213. [CrossRef]
69. Suren Garg S, Kushwaha K, Dubey R, Gupta J. Association between obesity, inflammation and insulin resistance: Insights into signaling pathways and therapeutic interventions. Diabetes Res Clin Pract 2023;200:110691. [CrossRef]
70. Ziogas IA, van der Windt DJ, Wilson GC, Furlan A, Nalesnik MA, Tohme S, et al. Surgical Management of Ciliated Hepatic Foregut Cyst. Hepatology 2020;71(1):386-388. [CrossRef]
71. Paul C, Tang R, Longobardi C, Lattanzio R, Eguether T, Turali H, et al. Loss of primary cilia promotes inflammation and carcinogenesis. EMBO Rep 2022;23(12):e55687. [CrossRef]
72. Han YG, Spassky N, Romaguera-Ros M, Garcia-Verdugo JM, Aguilar A, Schneider-Maunoury S, et al. Hedgehog signaling and primary cilia are required for the formation of adult neural stem cells. Nat Neurosci 2008;11(3):277-284. [CrossRef]
73. Guemez-Gamboa A, Coufal NG, Gleeson JG. Primary cilia in the developing and mature brain. Neuron 2014;82(3):511-521. [CrossRef]
74. Qiu N, Fang WJ, Li HS, He ZM, Xiao ZS, Xiong Y. Impairment of primary cilia contributes to visceral adiposity of high fat diet-fed mice. J Cell Biochem 2018;119(2):1313-1325. [CrossRef]
75. Yang DJ, Hong J, Kim KW. Hypothalamic primary cilium: A hub for metabolic homeostasis. Exp Mol Med 2021;53(7):1109-1115. [CrossRef]
76. Siljee JE, Wang Y, Bernard AA, Ersoy BA, Zhang S, Marley A, et al. Subcellular localization of MC4R with ADCY3 at neuronal primary cilia underlies a common pathway for genetic predisposition to obesity. Nat Genet 2018;50(2):180-185. [CrossRef]
77. Fan W, Boston BA, Kesterson RA, Hruby VJ, Cone RD. Role of melanocortinergic neurons in feeding and the agouti obesity syndrome. Nature 1997;385(6612):165-168. [CrossRef]
78. Bernard A, Ojeda Naharros I, Yue X, Mifsud F, Blake A, Bourgain-Guglielmetti F, et al. MRAP2 regulates energy homeostasis by promoting primary cilia localization of MC4R. JCI Insight 2023;8(2):e155900. [CrossRef]
79. Han YM, Kang GM, Byun K, Ko HW, Kim J, Shin MS, et al. Leptin-promoted cilia assembly is critical for normal energy balance. J Clin Invest 2014;124(5):2193-2197. [CrossRef]
80. Fiorotto R, Raizner A, Morell CM, Torsello B, Scirpo R, Fabris L, et al. Notch signaling regulates tubular morphogenesis during repair from biliary damage in mice. J Hepatol 2013;59(1):124-130. [CrossRef]
81. Spirli C, Locatelli L, Fiorotto R, Morell CM, Fabris L, Pozzan T, et al. Altered store operated calcium entry increases cyclic 3′,5′-adenosine monophosphate production and extracellular signal-regulated kinases 1 and 2 phosphorylation in polycystin-2-defective cholangiocytes. Hepatology 2012;55(3):856-868. [CrossRef]
82. Iruzubieta P, Cantarero I, Monzón M, Lahoz M, Junquera C. Supporting Evidence of Human Enteric Nervous System Adult Neurogenesis: Presence of Primary Cilia and Adult Neurogenesis Markers. Cell Mol Neurobiol 2022;42(2):473-481. [CrossRef]
83. Sonnenburg JL, Bäckhed F. Diet-microbiota interactions as moderators of human metabolism. Nature 2016;535(7610):56-64. [CrossRef]
84. Bäckhed F, Manchester JK, Semenkovich CF, Gordon JI. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. Proc Natl Acad Sci U S A 2007;104(3):979-984. [CrossRef]
85. Sharon G, Sampson TR, Geschwind DH, Mazmanian SK. The Central Nervous System and the Gut Microbiome. Cell 2016;167(4):915-932. [CrossRef]
86. Boehlke C, Kotsis F, Patel V, Braeg S, Voelker H, Bredt S, et al. Primary cilia regulate mTORC1 activity and cell size through Lkb1. Nat Cell Biol 2010;12(11):1115-1122. [CrossRef]
87. Prosseda PP, Dannewitz Prosseda S, Tran M, Liton PB, Sun Y. Crosstalk between the mTOR pathway and primary cilia in human diseases. Curr Top Dev Biol 2023;155:1-37. [CrossRef]
88. Safaroghli-Azar A, Sanaei MJ, Pourbagheri-Sigaroodi A, Bashash D. Phosphoinositide 3-kinase (PI3K) classes: From cell signaling to endocytic recycling and autophagy. Eur J Pharmacol 2023;953:175827. [CrossRef]
89. Chiefari E, Mirabelli M, La Vignera S, Tanyolaç S, Foti DP, Aversa A, et al. Insulin Resistance and Cancer: In Search for a Causal Link. Int J Mol Sci 2021;22(20):11137. [CrossRef]
90. Nguyen Huu T, Park J, Zhang Y, Duong Thanh H, Park I, Choi JM, et al. The Role of Oxidative Inactivation of Phosphatase PTEN and TCPTP in Fatty Liver Disease. Antioxidants (Basel) 2023;12(1):120. [CrossRef]
91. Xu J, Lin H, Wu G, Zhu M, Li M. IL-6/STAT3 Is a Promising Therapeutic Target for Hepatocellular Carcinoma. Front Oncol 2021;11:760971. [CrossRef]
92. Xu F, Liu C, Zhou D, Zhang L. TGF-β/SMAD Pathway and Its Regulation in Hepatic Fibrosis. J Histochem Cytochem 2016;64(3):157-167. [CrossRef]
93. Yang C, Chen W, Chen Y, Jiang J. Smoothened transduces Hedgehog signal by forming a complex with Evc/Evc2. Cell Res 2012;22(11):1593-1604. [CrossRef]
94. Wang Y, Yao H, Zhang Y, Mu N, Lu T, Du Z, et al. TMEM216 promotes primary ciliogenesis and Hedgehog signaling through the SUFU-GLI2/GLI3 axis. Sci Signal 2024;17(820):eabo0465. [CrossRef]
95. Nair B, Kamath AJ, Pradeep G, Devan AR, Sethi G, Nath LR. Unveiling the role of the Hedgehog signaling pathway in chronic liver disease: Therapeutic insights and strategies. Drug Discov Today 2024;29(8):104064. [CrossRef]
96. Jiang Y, Peng J, Song J, He J, Jiang M, Wang J, et al. Loss of Hilnc prevents diet-induced hepatic steatosis through binding of IGF2BP2. Nat Metab 2021;3(11):1569-1584. [CrossRef]
97. Yang L, Inokuchi S, Roh YS, Song J, Loomba R, Park EJ, et al. Transforming growth factor-β signaling in hepatocytes promotes hepatic fibrosis and carcinogenesis in mice with hepatocyte-specific deletion of TAK1. Gastroenterology 2013;144(5):1042-1054.e4. [CrossRef]
98. Liu S, He Y, Li S, Gao X, Yang F. Kinesin family member 3A induces related diseases via wingless-related integration site/β-catenin signaling pathway. Sci Prog 2023;106(1):368504221148340. [CrossRef]
99. Simons M, Gloy J, Ganner A, Bullerkotte A, Bashkurov M, Krönig C, et al. Inversin, the gene product mutated in nephronophthisis type II, functions as a molecular switch between Wnt signaling pathways. Nat Genet 2005;37(5):537-543. [CrossRef]
100. Fujisawa H, Ota N, Shiojiri N. Inversin-deficient (inv) mice do not establish a polarized duct system in the liver and pancreas. Anat Rec (Hoboken) 2024;307(6):2197-2212. [CrossRef]
101. Thaiss CA, Levy M, Grosheva I, Zheng D, Soffer E, Blacher E, et al. Hyperglycemia drives intestinal barrier dysfunction and risk for enteric infection. Science 2018;359(6382):1376-1383. [CrossRef]
102. Yu J, Wang Z, Chen Y, Dong Y. Restraint Stress Disrupted Intestinal Homeostasis via 5-HT/HTR7/Wnt/β-Catenin/NF-kB Signaling. Int J Mol Sci 2025;26(9):4021. [CrossRef]

103.Mouries J, Brescia P, Silvestri A, Spadoni I, Sorribas M, Wiest R, et al. Microbiota-driven gut vascular barrier disruption is a prerequisite for non-alcoholic steatohepatitis development. J Hepatol 2019;71(6):1216-1228. [CrossRef]

104.Behari J, Yeh TH, Krauland L, Otruba W, Cieply B, Hauth B, et al. Liver-specific beta-catenin knockout mice exhibit defective bile acid and cholesterol homeostasis and increased susceptibility to diet-induced steatohepatitis. Am J Pathol 2010;176(2):744-753. [CrossRef]

105.Zhou H, Zhu X, Yao Y, Su Y, Xie J, Zhu M, et al. TMEM88 modulates lipid synthesis and metabolism cytokine by regulating Wnt/β-catenin signaling pathway in non-alcoholic fatty liver disease. Front Pharmacol 2021;12:798735. [CrossRef]

106.Zhu NL, Asahina K, Wang J, Ueno A, Lazaro R, Miyaoka Y, et al. Hepatic stellate cell-derived delta-like homolog 1 (DLK1) protein in liver regeneration. J Biol Chem 2012;287(13):10355-10367. [CrossRef]

107.Ezratty EJ, Stokes N, Chai S, Shah AS, Williams SE, Fuchs E. A role for the primary cilium in Notch signaling and epidermal differentiation during skin development. Cell 2011;145(7):1129-1141. [CrossRef]

108.Jurisch-Yaksi N, Rose AJ, Lu H, Raemaekers T, Munck S, Baatsen P, et al. Rer1p maintains ciliary length and signaling by regulating γ-secretase activity and Foxj1a levels. J Cell Biol 2013;200(6):709-720. [CrossRef]

109.Zhu C, Kim K, Wang X, Bartolome A, Salomao M, Dongiovanni P, et al. Hepatocyte Notch activation induces liver fibrosis in nonalcoholic steatohepatitis. Sci Transl Med 2018;10(468):eaat0344. [CrossRef]

110.Luedde T, Schwabe RF. NF-κB in the liver--linking injury, fibrosis and hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol 2011;8(2):108-118. [CrossRef]

111.Yu J, Zhu C, Wang X, Kim K, Bartolome A, Dongiovanni P, et al. Hepatocyte TLR4 triggers inter-hepatocyte Jagged1/Notch signaling to determine NASH-induced fibrosis. Sci Transl Med 2021;13(599):eabe1692. [CrossRef]

112.Lilly AC, Astsaturov I, Golemis EA. Intrapancreatic fat, pancreatitis, and pancreatic cancer. Cell Mol Life Sci 2023;80(8):206. [CrossRef]

113.Ma R, Kutchy NA, Chen L, Meigs DD, Hu G. Primary cilia and ciliary signaling pathways in aging and age-related brain disorders. Neurobiol Dis 2022;163:105607. [CrossRef]

114.Cheng Z, Chu H, Seki E, Lin R, Yang L. Hepatocyte programmed cell death: the trigger for inflammation and fibrosis in metabolic dysfunction-associated steatohepatitis. Front Cell Dev Biol 2024;12:1431921. [CrossRef]

115.Wang P, Liu T, Cong M, Wu X, Bai Y, Yin C, et al. Expression of extracellular matrix genes in cultured hepatic oval cells: an origin of hepatic stellate cells through transforming growth factor beta? Liver Int 2009;29(4):575-584. [CrossRef]

116.Sun JS, Yang DJ, Kinyua AW, Yoon SG, Seong JK, Kim J, et al. Ventromedial hypothalamic primary cilia control energy and skeletal homeostasis. J Clin Invest 2021;131(1):e138107. [CrossRef]

117.Adori C, Daraio T, Kuiper R, Barde S, Horvathova L, Yoshitake T, et al. Disorganization and degeneration of liver sympathetic innervations in nonalcoholic fatty liver disease revealed by 3D imaging. Sci Adv 2021;7(30):eabg5733. [CrossRef]

118.Lambert GW, Straznicky NE, Lambert EA, Dixon JB, Schlaich MP. Sympathetic nervous activation in obesity and the metabolic syndrome--causes, consequences and therapeutic implications. Pharmacol Ther 2010;126(2):159-172. [CrossRef]

119.Hurr C, Simonyan H, Morgan DA, Rahmouni K, Young CN. Liver sympathetic denervation reverses obesity-induced hepatic steatosis. J Physiol 2019;597(17):4565-4580. [CrossRef]

120.Saternos HC, Forero KV, Meqdad MA, Buqaileh R, Sunderman CL, Gallagher G, et al. Muscarinic acetylcholine receptor 3 localized to primary endothelial cilia regulates blood pressure and cognition. Sci Rep 2025;15(1):3745. [CrossRef]

121.Ungvari Z, Sun D, Huang A, Kaley G, Koller A. Role of endothelial [Ca2+]i in activation of eNOS in pressurized arterioles by agonists and wall shear stress. Am J Physiol Heart Circ Physiol 2001;281(2):H606-H612. [CrossRef]

122.Maeda H, Ishima Y, Saruwatari J, Mizuta Y, Minayoshi Y, Ichimizu S, et al. Nitric oxide facilitates the targeting Kupffer cells of a nano-antioxidant for the treatment of NASH. J Control Release 2022;341:457-474. [CrossRef]

123.Tencerova M, Aouadi M, Vangala P, Nicoloro SM, Yawe JC, Cohen JL, et al. Activated Kupffer cells inhibit insulin sensitivity in obese mice. FASEB J 2015;29(7):2959-2969. [CrossRef]

124.Deng J, Wang M, Guo Y, Fischer H, Yu X, Kem D, et al. Activation of α7nAChR via vagus nerve prevents obesity-induced insulin resistance via suppressing endoplasmic reticulum stress-induced inflammation in Kupffer cells. Med Hypotheses 2020;140:109671. [CrossRef]

125.Hamdan N, Kritsiligkou P, Grant CM. ER stress causes widespread protein aggregation and prion formation. J Cell Biol 2017;216(8):2295-2304. [CrossRef]

126.Xu FF, Li ZC, Zhang WJ, Li Q, Li DJ, Meng HB, et al. Activation of α7 Nicotinic Acetylcholine Receptors Inhibits Hepatic Necroptosis and Ameliorates Acute Liver Injury in Mice. Anesthesiology 2024;141(6):1119-1138. [CrossRef]

127.Sampson TR, Mazmanian SK. Control of brain development, function, and behavior by the microbiome. Cell Host Microbe 2015;17(5):565-576. [CrossRef]

128.Mansini AP, Lorenzo Pisarello MJ, Thelen KM, Cruz-Reyes M, Peixoto E, Jin S, et al. MicroRNA (miR)-433 and miR-22 dysregulations induce histone-deacetylase-6 overexpression and ciliary loss in cholangiocarcinoma. Hepatology 2018;68(2):561-573. [CrossRef]

129.Pant K, Richard S, Gradilone SA. Short-Chain Fatty Acid Butyrate Induces Cilia Formation and Potentiates the Effects of HDAC6 Inhibitors in Cholangiocarcinoma Cells. Front Cell Dev Biol 2021;9:809382. [CrossRef]

130.Chen X, Yu C, Hou X, Li J, Li T, Qiu A, et al. Histone deacetylase 6 inhibition mitigates renal fibrosis by suppressing TGF-β and EGFR signaling pathways in obstructive nephropathy. Am J Physiol Renal Physiol 2020;319(6):F1003-F1014. [CrossRef]

131.Zhang J, Li R, Liu Q, Zhou J, Huang H, Huang Y, et al. SB431542-loaded liposomes alleviate liver fibrosis by suppressing TGF-β signaling. Mol Pharm 2020;17(11):4152-4162. [CrossRef]

132.Sharma N, Singh L, Sharma A, Kumar A, Mahajan D. NAFLD-associated hepatocellular carcinoma (HCC) - A compelling case for repositioning of existing mTORc1 inhibitors. Pharmacol Res 2024;208:107375. [CrossRef]

133.Kwon H, Song K, Han C, Chen W, Wang Y, Dash S, et al. Inhibition of hedgehog signaling ameliorates hepatic inflammation in mice with nonalcoholic fatty liver disease. Hepatology 2016;63(4):1155-1169. [CrossRef]

134.Tao H, Zhang Y, Zeng X, Shulman GI, Jin S. Niclosamide ethanolamine-induced mild mitochondrial uncoupling improves diabetic symptoms in mice. Nat Med 2014;20(11):1263-1269. [CrossRef]

135.El-Ashmawy NE, Al-Ashmawy GM, Fakher HE, Khedr NF. The role of WNT/β-catenin signaling pathway and glutamine metabolism in the pathogenesis of CCl(4)-induced liver fibrosis: Repositioning of niclosamide and concerns about lithium. Cytokine 2020;136:155250. [CrossRef]

136.Zhang M, Wu P, Li M, Guo Y, Tian T, Liao X, et al. Inhibition of Notch1 signaling reduces hepatocyte injury in nonalcoholic fatty liver disease via autophagy. Biochem Biophys Res Commun 2021;547:131-138. [CrossRef]

137.Rose JP, Morgan DA, Sullivan AI, Fu X, Inigo-Vollmer M, Burgess SC, et al. FGF21 reverses MASH through coordinated actions on the CNS and liver. Cell Metab 2025;37(7):1515-1529.e6. [CrossRef]

138.Harrison SA, Frias JP, Neff G, Abrams GA, Lucas KJ, Sanchez W, et al. Safety and efficacy of once-weekly efruxifermin versus placebo in non-alcoholic steatohepatitis (HARMONY): a multicentre, randomised, double-blind, placebo-controlled, phase 2b trial. Lancet Gastroenterol Hepatol 2023;8(12):1080-1093. [CrossRef]

139.Loomba R, Sanyal AJ, Kowdley KV, Bhatt DL, Alkhouri N, Frias JP, et al. Randomized, Controlled Trial of the FGF21 Analogue Pegozafermin in NASH. N Engl J Med 2023;389(11):998-1008. [CrossRef]

140.Owyang C. Physiological mechanisms of cholecystokinin action on pancreatic secretion. Am J Physiol 1996;271(1 Pt 1):G1-G7. [CrossRef]

141.Rossi J, Herzig KH, Võikar V, Hiltunen PH, Segerstråle M, Airaksinen MS. Alimentary tract innervation deficits and dysfunction in mice lacking GDNF family receptor alpha2. J Clin Invest 2003;112(5):707-716. [CrossRef]

142.Yamada M, Miyakawa T, Duttaroy A, Yamanaka A, Moriguchi T, Makita R, et al. Mice lacking the M3 muscarinic acetylcholine receptor are hypophagic and lean. Nature 2001;410(6825):207-212. [CrossRef]

143.Bresch J, König J, Konrad M, Kollmann S, Dahmer-Heath M, Heinzow HS, et al. Non-invasive screening for liver fibrosis by acoustic radiation force impulse in patients with ciliopathies. Sci Rep 2025;15(1):13345. [CrossRef]

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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.[54] |

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.[55] 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.

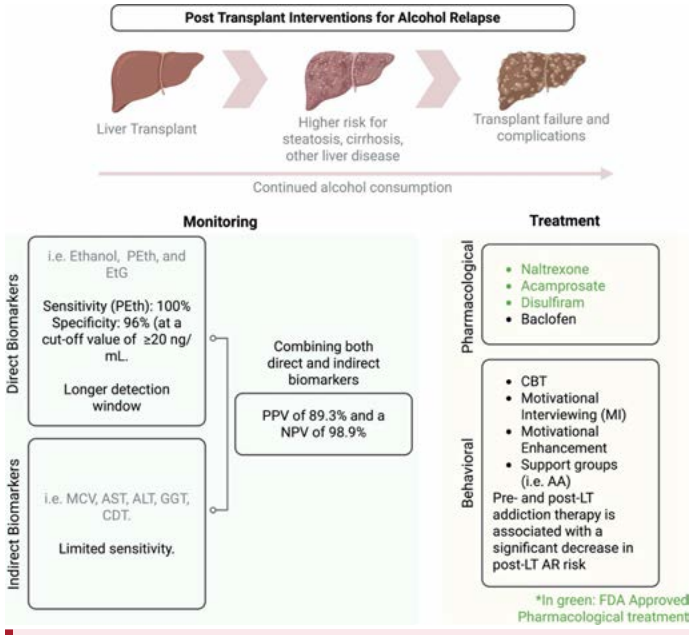



**Figure 1.** Overview of post-LT alcohol-relapse prevention strategies.

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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## References


1. Lucey MR, Furuya KN, Foley DP. Liver Transplantation. N Engl J Med 2023;389(20):1888-1900. [CrossRef]
2. Cholankeril G, Ahmed A. Alcoholic liver disease replaces hepatitis C virus infection as the leading indication for liver transplantation in the United States. Clin Gastroenterol Hepatol 2018;16(8):1356-1358. [CrossRef]
3. White AM, Castle IP, Powell PA, Hingson RW, Koob GF. Alcohol-related deaths during the COVID-19 pandemic. JAMA 2022;327(17):1704-1706. [CrossRef]
4. Lee BP, Dodge JL, Leventhal A, Terrault NA. Retail alcohol and tobacco sales during COVID-19. Ann Intern Med 2021;174(7):1027-1029. [CrossRef]
5. Rady ED, Anouti A, Mitchell MC, Cotter TG. Current clinical trials for alcohol-associated hepatitis. Am J Pathol 2026;196(1):182-191. [CrossRef]
6. Moskatel LS, Slusky DJG. The impact of COVID-19 on alcohol sales and consumption in the United States: A retrospective, observational analysis. Alcohol 2023;111:25-31. [CrossRef]
7. National Institute on Alcohol Abuse and Alcoholism (NIAAA). Understanding alcohol use disorder. Available at: https://www.niaaa.nih.gov/publications/brochures-and-fact-sheets/understanding-alcohol-use-disorder. Accessed: June 7, 2025
8. Arab JP, Izzy M, Leggio L, Bataller R, Shah VH. Management of alcohol use disorder in patients with cirrhosis in the setting of liver transplantation. Nat Rev Gastroenterol Hepatol 2022;19(1):45-59. [CrossRef]
9. Van Melkebeke L, Korf H, Tsochatzis EA, van der Merwe S, Nevens F, Verbeek J. Treatment of severe alcoholic hepatitis: A systematic review. Curr Opin Pharmacol 2021;60:91-101. [CrossRef]
10. Jadaun SS, Saigal S. Post-transplant complications in alcohol- and metabolic-associated steatotic liver disease. Metab Target Organ Damage 2025;5:1. [CrossRef]
11. Musto JA, Palmer G, Nemer M, Schell T, Waclawik G, Glover Q, et al. Early liver transplant for alcohol-associated liver disease has excellent survival but higher rates of harmful alcohol use. Clin Gastroenterol Hepatol 2024;22(8):1646-1656.e2. [CrossRef]
12. Kodali S, Kaif M, Tariq R, Singal AK. Alcohol relapse after liver transplantation for alcoholic cirrhosis-impact on liver graft and patient survival: a meta-analysis. Alcohol Alcohol 2018;53(2):166-172. [CrossRef]
13. Messinger JC, Hanto DW, Curry MP, Ladin K. Liver transplantation in alcohol-associated liver disease: ensuring equity through new processes. Liver Transpl 2023;29(5):539-547. [CrossRef]
14. Addolorato G, Mirijello A, Barrio P, Gual A. Treatment of alcohol use disorders in patients with alcoholic liver disease. J Hepatol 2016;65(3):618-630. [CrossRef]
15. World Health Organization. International guide for monitoring alcohol consumption and related harm. World Health Organization; 2000; Available at: https://iris.who.int/handle/10665/66529. Accessed on June 5, 2025.
16. Erard-Poinsot D, Dharancy S, Hilleret MN, Faure S, Lamblin G, Chambon-Augoyard C, et al. Natural history of recurrent alcohol-related cirrhosis after liver transplantation: fast and furious. Liver Transpl 2020;26(1):25-33. [CrossRef]
17. Faure S, Herrero A, Jung B, Duny Y, Daures JP, Mura T, et al. Excessive alcohol consumption after liver transplantation impacts on long-term survival, whatever the primary indication. J Hepatol 2012;57(2):306-312. [CrossRef]
18. Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, et al. Early liver transplantation for severe alcoholic hepatitis. N Engl J Med 2011;365(19):1790-1800. [CrossRef]
19. Herrick-Reynolds KM, Punchhi G, Greenberg RS, Strauss AT, Boyarsky BJ, Weeks-Groh SR, et al. Evaluation of Early vs Standard Liver Transplant for Alcohol-Associated Liver Disease. JAMA Surg 2021;156(11):1026-1034. [CrossRef]
20. Young K, Patel YA, Hoffman B, Peskoe S, Chow SC, Erhart K, et al. Alcohol relapse after liver transplantation: risk factors, outcomes, and a comparison of risk stratification models. Gastro Hep Adv 2024;4(1):100550. [CrossRef]
21. Legg K, Sparkes T, Booth I, Maluf D, Bhati C, Jakhete N, et al. Short-term alcohol abstinence prior to liver transplantation and impact on rejection. Journal of Liver Transplantation 2024;16:100240. [CrossRef]
22. Schuckit MA. Alcohol-use disorders. Lancet 2009;373(9662):492-501. [CrossRef]
23. Marti-Aguado D, Gougol A, Gomez-Medina C, Jamali A, Abo-Zed A, Morales-Arraez D, et al. Prevalence and clinical impact of alcohol withdrawal syndrome in alcohol-associated hepatitis and the potential role of prophylaxis: a multinational, retrospective cohort study. EClinicalMedicine 2023;61:102046. [CrossRef]
24. Attilia ML, Lattanzi B, Ledda R, Galli AM, Farcomeni A, Rotondo C, et al. The multidisciplinary support in preventing alcohol relapse after liver transplantation: A single-center experience. Clin Transplant 2018;32(5):e13243. [CrossRef]
25. De Gottardi A, Spahr L, Gelez P, Morard I, Mentha G, Guillaud O, et al. A simple score for predicting alcohol relapse after liver transplantation: results from 387 patients over 15 years. Arch Intern Med 2007;167(11):1183-1188. [CrossRef]
26. Gish RG, Lee A, Brooks L, Leung J, Lau JY, Moore DH 2nd. Long-term follow-up of patients diagnosed with alcohol dependence or alcohol abuse who were evaluated for liver transplantation. Liver Transpl 2001;7(7):581-7. [CrossRef]

27. Maldonado J, Sher Y, Lolak S, Swendsen H, Skibola D, Neri E, et al. The Stanford integrated psychosocial assessment for transplantation: a prospective study of medical and psychosocial outcomes. Psychosomatic Medicine 2015;77(9):1018-1030. [CrossRef]
28. Lee BP, Chen PH, Haugen C, Hernaez R, Gurakar A, Philosophe B, et al. Three-year results of a pilot program in early liver transplantation for severe alcoholic hepatitis. Ann Surg 2017;265(1):20-29. [CrossRef]
29. Lee BP, Vittinghoff E, Hsu C, Han H, Therapondos G, Fix OK, et al. Predicting low risk for sustained alcohol use after early liver transplant for acute alcoholic hepatitis: the sustained alcohol use post-liver transplant score. Hepatology 2019;69(4):1477-1487. [CrossRef]
30. Satapathy SK, Thornburgh C, Heda R, Jiang Y, Kedia SK, Nair SP, et al. Predicting harmful alcohol relapse after liver transplant: The HALT score. Clin Transplant 2020;34(9):e14003. [CrossRef]
31. Weeks SR, Sun Z, McCaul ME, Zhu H, Anders RA, Philosophe B, et al. Liver transplantation for severe alcoholic hepatitis, updated lessons from the world's largest series. J Am Coll Surg 2018;226(4):549-557. [CrossRef]
32. Ting PS, Gurakar A, Wheatley J, Chander G, Cameron AM, Chen PH. Approaching alcohol use disorder after liver transplantation for acute alcoholic hepatitis. Clin Liver Dis 2021;25(3):645-671. [CrossRef]
33. Schröck A, Thierauf-Emberger A, Schürch S, Weinmann W. Phosphatidylethanol (PEth) detected in blood for 3 to 12 days after single consumption of alcohol-a drinking study with 16 volunteers. Int J Legal Med 2017;131(1):153-160. [CrossRef]
34. Andresen-Streichert H, Beres Y, Weinmann W, Schröck A, Müller A, Skopp G, et al. Improved detection of alcohol consumption using the novel marker phosphatidylethanol in the transplant setting: results of a prospective study. Transpl Int 2017;30(6):611-620. [CrossRef]
35. Kenan N, Larsson A, Axelsson O, Helander A. Changes in transferrin glycosylation during pregnancy may lead to false-positive carbohydrate-deficient transferrin (CDT) results in testing for riskful alcohol consumption. Clin Chim Acta 2011;412(1-2):129-133. [CrossRef]
36. Van Uytfanghe K, De Boosere E, Stove CP. Monitoring the use of alcohol-A critical overview of the state-of-the-art biomarkers. WIREs Forens Sci 2022;4(5):e1457. [CrossRef]
37. Staufer K, Andresen H, Vettorazzi E, Tobias N, Nashan B, Sterneck M. Urinary ethyl glucuronide as a novel screening tool in patients pre- and post-liver transplantation improves detection of alcohol consumption. Hepatology 2011;54(5):1640-1649. [CrossRef]
38. Bernstein EY, Baggett TP, Trivedi S, Herzig SJ, Anderson TS. Outcomes after initiation of medications for alcohol use disorder at hospital discharge. JAMA Netw Open 2024;7(3):e243387. [CrossRef]
39. Yaseen W, Mong J, Zipursky J. Sobering perspectives on the treatment of alcohol use disorder. JAMA Netw Open 2024;7(3):e243340. [CrossRef]
40. Ayyala-Somayajula D, Bottyan T, Shaikh S, Lee BP, Cho SH, Dodge JL, et al. Safety of acamprosate for alcohol use disorder after liver transplant: A pilot randomized controlled trial. Liver Transpl 2025;31(4):498-507. [CrossRef]
41. U.S. Food and Drug Administration Website. VIVITROL® (naltrexone for extended-release injectable suspension) Intramuscular. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021897s015lbl.pdf. Accessed on Jun 20, 2025.
42. Díaz LA, Collier S, Yin J, Loomba R. Safety and tolerability of injectable extended-release naltrexone for the management of alcohol use disorder in advanced alcohol-associated liver disease. Aliment Pharmacol Ther 2025;62(7):692-698. [CrossRef]
43. Ray LA, Bujarski S, Grodin E, Hartwell E, Green R, Venegas A, et al. State-of-the-art behavioral and pharmacological treatments for alcohol use disorder. Am J Drug Alcohol Abuse 2019;45(2):124-140. [CrossRef]
44. Rösner S, Hackl-Herrwerth A, Leucht S, Lehert P, Vecchi S, Soyka M. Acamprosate for alcohol dependence. Cochrane Database Syst Rev 2010;2010(9):CD004332. [CrossRef]
45. NIH. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Available at: http://www.ncbi.nlm.nih.gov/books/NBK548103/. Accessed: June 20, 2025.
46. Garbutt JC, Kampov-Polevoy AB, Pedersen C, Stansbury M, Jordan R, Willing L, et al. Efficacy and tolerability of baclofen in a U.S. community population with alcohol use disorder: a dose-response, randomized, controlled trial. Neuropsychopharmacology 2021;46(13):2250-2256. [CrossRef]
47. Colombo G, Agabio R, Carai MA, Lobina C, Pani M, Reali R, et al. Ability of baclofen in reducing alcohol intake and withdrawal severity: I-Preclinical evidence. Alcohol Clin Exp Res 2000;24(1):58-66. [CrossRef]
48. Kumar A, Sharma A, Bansal PD, Bahetra M, Gill HK, Kumar R. A comparative study on the safety and efficacy of naltrexone versus baclofen versus acamprosate in the management of alcohol dependence. Indian J Psychiatry 2020;62(6):650-658. [CrossRef]
49. Farokhnia M, Tazare J, Pince CL, Bruns N 6th, Gray JC, Lo Re V 3rd, et al. Glucagon-like peptide-1 receptor agonists, but not dipeptidyl peptidase-4 inhibitors, reduce alcohol intake. J Clin Invest 2025;135(9):e188314. [CrossRef]
50. John BV, Bastaich D, Marchetti D, Perumalswami P, Mustafa MZ, Dahman B, et al. Association of glucagon-like peptide-1 receptor agonists with liver-related outcomes and all-cause mortality in patients with harmful alcohol use: a target trial emulation study. Am J Gastroenterol 2026;121(3):697-709. [CrossRef]
51. Hendershot CS, Bremmer MP, Paladino MB, Kostantinis G, Gilmore TA, Sullivan NR, et al. Once-weekly semaglutide in adults with alcohol use disorder: a randomized clinical trial. JAMA Psychiatry 2025;82(4):395-405. [CrossRef]
52. Lähteenvuo M, Tiihonen J, Solismaa A, Tanskanen A, Mittendorfer-Rutz E, Taipale H. Repurposing semaglutide and liraglutide for alcohol use disorder. JAMA Psychiatry 2025;82(1):94-98. [CrossRef]
53. de Faria Moraes B, André Pedral Diniz Leite G, André Pedral Diniz Leite G, Silveira IB, Lana NV, Cançado GGL. Impact of glucagon-like peptide-1 receptor agonists on alcohol consumption and liver-related outcomes: A systematic review and meta-analysis. Drug Alcohol Depend 2025;275:112840. [CrossRef]
54. Schlagintweit HE, Lynch MJ, Hendershot CS. A review of behavioral alcohol interventions for transplant candidates and recipients with alcohol-related liver disease. Am J Transplant 2019;19(10):2678-2685. [CrossRef]
55. Krist AH, Bradley KA. Addressing Alcohol Use. N Engl J Med 2025;392(17):1721-1731. [CrossRef]
56. Ting PS, Wheatley J, Chen PH. Behavioral treatment for patients with alcohol-related liver disease: a primer for hepatologists. Clin Liver Dis (Hoboken) 2020;15(1):31-35. [CrossRef]
57. Weinrieb RM, Van Horn DH, Lynch KG, Lucey MR. A randomized, controlled study of treatment for alcohol dependence in patients awaiting liver transplantation. Liver Transpl 2011;17(5):539-547. [CrossRef]
58. Ness C, Hardie K, Holbeck M, Saucedo-Crespo H, Auvenshine C, Steers

J, et al. Integration of addiction treatment and behavioral therapies in comprehensive liver transplantation care to augment adherence and reduce alcohol relapse. J Liv Transpl 2022;5:100061. [CrossRef]

59. Dienstag A, Dienstag P, Mohan K, Mirza O, Schubert E, Ford L, et al. An assessment of the psychosocial evaluation for early liver transplantation in patients with acute alcoholic hepatitis in the context of alcohol use disorder, a case-control study. Subst Abuse 2022;16:11782218221115659. [CrossRef]

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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

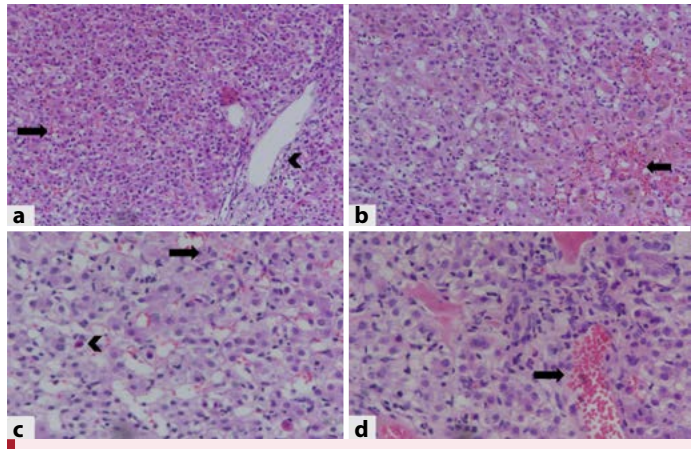



**Figure 1. (a)** Apoptotic hepatocytes (arrow) and mild portal inflammation (arrowhead) are visible. **(b)** Prominent hepatocellular cholestasis is observed (arrow). **(c)** Presence of eosinophils (arrow) and single-cell hepatocyte necrosis (arrowhead). **(d)** Congestion in the hepatic parenchyma 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 4$^{th}$ week, and the patient was discharged with outpatient monitoring and a plan for re-biopsy if needed.

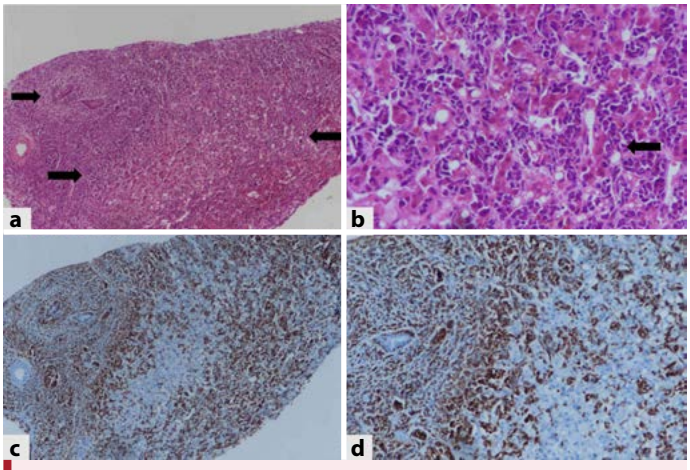



**Figure 2. (a)** Low-power view showing dense lymphoid cell infiltration extending from the portal areas into the hepatic parenchyma, leading to disruption of the porto-parenchymal interface (black arrows) (Hematoxylin and Eosin stain, ×100). **(b)** High-power view of atypical lymphoid cells with hyperchromatic 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.

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## References

1. Pratt DS, Kaplan MM. Evaluation of abnormal liver-enzyme results in asymptomatic patients. N Engl J Med 2000;342(17):1266-1271. [CrossRef]
2. Choi WT, Gill RM. Hepatic lymphoma diagnosis. Surg Pathol Clin 2018;11(2):389-402. [CrossRef]
3. Noronha V, Shafi NQ, Obando JA, Kummar S. Primary non-Hodgkin's lymphoma of the liver. Crit Rev Oncol Hematol 2005;53(3):199-207. [CrossRef]
4. Aozasa K, Mishima K, Ohsawa M. Primary malignant lymphoma of the liver. Leuk Lymphoma 1993;10(4-5):353-357. [CrossRef]
5. Caccamo D, Pervez NK, Marchevsky A. Primary lymphoma of the liver in the acquired immunodeficiency syndrome. Arch Pathol Lab Med 1986;110(6):553-555.
6. Lei KI. Primary non-Hodgkin's lymphoma of the liver. Leuk Lymphoma 1998;29(3-4):293-299. [CrossRef]
7. Page RD, Romaguera JE, Osborne B, Medeiros LJ, Rodriguez J, North L, et al. Primary hepatic lymphoma: favorable outcome after combination chemotherapy. Cancer 2001;92(8):2023-2029. [CrossRef]
8. Peng Y, Qing AC, Cai J, Yue C, French SW, Qing X. Lymphoma of the liver: Clinicopathological features of 19 patients. Exp Mol Pathol 2016;100(2):276-280. [CrossRef]
9. Ugurluer G, Miller RC, Li Y, Thariat J, Ghadjar P, Schick U, et al. Primary hepatic lymphoma: A retrospective, multicenter rare cancer network study. Rare Tumors 2016;8(3):6502. [CrossRef]
10. Stancu M, Jones D, Vega F, Medeiros LJ. Peripheral T-cell lymphoma arising in the liver. Am J Clin Pathol 2002;118(4):574-581. [CrossRef]
11. Peng Y, Cai J, Yue C, Qing X. Primary hepatic Epstein-Barr virus-associated CD30-positive peripheral T-cell lymphoma of cytotoxic phenotype. Exp Mol Pathol 2016;100(1):207-211. [CrossRef]

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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]

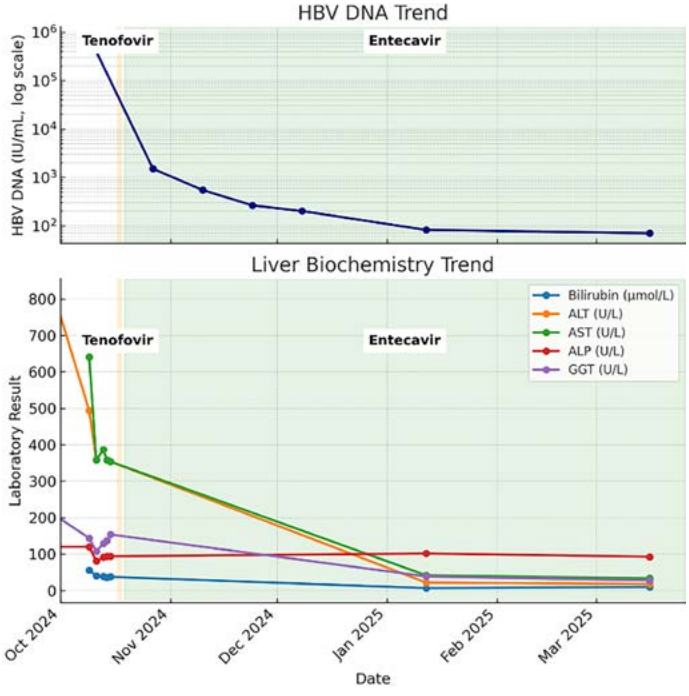



**Figure 1.** Trends in hepatitis B virus DNA and liver biochemistry.

**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 |
| Comorbities/ 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.

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## References


1. Chen G, Wang C, Chen J, Ji D, Wang Y, Wu V, et al. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: A systematic review and meta-analysis. Hepatology 2017;66(1):13-26. [CrossRef]
2. Freudiger H, Sitavanc R. Reverse seroconversion of hepatitis B in a haemodialysis patient. Nephrol Dial Transplant 2004;19(1):238-241. [CrossRef]
3. Deroux A, Larrat S, Hilleret MN, Baccard M, Qin W, Billet G, et al. Case report: Detection of a hepatitis B surface antigen variant emerging in an elderly patient after an ischemic cerebral vascular accident. J Med Virol 2012;84(12):1897-1900. [CrossRef]
4. Ozturk Cerik H, Aldemir O. Spontaneous reactivation of resolved HBV infection in the absence of immunosuppression: case report and literature review. Diagn Microbiol Infect Dis 2025;111(3):116675. [CrossRef]
5. Kamitsukasa H, Iri M, Tanaka A, Nagashima S, Takahashi M, Nishizawa T, et al. Spontaneous reactivation of hepatitis B virus (HBV) infection in patients with resolved or occult HBV infection. J Med Virol 2015;87(4):589-600. [CrossRef]
6. Kim DH, Kim SB. Hepatic failure by spontaneous reactivation of hepatitis B virus without a trigger factor in a patient with anti-HBs. Case Rep Gastroenterol 2018;12(2):286-291. [CrossRef]
7. Kruse RL, Kramer JR, Tyson GL, Duan Z, Chen L, El-Serag HB, et al. Clinical outcomes of hepatitis B virus coinfection in a United States cohort of hepatitis C virus-infected patients. Hepatology 2014;60(6):1871-1878. [CrossRef]
8. Li Y, Yang Y, Li T, Wang Z, Gao C, Deng R, et al. Activation of AIM2 by hepatitis B virus results in antiviral immunity that suppresses hepatitis C virus during coinfection. J Virol 2023;97(10):e0109023. [CrossRef]
9. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2025;83(2):502-583.

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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

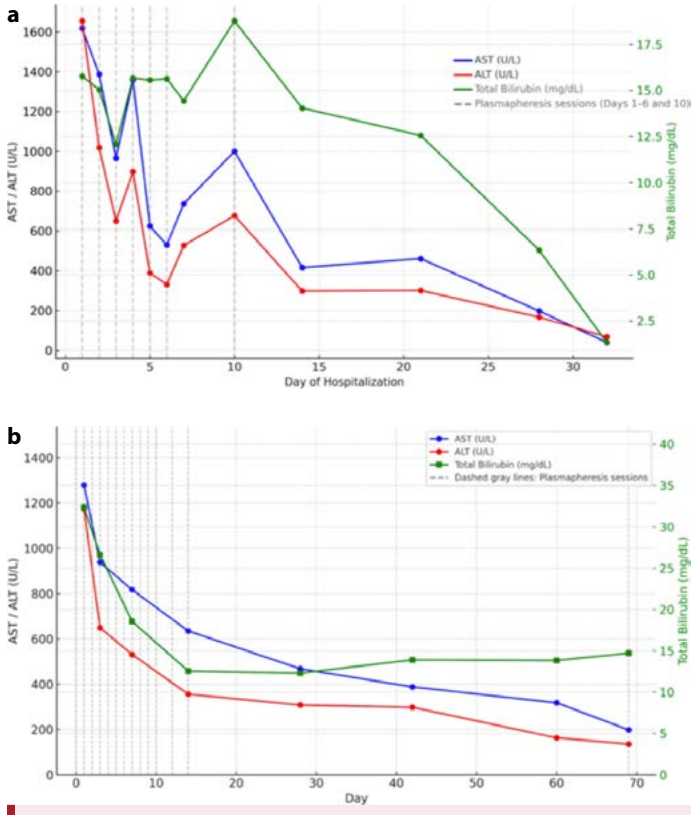



**Figure 1.** Dynamic changes in liver biochemistry during hospitalization. **(a)** Patient 1 showing progressive decline in AST, ALT, and total bilirubin levels following supportive management. **(b)** Patient 2 showing gradual improvement in AST, ALT, and total bilirubin levels throughout hospitalization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

## References

1. Navarro VJ, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. Hepatology 2017;65(1):363-373. [CrossRef]
2. Khorram H, Hamedi S, Musa-al-Reza S, Rezaeizadeh H, Heidari M, Zargaran A. Gastrointestinal effects of *Artemisia absinthium* Linn. based on traditional Persian medicine and new studies. Tradit Med Res 2020;5(5):498-506. [CrossRef]
3. European Medicines Agency (EMA). Assessment Report on *Artemisia absinthium* L., Herba. London: EMA; 2010.
4. World Health Organization (WHO). WHO Monographs on Selected Medicinal Plants. Vol 2. Geneva: World Health Organization; 2002.
5. Barreto II, Gonçalves LR, Corrêa AF, Marin-Morales MA, Moraes KCM. Predictive toxicological effects of *Artemisia absinthium* essential oil on hepatic stellate cells. Toxicol In Vitro 2024;95:105738. [CrossRef]
6. Kumar S, Kacholia K, Duseja A, Chawla Y. Cholestatic liver injury secondary to artemisinin. Hepatology 2015;62(3):973-974. [CrossRef]
7. Ruperti-Repilado FJ, Haefliger S, Rehm S, Rentsch KM, Zimmermann A, Stickel F. Danger of herbal tea: a case of acute cholestatic hepatitis due to Artemisia annua tea. Front Med (Lausanne) 2019;6:221. [CrossRef]
8. Mihajilov-Krstev T, Jovanović B, Jović J, Ilić B, Miladinović D, Matejić J, et al. Antimicrobial, antioxidative, and insect-repellent effects of *Artemisia absinthium* essential oil. Planta Med 2014;80(18):1698-1705. [CrossRef]
9. Pelkonen O, Abass K, Wiesner J. Thujone and thujone-containing herbal medicinal and botanical products: toxicological assessment. Regul Toxicol Pharmacol 2013;65(1):100-107. [CrossRef]

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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 95$^{th}$ 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 (µ/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

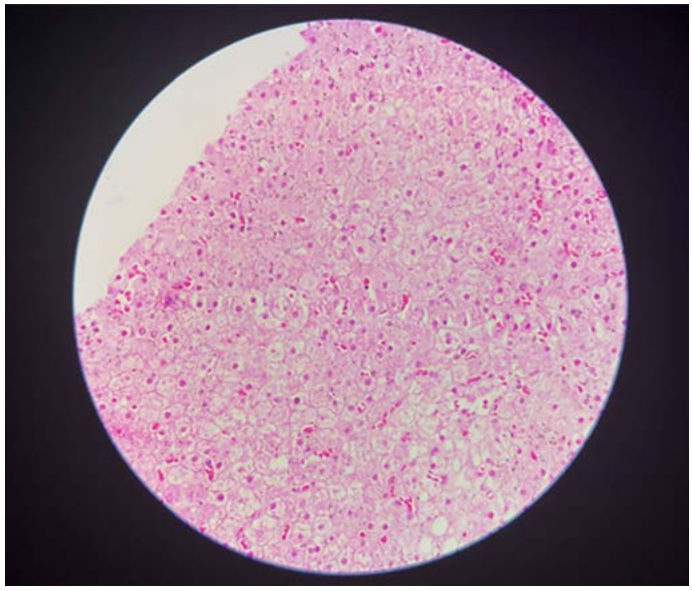


**Figure 1.** Liver histopathology with PAS staining showing glycogen accumulation in cytoplasm of hepatocytes.

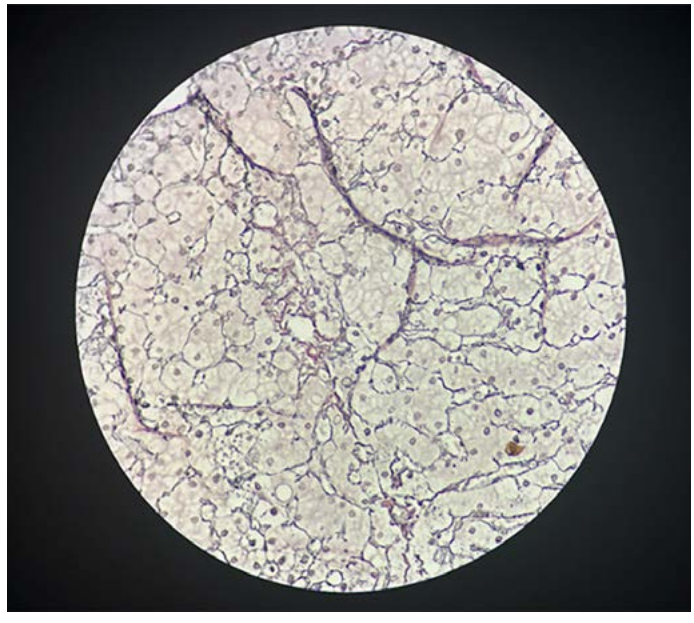


**Figure 2.** Liver histopathology showing pale swelling of hepatocytes.

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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**Author Contributions:** Concept: HM, PA, PKK; Design: HM, PA, PKK; Supervision: BC, SJ, AB, NM; Analysis and/or Interpretation: HM, PA, PKK; Literature Search: HM, PA, PKK; Writing: HM, PA, PKK; Critical Review: HM.

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## References

1. Torres JO, Martins DC, Matias AA, Gião N, Dutra E, Malheiro R, et al. Mauriac syndrome: a rare complication in patients with type 1 diabetes mellitus. Endocrinol Diabetes Metab Case Rep 2025;2025(3):e250035. [CrossRef]
2. Kim MS, Quintos JB. Mauriac syndrome: growth failure and type 1 diabetes mellitus. Pediatr Endocrinol Rev 2008;5(Suppl 4):989-993.
3. Chatila R, West AB. Hepatomegaly and abnormal liver tests due to glycogenosis in adults with diabetes. Medicine (Baltimore) 1996;75(6):327-333. [CrossRef]
4. Giordano S, Martocchia A, Toussan L, Stefanelli M, Pastore F, Devito A, et al. Diagnosis of hepatic glycogenosis in poorly controlled type 1 diabetes mellitus. World J Diabetes 2014;5(6):882-888. [CrossRef]
5. Munns CF, McCrossin RB, Thomsett MJ, Batch J. Hepatic glycogenosis: reversible hepatomegaly in type 1 diabetes. J Paediatr Child Health 2000;36(5):449-452. [CrossRef]
6. Nambam B, Schatz D. Growth hormone and insulin-like growth factor-I axis in type 1 diabetes. Growth Horm IGF Res 2018;38:49-52. [CrossRef]
7. Hudacko RM, Manoukian AV, Schneider SH, Fyfe B. Clinical resolution of glycogenic hepatopathy following improved glycemic control. J Diabetes Complications 2008;22(5):329-330. [CrossRef]

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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"

**Sufwan Ullah Khan, Aun Muhammad Shoro**

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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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## References

1. Helal AE, ElBasiony M, Abdel-Razik A, Mousa N, Shiha G. Endoscopic ultrasound strain elastography in metabolic dysfunction-associated steatotic liver disease: Evaluation against transient elastography and non-invasive markers. Hepatol Forum 2026;7(3):269-276. [CrossRef]
2. Papatheodoridi M, Cholongitas E. Diagnosis of non-alcoholic fatty liver disease (NAFLD): Current concepts. Curr Pharm Des 2018;24(38):4574-4586. [CrossRef]
3. Shiha G, Soliman R, Mikhail NNH, Alswat K, Abdo A, Sanai F, et al. Development and multicenter validation of FIB-6: A novel, machine learning, simple bedside score to rule out liver cirrhosis and compensated advanced chronic liver disease in patients with chronic hepatitis C. Hepatol Res 2022;52(2):165-175. [CrossRef]
4. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143(1):29-36. [CrossRef]
5. Tripepi G, Jager KJ, Dekker FW, Zoccali C. Selection bias and information bias in clinical research. Nephron Clin Pract 2010;115(2):c94-c99. [CrossRef]
6. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Lancet 2007;370(9596):1453-1457. [CrossRef]

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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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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.

### References

1. Khan SU, Shoro AM. Response to endoscopic ultrasound strain elastography in metabolic dysfunction-associated steatotic liver disease: Evaluation against transient elastography and non-invasive markers. Hepatol Forum 2026;7(4):432–433.
2. Helal AE, ElBasiony M, Abdel-Razik A, Mousa N, Shiha G. Endoscopic ultrasound strain elastography in MASLD: Evaluation against transient elastography and non-invasive markers. Hepatol Forum 2026;7(3):269-276. [CrossRef]
3. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. BMJ Open 2016;6(11):e012799. [CrossRef]
4. Schulman AR, Lin MV, Rutherford A, Chan WW, Ryou M. A prospective blinded study of endoscopic ultrasound elastography in liver disease: towards a virtual biopsy. Clin Endosc 2018;51(2):181-185. [CrossRef]
5. Robles-Medranda C, Oleas R, Puga-Tejada M, Valero M, Valle RD, Ospina J, et al. Results of liver and spleen endoscopic ultrasonographic elastography predict portal hypertension secondary to chronic liver disease. Endosc Int Open 2020;8(11):E1623-E1632. [CrossRef]
6. AbiMansour J, Chin JY, Kaur J, Vargas EJ, Abu Dayyeh BK, Law R, et al. Endoscopic ultrasound-based shear wave elastography for detection of advanced liver disease. J Clin Gastroenterol 2025;59(3):256-261. [CrossRef]
7. Squier W, Mack J, Lantz PE, Barnes PD, Scheimberg I, Eastman JT, et al. Circular reasoning. Minn Med 2010;93(3):8. [CrossRef]
8. Shiha G, Soliman R, Mikhail NNH, Alswat K, Abdo A, Sanai F, et al. Development and multicenter validation of FIB-6: A novel, machine learning, simple bedside score to rule out liver cirrhosis and compensated advanced chronic liver disease in patients with chronic hepatitis C. Hepatol Res 2022;52(2):165-175. [CrossRef]
9. Anushiravani A, Alswat K, Dalekos GN, Zachou K, Örmeci N, Al-Busafi S, et al. Multicenter validation of FIB-6 as a novel machine learning non-invasive score to rule out liver cirrhosis in biopsy-proven MAFLD. Eur J Gastroenterol Hepatol 2023;35(11):1284-1288. [CrossRef]
10. Alswat K, Soliman R, Mikhail NNH, Örmeci N, Dalekos GN, Derbala MFM, et al. Validation of FIB-6 score in assessment of liver fibrosis in chronic hepatitis B. Saudi J Gastroenterol 2024;30(3):138-144. [CrossRef]
11. Kahramanoğlu Aksoy E, Ayte MR, Çobanoğlu H, Korlaelçi F, Aktaş B, Özgül S, et al. Assessment of fibrosis in chronic hepatitis B using APRI, FIB-4, FIB-5, FIB-6, and S-Index: Comparison with histology. Medicine (Baltimore) 2026;105(24):e49328. [CrossRef]
12. Simas D, Gonçalves AR, Gomes P, Caetano I, Gomes AC, Russo P, et al. Beyond biopsy: real-world evaluation of the fibrosis-6 score in a Portuguese cohort. GE Port J Gastroenterol 2026;33(1):483-492. [CrossRef]

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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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