Cureus
Part of SPRINGER NATURE

Open Access Original Article

Clinical and Laboratory Factors of Advanced Fibrosis in Patients With Metabolic Dysfunction-Associated Steatohepatitis (MASH)

Review began 09/06/2026
Review ended 11/03/2026
Published 11/05/2026

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DOI: 10.7759/cureus.119198

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Abstract

Background: Metabolic dysfunction-associated steatohepatitis (MASH) is most strongly linked to adverse outcomes by the presence and severity of advanced liver fibrosis. Identifying clinical and laboratory factors associated with advanced fibrosis may provide useful information for risk stratification, particularly in resource-limited settings.

Methods: This analytical cross-sectional study included 700 adults with MASH who underwent transient elastography (FibroScan® system; Echosens, Paris, France) for fibrosis assessment. We categorized participants into two groups: non-advanced (F0-F2) and advanced (F3-F4) fibrosis. We compared the groups by demographics, metabolic comorbidities, anthropometric parameters, and lab parameters. We used multivariable binary logistic regression to identify independent factors associated with advanced fibrosis.

Results: Overall, 219 participants (31.3%) had advanced fibrosis. Participants with advanced fibrosis had significantly higher mean age, BMI, waist circumference, AST, ALT, and HbA1c levels and significantly lower platelet count and serum albumin levels (all $p < 0.001$). Multivariable analysis showed that age (AOR = 1.068), BMI (AOR = 1.117), waist circumference (AOR = 1.036), AST (AOR = 1.019), ALT (AOR = 1.012), and HbA1c (AOR = 1.751) were independently associated with higher odds of advanced fibrosis. In contrast, higher serum albumin and platelet counts were inversely associated with advanced fibrosis.

Conclusions: Routinely available clinical and laboratory parameters were independently associated with advanced fibrosis in patients with MASH and may provide useful information for risk stratification and prioritization of patients for further fibrosis assessment. These findings are exploratory and should be validated prospectively and in independent populations before clinical implementation, particularly in resource-limited settings.

Categories: Internal Medicine, Gastroenterology
Keywords: liver fibrosis, liver function tests, metabolic dysfunction-associated steatohepatitis, metabolic dysfunction-associated steatotic liver disease, transient elastography

Introduction

Metabolic dysfunction-associated steatohepatitis (MASH), also known as nonalcoholic steatohepatitis (NASH), is the inflammatory stage of metabolic dysfunction-associated steatotic liver disease (MASLD) that has emerged as a global epidemic and is one of the leading causes of chronic liver disease globally [1,2]. The burden of MASH has also increased with the increase in obesity, type 2 diabetes mellitus, dyslipidemia, and metabolic syndrome and has been associated with progressive inflammation and fibrosis of the liver, cirrhosis, hepatocellular carcinoma (HCC), and liver disease-related death [3].

Liver fibrosis is the principal histopathological feature of MASH, and advanced fibrosis has been linked to significantly higher risks of hepatic decompensation, liver-related adverse events, HCC, and mortality [4,5]. Thus, early detection of patients with advanced fibrosis has become a major clinical challenge, requiring early intervention and better prognosis [6].

Liver biopsy remains the reference standard for assessing the stage of hepatic fibrosis, but the procedure is invasive; it can vary depending on the area of the liver biopsied; it is expensive; and it can have procedure-related complications [7,8]. This has led to increasing interest in identifying easily available clinical and

laboratory parameters that can accurately predict advanced fibrosis in patients with MASH [9].

Demographic factors, metabolic comorbidities (obesity and diabetes mellitus), and many routinely measured biochemical parameters, such as liver enzymes, platelet count, serum albumin, and glycemic indices, have been correlated with fibrosis severity [10]. Also, the role of the commonly available clinical and laboratory parameters in the newly established nomenclature of MASLD/MASH is being assessed, especially where access to imaging or proprietary biomarkers may be limited in resource-limited healthcare systems [11,12]. This gap could help develop real-world, practical, and cost-effective fibrosis risk stratification strategies.

Thus, the current cross-sectional study aimed to identify clinical and laboratory parameters independently associated with the presence of advanced fibrosis in patients with MASH. After characterizing demographic characteristics, metabolic risk factors, anthropometric parameters, and routinely collected laboratory measures, the primary objective was to determine which factors were independently associated with transient elastography-defined advanced fibrosis (F3-F4). A secondary exploratory objective was to assess the discriminatory performance of the multivariable logistic regression model using receiver operating characteristic (ROC) analysis. The integrated assessment of readily available clinical and biochemical parameters was intended to provide clinically relevant information for risk stratification and prioritization of patients for further fibrosis assessment, particularly in settings where advanced fibrosis evaluation resources may be limited. These potential clinical implications were considered in the context of the cross-sectional design. They were not intended to imply causal relationships, prediction of future fibrosis progression, or demonstrated reductions in invasive testing.

Materials And Methods

Study design and study setting

This cross-sectional analytical study aimed to identify clinical and laboratory risk factors for advanced fibrosis among patients with MASH. The study was conducted at hepatology and gastroenterology outpatient clinics and liver disease assessment units of Nishtar Hospital, Multan, Pakistan. Patients were screened for eligibility at the clinic visits, and consecutive patients were enrolled during the study period. All clinical assessments, laboratory tests, and FibroScans were conducted in accordance with the hospital's standard clinical practice. After obtaining ethical clearance from the institutional review board, the study period was set, and data collection was conducted. The study was conducted from April 2026 to June 2026.

Study population

Patients included in the study were adults with a diagnosis of MASH. Eligible participants were identified during routine clinical visits and invited to participate after confirmation of the study's inclusion criteria. MASH diagnosis was established through histological assessment of liver biopsy specimens, alongside clinical evaluation and relevant investigations. Liver fibrosis severity was assessed separately using transient elastography performed by trained operators with the FibroScan® system (Echosens, Paris, France).

Participants underwent transient elastography according to standardized procedures, with the appropriate M or XL probe selected according to body habitus. Measurements were obtained with participants in the standard examination position after appropriate fasting. The examination was considered reliable only if it included at least 10 valid measurements, a success rate >60%, and an interquartile range-to-median ratio <30% [13]. Fibrosis stages were classified using liver stiffness measurement (LSM) thresholds derived from validated transient elastography criteria: LSM <8.2 kPa was classified as F0-F1, 8.2-9.6 kPa as F2, 9.7-13.5 kPa as F3, and ⩾13.6 kPa as F4 [14]. For the primary analysis, participants classified as F0-F2 were considered to have non-advanced fibrosis, whereas those classified as F3-F4 were considered to have advanced fibrosis.

Sample size

This study enrolled 700 people with MASH. The sample size was determined based on an expected prevalence of 50% for advanced fibrosis, a 95% confidence level, and a 5% margin of error. The minimum required sample size was 385 participants. Thus, the sample size of 700 patients exceeded the desired sample size and improved the precision of the study estimates. All patients who visited the participating center during the study period, met the eligibility criteria, and provided written informed consent were enrolled.

Sampling technique

Eligible participants were enrolled through consecutive non-probability sampling. All patients presenting to the hepatology and gastroenterology clinics during the study period who met the eligibility criteria were approached consecutively for participation. Recruitment continued throughout the study period until the target sample size was achieved.

Eligibility criteria

Eligibility was restricted to participants aged ⩾18 years with a confirmed diagnosis of MASH and who

provided written informed consent. We included patients who had been assessed with FibroScan and had completed the study laboratory investigations.

Participants were excluded if they had significant alcohol consumption, defined as an average daily alcohol intake of ⩾30 g in men or ⩾20 g in women; chronic hepatitis B or C infection; autoimmune liver disease; drug-induced liver injury; pregnancy; hepatic malignancy; or another chronic liver disease that could independently affect liver fibrosis. Among the screened patients, 15 were excluded because of incomplete clinical data, 10 because of missing FibroScan results, five because of unsuccessful transient elastography examinations, and 20 because of unreliable examinations. Following these exclusions, the final analytical sample comprised 700 participants.

Data collection tools

A structured data collection proforma was used to collect study data. The proforma comprised four sections. The first section recorded demographic and anthropometric characteristics, including age, sex, height, weight, body mass index (BMI), and waist circumference. The second section recorded type 2 diabetes mellitus, hypertension, dyslipidemia, and smoking status. These comorbidities were identified from documented physician diagnoses, participants' medical histories, and available medical records. The third section included laboratory parameters, such as platelet count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum albumin, and glycated hemoglobin (HbA1c). The fourth section recorded FibroScan findings, including LSMs in kilopascals, fibrosis stage, and classification as non-advanced or advanced fibrosis. Laboratory investigations and transient elastography were performed on the same day for all participants. Hepatology specialists reviewed the data collection proforma before implementation to ensure its completeness and clinical relevance.

Data collection procedure

The treating physicians identified eligible patients attending the hepatology outpatient clinics. Each participant was asked about the study aims and the procedures, and written informed consent was obtained. Data regarding demographic information, medical history, and clinical features were gathered using patient interviews and medical record review. Weight and height were measured using a calibrated digital scale and stadiometer, respectively, with participants wearing light clothing and without shoes. BMI was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured using a non-stretchable measuring tape at the midpoint between the lowest rib and the iliac crest at the end of normal expiration.

Venous blood samples were taken routinely and sent to a certified clinical laboratory in the hospital for a complete blood count, liver function tests, and HbA1c. Standardized automated analyzers were used in the laboratory in accordance with the manufacturer's quality assurance procedures. Trained staff performed FibroScan using standardized procedures and techniques. LSMs were obtained in kilopascals, and the fibrosis stage was defined based on predefined cutoff values as F0 to F4. Trained research staff tabulated the data from all materials and cross-checked them for accuracy and completeness before statistical analysis.

Outcome assessment

The primary outcome of the study was advanced liver fibrosis. Liver fibrosis was evaluated by the validated, non-invasive LSM obtained with transient elastography (FibroScan®). Participants with fibrosis stages F0, F1, or F2 were categorized as having non-advanced fibrosis, whereas those with fibrosis stages F3 or F4 were classified as having advanced fibrosis. This dichotomous outcome variable was used as the dependent variable in further comparative and multivariable analyses.

Statistical analysis

All statistical analyses were carried out with IBM SPSS Statistics for Windows, Version 26 (Released 2019; IBM Corp., Armonk, New York). Data for continuous variables were checked for normality by the Shapiro-Wilk test and presented as mean ± SD or median (IQR) as appropriate, whereas data for categorical variables were presented as frequencies and percentages. The non-advanced fibrosis (F0-F2) group was compared with the advanced fibrosis (F3-F4) group by an independent-samples t-test or Mann-Whitney U test (for continuous variables) or by a Pearson chi-squared test (for categorical variables). Factors independently associated with advanced fibrosis were identified using multivariable binary logistic regression. All prespecified demographic, clinical, anthropometric, and laboratory variables included in the final model were entered simultaneously using the Enter method. Continuous variables were entered in their original continuous form, whereas categorical variables were entered according to their prespecified reference categories. Multicollinearity was assessed using variance inflation factors (VIFs), and model calibration was evaluated using the Hosmer-Lemeshow test. ROC analysis was performed using the predicted probabilities from the multivariable logistic regression model to assess its discriminatory performance for advanced fibrosis. The optimal predicted-probability threshold was selected using the maximum Youden index. No internal validation was performed. A two-sided p-value < 0.05 was considered statistically significant. No missing data were present in the final analysis.

Ethical considerations

The Institutional Review Board of Nishtar Medical College approved the study before data collection (approval no. 8803NMC). The study adhered to the ethical principles outlined in the Declaration of Helsinki and its subsequent amendments. All participants received detailed information about the study's aims and procedures, the benefits of participation, and their rights and provided written informed consent before entering the study. Participation was voluntary, and participants could withdraw at any time without affecting their medical care. Participant information was kept confidential by assigning each participant a unique identifier and by excluding any information that could identify a participant from the study database. Only the research team could access study data, and electronic records were password-protected to safeguard participant anonymity and data security.

Results

Table *1* summarizes the categorical characteristics of the 700 study participants. Overall, 219 participants (31.3%) had advanced fibrosis (F3-F4), whereas 481 (68.7%) had non-advanced fibrosis (F0-F2). The table also presents the distribution of sex, smoking status, individual fibrosis stages, and metabolic comorbidities, including type 2 diabetes mellitus, hypertension, and dyslipidemia.

Characteristics	N	%
Sex		
Male	320	45.7
Female	380	54.3
Type 2 diabetes mellitus		
No	504	72.0
Yes	196	28.0
Hypertension		
No	438	62.6
Yes	262	37.4
Dyslipidemia		
No	436	62.3
Yes	264	37.7
Smoking status		
Never a smoker	394	56.3
Former smoker	153	21.9
Current smoker	153	21.9
Fibrosis stage		
F0–F1	298	42.6
F2	183	26.1
F3	149	21.3
F4	70	10.0
Advanced fibrosis status		
Non-advanced fibrosis, F0–F2	481	68.7
Advanced fibrosis, F3–F4	219	31.3

TABLE 1: Categorical Characteristics of the Study Participants (N = 700)

Note: N = 700. Values are presented as frequency (N) and percentage. There were no missing observations for the variables presented. LSM <8.2 kPa was classified as F0–F1, 8.2–9.6 kPa as F2, 9.7–13.5 kPa as F3, and ≥13.6 kPa as F4.

Table *2* presents the descriptive characteristics of the 700 study participants. The mean age was 49.63 ± 10.94 years, and the mean BMI was 29.97 ± 4.22 kg/m^2, indicating that the study population was generally overweight. The mean waist circumference was 88.23 ± 9.30 cm. Regarding laboratory parameters, the mean platelet count was 246.16 ± 46.09 × 10^9/L, mean AST was 40.73 ± 16.45 U/L, and mean ALT was 55.55 ± 26.36 U/L. The mean albumin concentration was 4.28 ± 0.28 g/dL, while the mean HbA1c was 5.74 ± 0.85%. LSMs had a mean of 11.18 ± 6.22 kPa and a median of 9.50 kPa (IQR, 6.70 kPa). Based on the prespecified liver stiffness thresholds, 481 participants (68.7%) had non-advanced fibrosis (F0-F2), whereas 219 (31.3%) had advanced fibrosis (F3-F4).

Variable	Mean ± SD	95% CI for Mean	Median	IQR	Minimum–Maximum
Age, years	49.63 ± 10.94	48.82–50.45	49.00	15.00	22–78
Body mass index, kg/m²	29.97 ± 4.22	29.65–30.28	30.30	5.88	19.00–42.10
Waist circumference, cm	88.23 ± 9.30	87.54–88.92	87.60	13.47	70.00–119.50
Platelet count, ×10⁹/L	246.16 ± 46.09	242.74–249.58	247.00	64.00	103–365
AST, U/L	40.73 ± 16.45	39.51–41.95	37.45	18.50	14.00–111.70
ALT, U/L	55.55 ± 26.36	53.59–57.50	49.10	31.58	15.20–216.80
Albumin, g/dL	4.28 ± 0.28	4.26–4.30	4.27	0.40	3.18–5.10
HbA1c, %	5.74 ± 0.85	5.68–5.80	5.70	1.20	4.40–8.70
Liver stiffness, kPa	11.18 ± 6.22	10.72–11.64	9.50	6.70	3.70–34.70

TABLE 2: Descriptive Statistics for Continuous Variables (N = 700)

Note: N = 700. The fibrosis stage was classified using LSM thresholds of <8.2 kPa for F0–F1, 8.2–9.6 kPa for F2, 9.7–13.5 kPa for F3, and ≥13.6 kPa for F4. Accordingly, 481 participants (68.7%) had non-advanced fibrosis (F0–F2) and therefore had LSM values below 9.7 kPa, whereas 219 participants (31.3%) had advanced fibrosis (F3–F4). The overall median LSM must therefore be below 9.7 kPa.

SD = standard deviation; CI = confidence interval; IQR = interquartile range; AST = aspartate aminotransferase; ALT = alanine aminotransferase; HbA1c = glycated hemoglobin; LSM = liver stiffness measurement.

Participants with advanced fibrosis (F3-F4) had significantly higher AST and ALT levels than those with non-advanced fibrosis (F0-F2), with moderate effect sizes for both comparisons ($p < 0.001$; Table 3).

Variable	Advanced Fibrosis	N	Mean Rank	Sum of Ranks	U	Z	p	r
AST, U/L	Non-advanced (F0–F2)	481	307.79	148049	-	-	-	-
	Advanced (F3–F4)	219	444.3	97301.5	32,127.50	−8.28	<0.001***	0.31
ALT, U/L	Non-advanced (F0–F2)	481	313.32	150709	-	-	-	-
	Advanced (F3–F4)	219	432.15	94641.5	34,787.50	−7.21	<0.001***	0.27

TABLE 3: Comparison of AST and ALT Between Participants With Non-advanced and Advanced Fibrosis Using Mann–Whitney U test (N = 700)

Note: N = 700. Mann–Whitney U tests were used because AST and ALT demonstrated substantial positive skewness; higher mean ranks indicate generally higher enzyme concentrations; effect size was calculated (approximate interpretation guidelines are 0.10 = small, 0.30 = moderate, and 0.50 = large). $p < 0.001$*** were considered significant.

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Participants with advanced fibrosis (F3-F4) were significantly older and had higher BMI, waist circumference, and HbA1c levels than those with non-advanced fibrosis (F0-F2). In contrast, the advanced fibrosis group had significantly lower levels of serum albumin and platelet count (all $p < 0.001$; Table 4). Moderate to large effect sizes were observed for these differences.

Variable	Non-advanced Fibrosis, F0–F2; (N = 481); M ± SD	Advanced Fibrosis, F3–F4; (N = 219); M ± SD	Mean Difference (95% CI)	t(df)	p	Cohen's d
Age, years	46.49 ± 10.08	56.54 ± 9.52	−10.05 (−11.63 to −8.46)	−12.44 (698)	<0.001***	1.01
Body mass index, kg/m²	28.94 ± 3.98	32.23 ± 3.85	−3.29 (−3.92 to −2.66)	−10.25 (698)	<0.001***	0.84
Waist circumference, cm	86.12 ± 8.60	92.87 ± 9.11	−6.76 (−8.16 to −5.35)	−9.46 (698)	<0.001***	0.77
Albumin, g/dL	4.35 ± 0.27	4.14 ± 0.24	0.21 (0.16 to 0.25)	9.68 (698)	<0.001***	0.79
Platelet count, ×10⁹/L	255.12 ± 44.15	226.47 ± 44.17	28.65 (21.58 to 35.72)	7.96 (698)	<0.001***	0.65
HbA1c, %	5.54 ± 0.75	6.18 ± 0.87	−0.65 (−0.78 to −0.51)	−9.46 (370.66)	<0.001***	0.82

TABLE 4: Comparison of Continuous Variables Between Participants With Non-advanced and Advanced Fibrosis Using Independent Sample t-test (N = 700)

Note: Mean differences were calculated as non-advanced fibrosis minus advanced fibrosis. Therefore, negative values indicate higher measurements in the advanced-fibrosis group, whereas positive values indicate higher measurements in the non-advanced group. Equal-variance independent-samples t-tests were used for the variables; Cohen's d values are reported as absolute magnitudes. ***p < 0.001 were considered significant.

CI = confidence interval; HbA1c = glycated hemoglobin.

In univariable analysis, type 2 diabetes mellitus, hypertension, and dyslipidemia were significantly associated with advanced fibrosis (all p < 0.001; Table 5). Among these comorbidities, the strongest association with advanced fibrosis was with type 2 diabetes mellitus.

Variable	Non-advanced Fibrosis, F0–F2; N (%)	Advanced Fibrosis, F3–F4; N (%)	Total (%)	χ^2(df=1)	p	Cramer's V
Type 2 diabetes mellitus						
No	400 (83.2%)	104 (47.5%)	504 (72.0%)	-	-	-
Yes	81 (16.8%)	115 (52.5%)	196 (28.0%)	-	-	-
Total (%)	481 (100%)	219 (100%)	700 (100%)	94.98	<0.001***	0.37
Hypertension						
No	344 (71.5%)	94 (42.9%)	438 (62.6%)	-	-	-
Yes	137 (28.5%)	125 (57.1%)	262 (37.4%)	-	-	-
Total (%)	481 (100%)	219 (100%)	700 (100%)	52.54	<0.001***	0.27
Dyslipidemia						
No	323 (67.2%)	113 (51.6%)	436 (62.3%)	-	-	-
Yes	158 (32.8%)	106 (48.4%)	264 (37.7%)	-	-	-
Total (%)	481 (100%)	219 (100%)	700 (100%)	15.50	<0.001***	0.15

TABLE 5: Associations Between Metabolic Comorbidities and Advanced Fibrosis Status (N = 700)

Note: N = 700. Percentages are calculated within advanced-fibrosis groups; Pearson chi-square tests were used because no expected cell count was below 5; Cramer's V represents the strength of association; For a 2 × 2 table, Phi and Cramer's V are identical. ***p < 0.001 were considered significant.

Table 6 presents the multivariable binary logistic regression analysis of factors associated with advanced liver fibrosis. Older age (adjusted OR = 1.068, 95% CI: 1.040-1.098; p < 0.001), higher BMI (adjusted OR = 1.117, 95% CI: 1.040-1.199; p = 0.002), greater waist circumference (adjusted OR = 1.036, 95% CI: 1.007-1.065; p = 0.016), higher AST (adjusted OR = 1.019, 95% CI: 1.004-1.034; p = 0.013), higher ALT (adjusted OR = 1.012, 95% CI: 1.002-1.021; p = 0.013), and higher HbA1c (adjusted OR = 1.751, 95% CI: 1.252-2.450; p = 0.001) were independently associated with increased odds of advanced fibrosis. Conversely, higher serum albumin (adjusted OR = 0.148, 95% CI: 0.060-0.365; p < 0.001) and higher platelet count (adjusted OR = 0.988, 95% CI: 0.982-0.993; p < 0.001) were associated with lower odds. Dyslipidemia was also significantly associated with advanced fibrosis; participants without dyslipidemia had lower odds than those with dyslipidemia (adjusted OR = 0.582, 95% CI: 0.370-0.914; p = 0.019). Sex, type 2 diabetes mellitus, and hypertension were not statistically significant in the adjusted model. The model demonstrated a Nagelkerke R^2 of 0.550 and no statistically significant evidence of poor fit according to the Hosmer-Lemeshow test (χ^2 = 11.49, p = 0.175).

Predictor	B	SE	Wald χ^2	Adjusted OR	95% CI for OR	p
Age, years	0.066	0.014	22.81	1.068	(1.040–1.098)	<0.001***
Sex: Male vs. female (reference)	−0.093	0.235	0.16	0.911	(0.575–1.445)	0.693
Body mass index, kg/m²	0.110	0.036	9.20	1.117	(1.040–1.199)	0.002**
Waist circumference, cm	0.035	0.014	5.80	1.036	(1.007–1.065)	0.016*
Type 2 diabetes mellitus: No vs. yes (reference)	−0.445	0.293	2.30	0.641	(0.361–1.138)	0.129
Hypertension: No vs. yes (reference)	−0.431	0.232	3.45	0.650	(0.412–1.024)	0.063
Dyslipidemia: No vs. yes (reference)	−0.542	0.230	5.53	0.582	(0.370–0.914)	0.019*
AST, U/L	0.019	0.008	6.19	1.019	(1.004–1.034)	0.013*
ALT, U/L	0.012	0.005	6.12	1.012	(1.002–1.021)	0.013*
Albumin, g/dL	−1.911	0.461	17.18	0.148	(0.060–0.365)	<0.001***
Platelet count, ×10⁹/L	−0.012	0.003	21.33	0.988	(0.982–0.993)	<0.001***
HbA1c, %	0.560	0.171	10.70	1.751	(1.252–2.450)	0.001**
Constant	-4.976	2.790	3.180	0.007	-	0.075

TABLE 6: Multivariable Binary Logistic Regression Predicting Advanced Liver Fibrosis (N = 700)

Note: The dependent variable was advanced liver fibrosis, coded 0 = non-advanced fibrosis (F0–F2) and 1 = advanced fibrosis (F3–F4). Model statistics: −2 log likelihood = 522.65; Cox and Snell R^2 = .391; Nagelkerke R^2 = .550; Hosmer–Lemeshow $\chi^2(8)$ = 11.49, p = .175; N = 700. Categorical predictors were coded as follows: sex, 1 = male and 2 = female; type 2 diabetes mellitus, hypertension, and dyslipidemia, 0 = no and 1 = yes. The last category was specified as the reference category in SPSS. Therefore, female was the reference category for sex, and Yes was the reference category for type 2 diabetes mellitus, hypertension, and dyslipidemia. Accordingly, the reported odds ratios for these binary clinical predictors represent No relative to Yes. *p < 0.05, **p < 0.01, ***p < 0.001.

OR = odds ratio; CI = confidence interval; AST = aspartate aminotransferase; ALT = alanine aminotransferase; HbA1c = glycated hemoglobin.

Figure *1* shows the ROC curve for the multivariable logistic regression model. The model demonstrated good discriminatory performance for advanced fibrosis, with an area under the curve (AUC) of 0.890. The optimal predicted-probability cutoff was 0.383, corresponding to a sensitivity of 76.3%, specificity of 86.7%, and overall accuracy of 83.4%; the Youden index was 0.630.

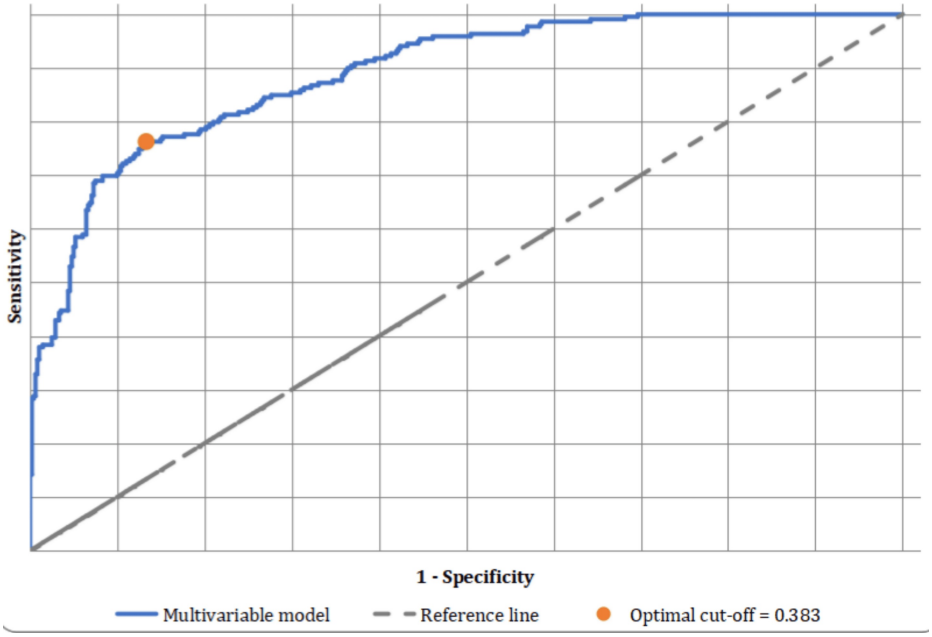


FIGURE 1: Receiver Operating Characteristic Curve for the Multivariable Model

Note: The receiver operating characteristic curve was generated from the predicted probabilities of the multivariable logistic-regression model. Area under curve (AUC) = 0.890; optimal probability cutoff = 0.383; sensitivity = 76.3%; specificity = 86.7%; Youden index = 0.630; overall accuracy = 83.4%.

Discussion

The present study found multiple readily available clinical and laboratory parameters that were independently associated with advanced liver fibrosis in patients with MASH. Older age, higher BMI, greater waist circumference, and elevated AST, ALT, and HbA1c levels were independently associated with increased odds of advanced fibrosis. In contrast, higher serum albumin and platelet counts were inversely associated with advanced fibrosis. Dyslipidemia also showed an independent statistical association with advanced fibrosis. However, this finding should be interpreted cautiously in view of the reference-category coding and the absence of systematic medication data. These results reinforce the potential value of routinely measured clinical and laboratory parameters for risk stratification of patients with MASH [3,9,10]. Taken together, these findings are consistent with the multifactorial nature of advanced fibrosis, involving metabolic dysfunction, persistent liver injury, and impaired liver function [15,16].

Age was one of the strongest factors independently associated with advanced fibrosis, consistent with recent studies demonstrating that advancing age is linked with increasing fibrosis severity and a higher risk of advanced fibrosis in patients with MASLD, particularly in the presence of metabolic risk factors [17,18]. Similarly, higher BMI and waist circumference were associated with greater fibrosis severity, highlighting the important role of both general and central obesity in disease progression. Several recent studies have shown that overweight/obesity is strongly and independently associated with advanced fibrosis and that central obesity is independently associated with fibrosis beyond the effects of BMI and metabolic risk factors [19,20]. Visceral adiposity may contribute to insulin resistance, chronic inflammation, and hepatic stellate cell activation, mechanisms that have been implicated in fibrosis development [16].

In our study, AST and ALT remained independent factors associated with advanced fibrosis after multivariable adjustment. This result is consistent with the available clinical evidence for the use of aminotransferases in fibrosis risk assessment [20,21]. Liver enzymes are useful in combination with metabolic risk factors and validated non-invasive fibrosis assessment tests to stage liver fibrosis accurately, but they are not sufficient on their own. On the other hand, lower levels of serum albumin and platelet counts were independently associated with advanced fibrosis, consistent with previous studies showing a close association between these laboratory markers and fibrosis severity and their important prognostic value in chronic liver disease [22,23].

Poor glycemic control, represented by higher HbA1c levels, was another significant factor independently associated with advanced fibrosis. This result is in line with previous biopsy-proven data, showing that elevated HbA1c is an independent factor of fibrosis severity in those with NAFLD/NASH [24]. Interestingly, both diabetes mellitus and hypertension were linked with advanced fibrosis in univariate analysis but were

not independent in our cohort after multivariable adjustment. This is in contrast to some earlier studies that found type 2 diabetes and hypertension as standalone risk factors for advanced fibrosis [25,26]. This difference may reflect differences in the study populations, fibrosis assessment techniques, and our use of biochemical markers in the multivariable model, which may have accounted for the metabolic effects of these comorbidities.

Notably, dyslipidemia was independently associated with lower odds of advanced fibrosis after multivariable adjustment. This unexpected association should be interpreted cautiously and should not be taken to imply a protective effect of dyslipidemia itself. Although differences in lipid-lowering treatment, including statin use, could potentially influence this association, previous studies have reported beneficial effects of statins on liver enzymes and histological features in patients with NAFLD [27]. However, medication exposure was not systematically assessed in the present study and therefore cannot be evaluated as an explanation for the observed association. Residual confounding or differences in participant characteristics may also have contributed to this finding. Further prospective studies incorporating detailed medication and metabolic profiles are warranted to clarify this relationship.

The findings may have clinical relevance, particularly in resource-limited settings where access to liver biopsy, magnetic resonance elastography, or specialized biomarkers may be limited. The observed associations between routinely available clinical and laboratory parameters and advanced fibrosis may provide useful information for risk stratification and prioritization of patients for further fibrosis assessment. However, the present study did not evaluate clinical outcomes, cost-effectiveness, referral patterns, or reductions in invasive testing; therefore, these potential applications require prospective evaluation before implementation in routine practice.

Limitations

This study has several limitations. First, its cross-sectional design limits causal inference and does not allow assessment of future fibrosis progression. Second, the study was conducted at a single tertiary-care hospital, which may introduce selection bias and limit the generalizability of the findings to community-based or lower-risk populations. Third, fibrosis was assessed using transient elastography rather than liver biopsy; although transient elastography is a validated non-invasive method, misclassification remains possible. Fourth, medication use, diet, physical activity, genetic susceptibility, and inflammatory markers were not systematically assessed and may have contributed to residual confounding, particularly regarding the observed association with dyslipidemia. Fifth, participants with incomplete clinical data or inadequate transient elastography measurements were excluded, which may also have introduced selection effects. Sixth, the multivariable model was not internally or externally validated; therefore, its observed discriminatory performance should be considered exploratory and requires validation in independent populations. Seventh, FIB-4 and other established non-invasive fibrosis scores were not directly compared with the multivariable model, so its incremental value over existing readily available approaches could not be determined. Finally, the study did not directly evaluate cost-effectiveness, referral patterns, clinical outcomes, or reductions in invasive testing, and these potential clinical benefits therefore cannot be inferred from the present findings.

Recommendations

Future prospective multicenter studies should externally validate these findings in independent populations and compare their discriminatory performance with established non-invasive fibrosis scores such as FIB-4. External validation and assessment of clinical utility, including effects on referral decisions and resource use, are warranted before these factors are incorporated into routine risk-stratification strategies.

Conclusions

Advanced liver fibrosis in patients with MASH was independently associated with older age, higher BMI, greater waist circumference, elevated AST, ALT, and HbA1c levels, and lower serum albumin and platelet counts. Dyslipidemia also showed an independent statistical association, although this finding should be interpreted cautiously given the observational design and absence of systematic medication data. These routinely available clinical and laboratory measures may provide useful information for risk stratification and prioritization of patients for further fibrosis assessment. However, the findings are exploratory, and prospective multicenter studies with comparison against established non-invasive fibrosis scores and external validation are needed before clinical implementation.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. The Institutional Review Board of Nishtar Medical College issued approval 8803NMC. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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