HEPATOLOGY FORUM

Volume 7, Issue 4, 2026 | 329–336 DOI: 10.14744/hf.2026.48815

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

Saima Fakih[1], Eda Kaya[2,3], Ali Kirik[4], Caglayan Keklikkiran[2,5], Yusuf Yilmaz[2,5,6]

1: Department of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, Virginia, USA
2: Department of Medicine, University Hospital Knappschaft Clinics Bochum, Ruhr University Bochum, Bochum, Germany
3: The Global NASH Council, Washington DC, USA
4: Department of Internal Medicine, School of Medicine, Balikesir University, Balikesir, Türkiye
5: Department of Gastroenterology, School of Medicine, Recep Tayyip Erdogan University, Rize, Türkiye
6: Dijitalpark Teknokent, Istanbul, Türkiye

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.

How to cite this article: Fakih S, Kaya E, Kirik A, Keklikkiran C, Yilmaz Y. 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. Hepatology Forum 2026; 7(4):329–336.

Received: May 01, 2026; **Revised:** August 31, 2026; **Accepted:** September 22, 2026; **Available Online:** October 30, 2026

Corresponding author: Eda Kaya; Department of Medicine, University Hospital Knappschaft Clinics Bochum, Ruhr University Bochum, Bochum, Germany
E-mail: eda.kaya@knappschaft-kliniken.de

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

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.

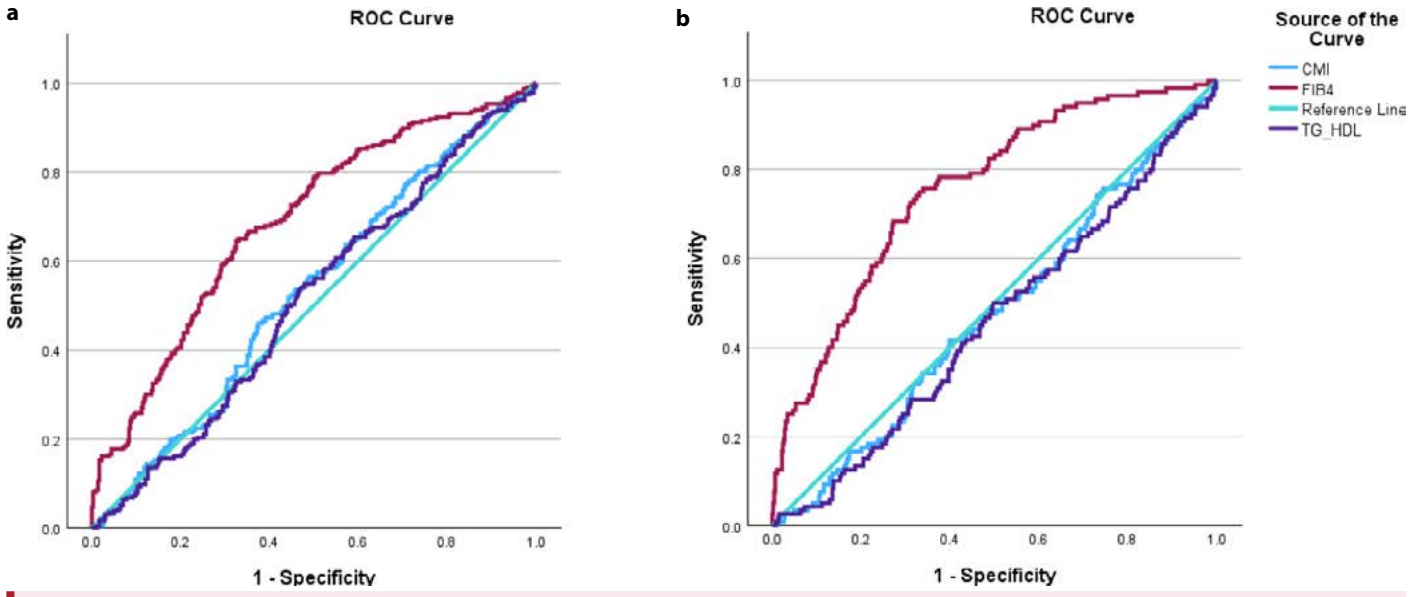


Figure 1. Receiver operating characteristic curves for the discrimination of histological fibrosis severity. **(a)** cardiometabolic index (CMI), triglyceride/high-density lipoprotein (TG/HDL) ratio, and fibrosis-4 index (FIB-4) for significant fibrosis; **(b)** CMI, TG/HDL ratio, and FIB-4 for advanced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

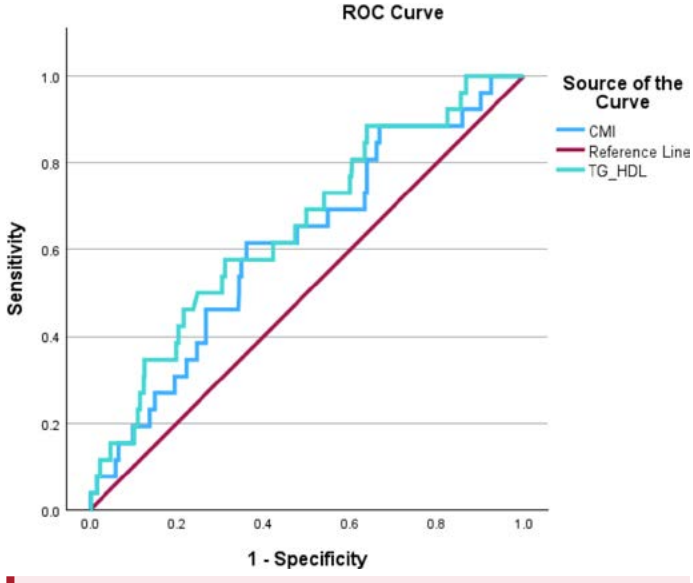


Figure 2. Receiver operating characteristic curves for the discrimination of cirrhosis using cardiometabolic index and the triglyceride/high density lipoprotein ratio. Both markers showed an inverse direction of discrimination, with lower values associated with cirrhosis (n=617).

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 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.

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

Use of AI for Writing Assistance: The authors did not use artificial intelligence (AI)-assisted technologies, including large language models, chatbots, or AI-generated image tools, in the preparation of this manuscript.

Author Contributions: Concept: EK, AK, YY; Design: EK, SF; Supervision: YY; Materials: YY; Data Collection and/or Processing: EK, CK; Analysis and/or Interpretation: EK, SF; Literature Search: EK, SF; Writing: SF, EK; Critical Reviews: SF, EK, AK, CK, YY.

Peer-review: Externally peer-reviewed.

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]