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The correlation between liver fibrosis and the 10-year estimated risk of cardiovascular disease in adults with metabolic-associated fatty liver disease: A cross-sectional study in Vietnam

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Abstract

Background and Aims: Metabolic-associated fatty liver disease (MAFLD) emerged as a novel term replacing nonalcoholic fatty liver disease (NAFLD) in 2020. While most MAFLD patients are asymptomatic, long-term hepatic fat accumulation may lead to liver fibrosis and cardiovascular disease (CVD). Nevertheless, the relationship between MAFLD and cardiovascular (CV) risk factors remains unclear. This study aimed to assess the 10-year estimated CVD risk in individuals diagnosed with MAFLD.

Methods: Between January 2022 and August 2023, this cross-sectional study enrolled 139 MAFLD patients. We employed the systematic coronary risk evaluation 2 (SCORE2) and the systematic coronary risk evaluation 2–older persons (SCORE2-OP) scoring systems to evaluate and categorize the 10-year CV risk. Liver fibrosis was assessed using biochemical parameters (FIB-4, AST/ALT, and APRI), and their correlation with CV risk was examined.

Results: Most MAFLD patients were categorized as having high or very high CV risk based on the SCORE2 and SCORE2-OP. Liver fibrosis, measured by the FIB-4 score, significantly differed among the various CV risk groups. Moreover, FIB-4 correlated positively with SCORE2 and SCORE2-OP ($r = 0.588$, $p < 0.001$), indicating its substantial predictive ability for identifying individuals at very high CV risk (AUC = 0.765, 95% CI: 0.686–0.845, $p < 0.001$). A FIB-4 score of 1.275 demonstrated 81% sensitivity and 64% specificity in predicting very high CV risk among MAFLD patients.

Conclusion: Patients with MAFLD predominantly face high or very high CV risks, with elevated liver fibrosis associated with increased 10-year estimated CVD risk. The FIB-4 score exhibits promising predictive value for identifying MAFLD patients at very high risk of CV disease.

KEYWORDS

cardiovascular risk, FIB-4, liver fibrosis, metabolic-associated fatty liver disease, SCORE2, SCORE2-OP

1 | INTRODUCTION

Metabolic-associated fatty liver disease (MAFLD) is garnering increasing attention in clinical practice.[1] MAFLD is a hepatic manifestation of metabolic dysregulation affecting multiple organs. Its causes, clinical manifestations, progression, and outcomes are diverse.[2] Typically, patients with MAFLD do not display clear clinical symptoms until the prolonged accumulation of hepatic fat triggers the development of liver fibrosis. However, the burden becomes pronounced once symptoms manifest.[3]

MAFLD was introduced as a new term for nonalcoholic fatty liver disease (NAFLD) in 2020 and is a significant contributor to chronic liver disease. Projections for the year 2030 estimated approximately 314.58 million cases of MAFLD, indicating a substantial impact of MAFLD in the upcoming decades.[3] Beyond mere semantics, the guidelines for approaching and managing MAFLD have also evolved compared to those for NAFLD.[4]

Previous reports on NAFLD have highlighted its role not only as a primary cause of chronic liver complications such as fibrosis, liver cancer, and transplantation but also as a driving force behind cardiovascular (CV) events.[1] Observational studies suggest a link between NAFLD diagnosis and an increased risk for cardiovascular disease (CVD) and CV events.[5,6] NAFLD was associated with a greater risk of CVD.[7]

Although NAFLD has been linked to CV pathology in previous studies, the transition from NAFLD to MAFLD and the altered approach to fatty liver disease prompt questions regarding the association between MAFLD and CV conditions. Hypotheses concerning the heightened CV risk posed by MAFLD remain unresolved. Additionally, the relationship between liver fibrosis and CV risk remains ambiguous. Recently, some authors have provided evidence supporting a link between MAFLD and CVD, and the importance of this association is well-recognized among hepatologists. However, as a novel CVD risk factor, MAFLD remains underappreciated and underdiagnosed.[8] Increasing awareness among clinical physicians about the adverse CV effects of MAFLD could potentially lead to better prevention of CV events in MAFLD patients. Significantly, there is a remarkable dearth of research in Vietnam concerning the evaluation and classification of CV risk among individuals with MAFLD. In light of this gap, our study endeavored to assess the 10-year CV risk utilizing the systematic coronary risk evaluation 2 (SCORE2) and systematic coronary risk evaluation 2–older persons (SCORE2-OP) scales in MAFLD patients. Moreover, we investigated the correlation between liver fibrosis and the 10-year CV risk in this patient cohort, with a particular focus on the Vietnamese population.

2 | METHODS

2.1 | Study population

This cross-sectional study was conducted on 139 patients who were diagnosed with MALFD at Hue Central Hospital between January 2022 and August 2023. The exclusion criteria for patients were as follows: unwilling to participate in the study or with acute hepatitis or life-threatening conditions. Informed consent was obtained from all study participants at the beginning of the study. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines and was conducted in accordance with the Declaration of Helsinki 2013. The study protocol was approved and endorsed by the Ethics Review Board of Hue University of Medicine and Pharmacy (Code: H2022/109).

2.2 | Clinical data

Baseline demographic information, lifestyle information, medical history, and medication use information were collected with a standardized questionnaire through face-to-face interviews. The following information was collected: (1) sex (male/female) and (2) year of birth (calculated based on the survey year minus the birth year). (3) Personal medical history: Inquiry about any history of internal diseases such as hypertension, hyperlipidemia, type 2 diabetes mellitus (T2DM), coronary artery disease, and so forth. (4) Smoking history: Patients responded with either yes or no. According to a report by the US Department of Health and Human Services, individuals who quit smoking (men after 10 years, women after 5 years) have a CV risk equivalent to that of nonsmokers.[9] Therefore, if the study subjects continuously quit smoking for the specified duration, they are considered nonsmokers. (5) Alcohol consumption history: Patients who responded with either yes or no alcohol consumption.

Height, weight, hip circumference, and body mass index (BMI) were measured through physical examination. Height and weight measurements were conducted meticulously, with weight measurements accurate to 0.5 kg and height measurements precise to 1 cm. BMI was calculated using the following formula: BMI = weight (kg)/(height [m])^2. Blood pressure measurements were performed according to the recommendations of the American Heart Association in 2019 using a sphygmomanometer (Model: aneroid sphygmomanometer no. 500-VN from ALPK2 Co.).[10]

2.3 | Laboratory measurements

Fasting blood samples were collected to measure platelet (PLT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels. PLT analysis was conducted using a Sysmex XS-1000i automated peripheral blood cell analyzer. Biochemical tests, including AST, ALT, TG, TC, LDL-C, and HDL-C, were performed on a Cobas 8000 automated biochemical analyzer using colorimetric methods with enzymatic reactions. Both types of analyzers were stationed in the Department of Biochemistry and the Department of Hematology at Hue Central Hospital.

We calculated non-HDL-C based on the values of TC and HDL-C. The equation is presented as follows: non-HDL-C = TC−HDL-C (mmol/L).[11]

2.4 | CV risk

Evaluation of CV risk using SCORE2 and SCORE2-OP. The SCORE2 and SCORE2-OP for individuals aged 40–69 years and those aged ≥70 years, respectively, were calculated based on variables such as sex, age, systolic blood pressure (SBP), smoking status, TC, and HDL-C and adjusted for the CV risk region in the population. In this study, we classified the CV risk groups in the surveyed population based on the statistical rate of CV mortality per 100,000 people, which were divided into four population groups according to the European Society of Clinical Oncology (ESC) 2021 recommendations: low risk (<100 CV deaths per 100,000 people), moderate risk (100 to <150 CV deaths per 100,000 people), high risk (150 to <300 CV deaths per 100,000 people), and very high risk (≥300 CV deaths per 100,000 people).[12]

According to information from the Vietnam Ministry of Health, approximately 200,000 people die annually from CVD, corresponding to a CV mortality rate of approximately 206/100,000 people per year, categorizing Vietnam as a country with a high CV mortality rate. This finding aligns with the recommendations of the VSH/VNHA regarding the use of SCORE2 and SCORE2-OP for populations with high CV risk in clinical practice in Vietnam.[13]

The estimated CV risk (mortality and immortality) within 10 years using the SCORE2 and SCORE2-OP systems. Interpretation of the results depends on the patient's age, as the cutoff risk levels are numerically different for various age groups: low-moderate CVD risk (<2.5% for <50 years; <5% for 50–69 years; <7.5% for ≥70 years), high CVD risk (2.5% to <7.5% for <50 years; 5% to <10% for 50–69 years; 7.5% to <15% for ≥70 years), and very high CVD risk (≥7.5% for <50 years; ≥10% for 50–69 years; ≥15% for ≥70 years).[12]

2.5 | Liver fibrosis

Evaluation of liver fibrosis indices based on FIB-4, the AST/ALT ratio, and the AST to platelet ratio index (APRI). Three formulas are employed to assess liver fibrosis, namely, FIB-4, the AST/ALT ratio, and the APRI: (1) FIB-4 = [age (years) × AST (U/L)]/{platelet count $(10^9/L) \times [ALT\ (U/L)]^{1/2}$}; (2) AST/ALT = AST (U/L)/ALT (U/L); (3) APRI score: APRI = [{AST (U/L)/(upper limit of AST)}/platelet count $(10^9/L)] \times 100$. These formulas provide quantitative measures for liver fibrosis, offering valuable insights into the extent of liver damage based on age, AST and ALT enzyme levels, and PLT count.[14,15]

2.6 | Ultrasound assessment of fatty liver

Patients underwent a general abdominal ultrasound. The evaluation of fatty liver on ultrasound was conducted as follows: (1) mild: minimal diffuse increase in liver echogenicity with a normal appearance of the hepatic and portal vasculature; (2) moderate: moderate diffuse increase in liver echogenicity with mildly impaired visualization of the hepatic and portal vasculature and the diaphragm; and (3) severe: marked increase in echogenicity with poor or no visualization of the posterior portion of the right hepatic lobe and absent or poorly visualized hepatic and portal vasculature.[16]

TABLE 1 The basal characteristics of the study population.

Characteristic	N = 139
Age (years)	62.27 ± 10.94
Female	103 (74.1)
BMI (kg/m^2)	23.44 [21.92–25.88]
WC (cm)	89.7 ± 8.41
SBP (mmHg)	138.42 ± 23.58
DBP (mmHg)	79.93 ± 10.87
Smoking	11 (7.91)
Alcohol consumption	12 (8.63)
Hepatitis B infection	2 (1.44)
Hypertension	81 (58.27)
Insulin resistance/T2DM	37 (26.62)
Hyperlipidemia	59 (42.45)
Coronary artery disease	12 (8.63)
Cerebrovascular disease	7 (5.04)
TC (mmol/L)	5.32 ± 1.25
TG (mmol/L)	2.00 [1.35–2.78]
HDL-C (mmol/L)	1.12 [0.94–1.36]
LDL-C (mmol/L)	3.62 ± 1.09
Non-HDL-C (mmol/L)	4.12 ± 1.14
AST (U/L)	26.0 [20.2–34.0]
ALT (U/L)	25.4 [16.3–37.1]
PLT (10^9/L)	259.89 ± 60.06
FIB-4	1.31 [0.95–1.64]
AST/ALT ratio	1.05 [0.81–1.34]
APRI	0.25 [0.19–0.36]
Low to moderate risk[a]	35 (25.2)
High risk[a]	52 (37.4)
Very high risk[a]	52 (37.4)

Note: The values are presented as the means ± standard deviations, medians [Q25–Q75], or numbers (%).

Abbreviations: ALT, alanine transaminase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate transaminase; BMI, body mass index; DBP, diastolic blood pressure; FIB-4, fibrosis-4; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol; PLT, platelet; SBP, systolic blood pressure; SCORE2, systematic coronary risk evaluation 2; TC, total cholesterol; TG, triglyceride; T2DM, type 2 diabetes mellitus; WC, waist circumference.

[a]CV risk estimated by SCORE2 and SCORE-OP.

TABLE 2 Comparison of liver fibrosis among CV risk groups.

Liver fibrosis index	Low-moderate risk (*n* = 35)	High risk (*n* = 52)	Very high risk (*n* = 52)	*p* Value
FIB-4	0.94 [0.77–1.13]	1.32 [1.00–1.65]	1.60 [1.33–2.03]	<0.001
AST/ALT ratio	0.97 [0.75–1.25]	1.00 [0.84–1.32]	1.12 [0.89–1.45]	0.09
APRI	0.21 [0.18–0.29]	0.25 [0.21–0.38]	0.27 [0.19–0.37]	0.19

Note: The values are presented as the medians [Q25–Q75].

Abbreviations: ALT, alanine transaminase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate transaminase; FIB-4, fibrosis-4; PLT, platelet.

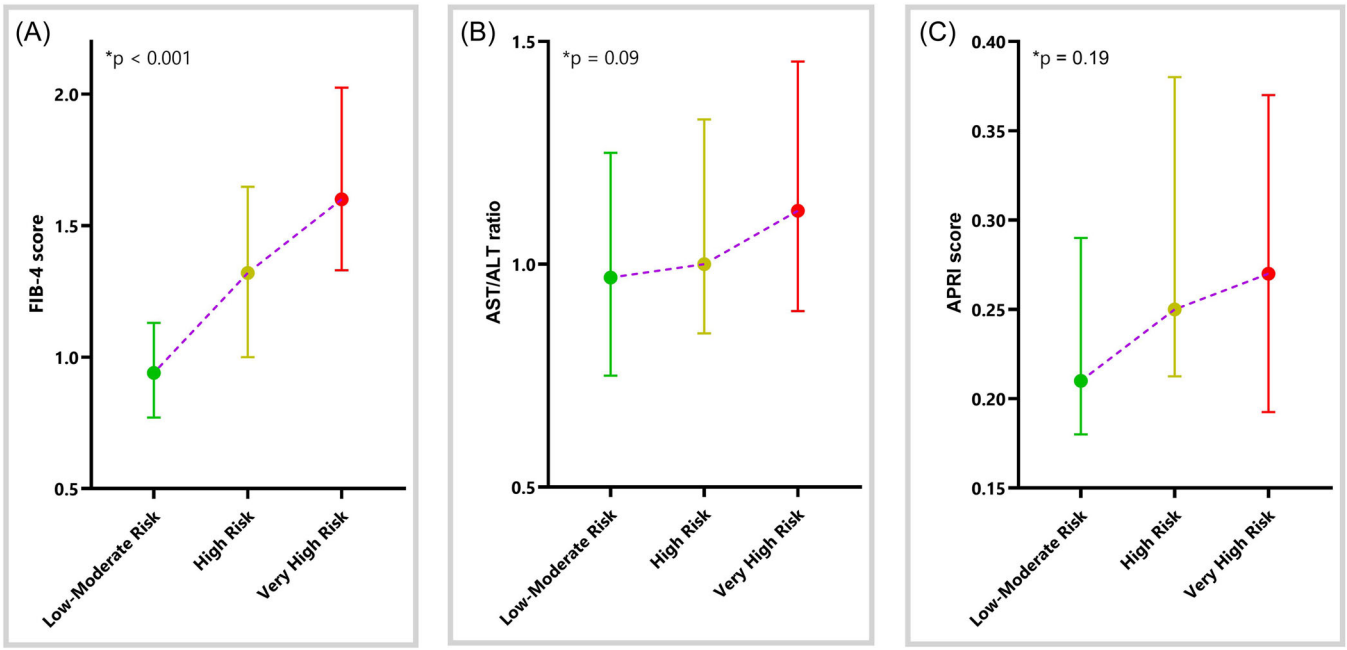

FIGURE 1 The chart illustrates the fibrosis scores for different CV risk groups. (A) displays the median FIB-4 score; (B) shows the median AST/ALT ratio, while (C) depicts the median APRI score. *p Values obtained from the Kruskal–Wallis test. ALT, alanine transaminase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate transaminase; FIB-4, fibrosis-4; PLT, platelet.

2.7 | MAFLD

MAFLD was diagnosed based on evidence of fatty liver through imaging studies, blood tests, or liver biopsy plus at least one of the following three criteria: overweight or obese (BMI ≥23 kg/m² in Asians) or T2DM or non-overweight (BMI <23 kg/m² in Asians) without T2DM but with at least two metabolic risk factors. Metabolic risk factors included the following: (1) waist circumference (WC) ≥90/80 cm in Asians (male/female); (2) blood pressure ≥130/85 mmHg or currently using antihypertensive medication; (3) TG ≥150 mg/dL (≥1.70 mmol/L) or currently using lipid-lowering medication; (4) HDL-C <40 mg/dL (<1 mmol/L) for men and <50 mg/dL (<1.3 mmol/L) for women or currently using lipid-lowering medication; (5) prediabetes (fasting blood sugar 100–125 mg/dL (5.6–6.9 mmol/L), 2 h postprandial glucose 140–199 mg/dL (7.8–11.0 mmol/L), or HbA1c 5.7%–6.4%); (6) homeostasis model assessment of insulin resistance (HOMA-IR) ≥2.5; and (7) plasma high-sensitivity C-reactive protein (CRP-hs) >2 mg/L.[4]

2.8 | Statistical analysis

All the statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM SPSS Statistics for Windows; Version 26.0; IBM Corp.). The normality of the distribution of variables was assessed by the Kolmogorov–Smirnov test. Continuous variables are expressed as the mean ± standard deviation, if normally distributed, and as medians (I and III quartiles); otherwise, categorical variables are reported as percentages. The research results were organized into tables and charts. One-way ANOVA with multiple comparisons was used for normally distributed data. The Kruskal-Wallis test is a nonparametric test that compares three or more unmatched groups. Missing data were excluded from the analyses. Correlations among FIB-4, the AST/ALT ratio, the APRI, and the SCORE2/SCORE2 OP were calculated using Spearman's correlation coefficient (r), and the corresponding p values were calculated to explore correlations between continuous variables. Receiver operating

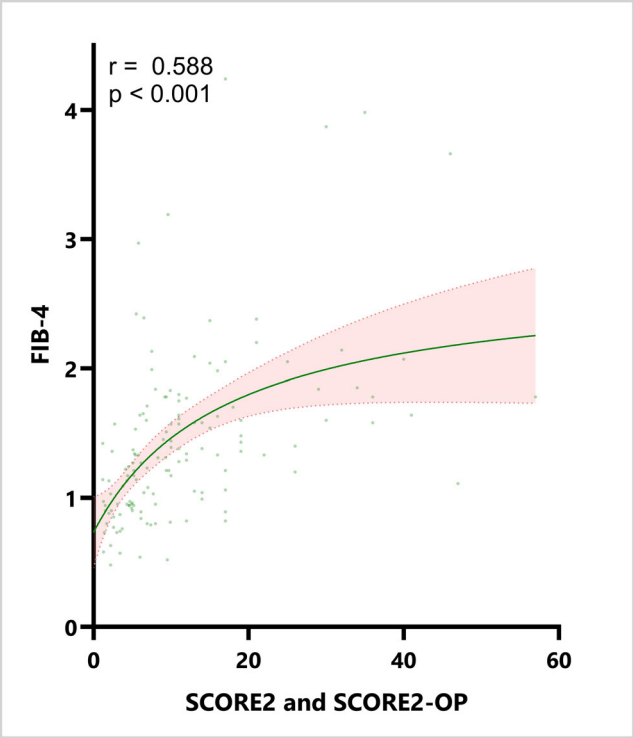

FIGURE 2 The correlation between FIB-4 and SCORE2, SCORE2-OP. APRI, aspartate aminotransferase-to-platelet ratio index; FIB-4, fibrosis-4; SCORE2, systematic coronary risk evaluation 2; SCORE2-OP, systematic coronary risk evaluation 2–older persons.

characteristic curve analysis was conducted to determine the cutoff values for FIB-4, the AST/ALT ratio, and the APRI score that are best for predicting very high CV risk utilizing the Wilson/Brown method. The cutoff values of FIB-4, the AST/ALT ratio, and the APRI were determined at the values where the Youden index was at its maximum. All the statistical tests were two-sided, with the significance level set at <0.05.

3 | RESULTS

3.1 | Baseline demographic and clinical features of the study population

The study encompassed 139 subjects, with an average age of 62.27 years (±10.94). Anthropometric measurements revealed WC at 89.7 cm (±8.41) and BMI at 23.44 kg/m^2 (range: 21.92–25.88). The SBP and diastolic blood pressure of the patients were 138.42 mmHg (±23.58) and 79.93 mmHg (±10.87), respectively. Regarding comorbidities, 58.27% of participants had hypertension, 26.62% had T2DM, and 42.45% had hyperlipidemia. The liver fibrosis indices, as measured by FIB-4, the AST/ALT ratio, and the APRI, were 1.31 (range: 0.95–1.64), 1.05 (range: 0.81–1.34), and 0.25 (range: 0.19–0.36), respectively. Notably, the majority of subjects fell into the high and very high CV risk categories, whereas only 25.2% were classified as low to moderate risk according to the SCORE2 and SCORE2-OP criteria. These detailed characteristics are summarized in Table 1.

3.2 | The association between liver fibrosis and CV risk

The incidence of liver fibrosis assessed by the FIB-4 score in patients with low to very high CV risk was 0.94 [0.77–1.13], 1.32 [1.00–1.65], and 1.60 [1.33–2.03], respectively, demonstrating statistically significant differences ($p < 0.001$). The detailed data are provided in Table 2 and Figure 1. There was a significant positive correlation between liver fibrosis measured by FIB-4 and both the SCORE2 and the SCORE2-OP ($r = 0.588$, $p < 0.001$) (see Figure 2).

3.3 | The value of liver fibrosis scores in predicting 10-year CV risk

The FIB-4 score exhibited a significant predictive capacity for stratifying individuals at very high CV risk, with an AUC of 0.765 (95% CI: 0.686–0.845, $p < 0.001$). The FIB-4 cutoff point was 1.275, indicating a sensitivity of 81% and specificity of 64% in predicting very high CV risk. Table 3 demonstrates the CV risk assessment capability of various liver fibrosis indices. Further details are presented in Table 3 and illustrated in Figure 3.

4 | DISCUSSION

In our study of 139 MAFLD patients, a majority were found to be at high or very high CV risk. Conversely, only 25.2% of the subjects had low to moderate risk according to the SCORE2 and SCORE2-OP. Consistent with global research, MAFLD patients exhibit a 1.43-fold greater incidence of CV events than normal individuals.[17] Evaluations of CV risk using Framingham and ASCVD scores by Tsutsumi et al. have indicated that MAFLD patients have a greater CV risk than NAFLD patients and normal controls.[18]

Several explanations for the increased CV risk in MAFLD patients are plausible. First, the mandatory criteria for MAFLD include the presence of overweight/obesity, T2DM, or other metabolic syndrome features, all of which are associated with an increased risk of CVD.[4] MAFLD patients with T2DM exhibit severe metabolic dysregulation and the worst prognosis.[19] Physiological pathways linking MAFLD and T2DM to increased CV risk may involve atherosclerotic lipid patterns as well as enhanced factors for thrombosis, insulin resistance, low-grade inflammation, and gastrointestinal dysfunction.[20]

Second, the MAFLD diagnosis criteria did not exclude patients who consumed alcohol or had viral hepatitis.[4] Indeed, studies suggest that MAFLD patients coinfected with viral hepatitis or using alcohol have a greater 10-year risk of CVD than those with MAFLD

TABLE 3 Predictive ability for the stratification of very high CV risk by liver fibrosis indices.

Parameter	AUC	95% CI		*p* Value	Cutoff point	Sensitivity	Specificity
FIB-4	0.765	0.686	0.845	<0.001	1.275	81%	64%
APRI	0.531	0.429	0.632	0.548	0.264	52%	61%
AST/ALT ratio	0.596	0.496	0.696	0.059	1.020	69%	55%

Abbreviations: ALT, alanine transaminase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate transaminase; AUC, area under the curve; CI, confidence interval; FIB-4, fibrosis-4; PLT, platelet.

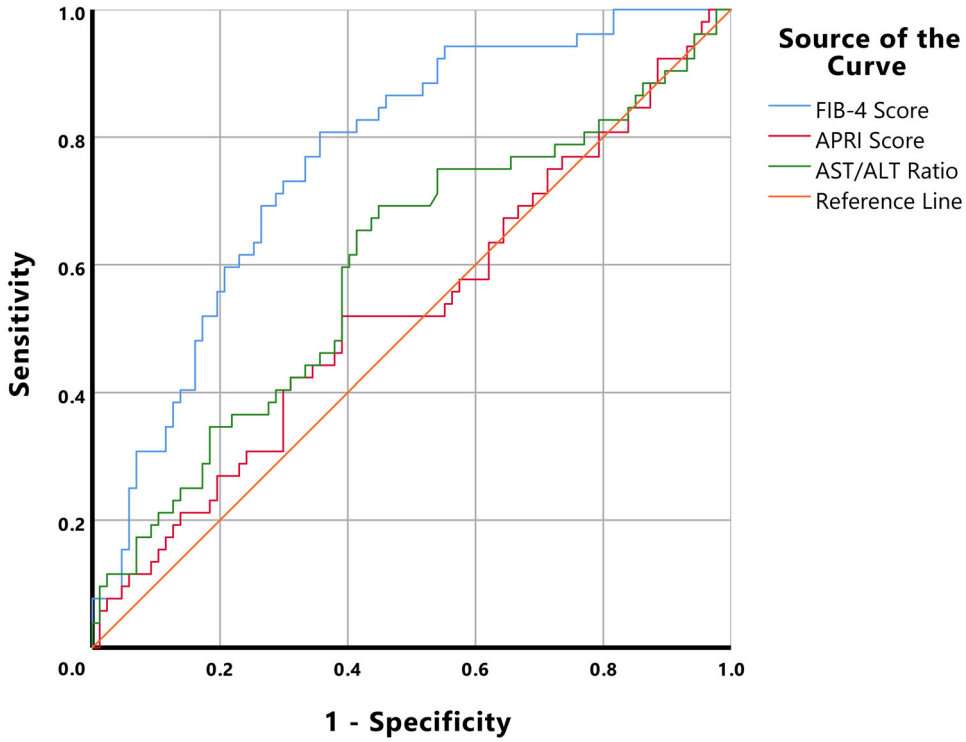

FIGURE 3 ROC curve of liver fibrosis indices in MAFLD predicting very high CV risk. The blue curve illustrates the superior predictive value of FIB-4 compared to the APRI and AST/ALT ratio in predicting very high CV risk in MAFLD patients. ALT, alanine transaminase; APRI, aspartate aminotransferase-to-platelet ratio index; AST, aspartate transaminase; FIB-4, fibrosis-4; MAFLD, metabolic-associated fatty liver disease; PLT, platelet; ROC, receiver operating characteristic.

alone.[21–23] Additionally, MAFLD patients exhibit an overproduction of reactive oxygen species (ROS), and excessive ROS production leads to inflammation and fibrosis, primarily through the activation of hepatic stellate cells (HSCs) in the liver.[24] Excessive ROS production also leads to the oxidation of LDL-C, potentially promoting the transformation of smooth muscle cells (SMCs) into foam cells, a crucial step in the development and progression of atherosclerotic plaques and atherosclerosis, including endothelial cell dysfunction and SMC proliferation.[20]

Insulin resistance is considered a core physiological change in MAFLD.[25] Insulin resistance promotes de novo fat synthesis in the liver and may impact micro- and macroenvironmental balances in various ways to promote accelerated atherosclerosis.[26] Moreover, previous studies have confirmed that chronic hyperglycemia damages vascular endothelial cells stimulates SMC proliferation, improves PLT activity, and causes excessive ROS production, thereby promoting the accelerated formation of atherosclerosis.[27] Low-grade inflammation further exacerbates endothelial dysfunction, alters blood vessel stiffness, and promotes the formation of atherosclerotic plaques.[28] All these mechanisms contribute to the development and progression of CVD, including vascular inflammation, lipid deposition, vascular remodeling, endothelial injury, and thrombosis.

In our study, we observed that patients with higher liver fibrosis scores had an increased risk of CV events. We utilized liver fibrosis indices such as FIB-4, APRI, and AST/ALT due to their practicality in Vietnam, where the components for calculating these scores are readily available. These scores are user-friendly and have high applicability with high specificity.[29,30] Multiple studies have corroborated that as liver fibrosis advances, the likelihood of CV events escalates.[31–33]

The pathophysiology of liver fibrosis is highly complex. Liver fibrosis is a dynamic process that continuously occurs as a healing response to liver injury.[34] During fibrosis, various immune cell reactions and signaling pathways are activated, releasing inflammatory mediators. Excessive inflammation promotes the activation of HSCs, which undergo morphological and functional changes before transforming into myofibroblasts that produce extracellular matrix (ECM).[35] Ultimately, excessive ECM accumulation hinders liver function, leading to fibrosis.[36] The strong positive correlation between liver fibrosis and CV risk is likely partially explained by the inflammatory factors contributing to the development and progression of both CVD and liver fibrosis. However, this question remains unanswered and requires further research.

4.1 | Limitations of the study

Due to local constraints, we exclusively computed noninvasive fibrosis scores due to limited access to liver biopsy techniques, which are considered the gold standard for evaluating liver fibrosis levels. Our cross-sectional study did not establish a causal relationship between fibrosis score and long-term mortality, nor did it clearly define the underlying mechanisms. Furthermore, longitudinal studies are necessary to address these gaps. The study's small sample size is a significant limitation, introducing potential bias and limiting statistical power. Larger sample sizes are warranted. Our single-center study is susceptible to biases and confounding factors that may have influenced the results, and its findings may not be generalizable beyond the Vietnamese population. Hence, there is a pressing need for multicenter studies to address this issue comprehensively, especially across diverse ethnic groups.

5 | CONCLUSION

Patients with MAFLD mostly have high and very high CV risks. Elevated liver fibrosis is associated with increased 10-year estimated CVD risk in MAFLD patients. The FIB-4 score has good predictive value for identifying patients at very high risk of CVD among patients with MAFLD.

AUTHOR CONTRIBUTIONS

Hai Nguyen Ngoc Dang: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; supervision; validation; visualization; writing—review and editing; writing—original draft. **Thang Viet Luong**: Investigation; validation; visualization; writing—review and editing; writing—original draft. **Toan Thanh Tran**: Writing—review and editing. **Tien Anh Hoang**: Supervision. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data sets used and/or analyzed during the current study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and legal considerations in the sampling region. The corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICS STATEMENT

Our research was approved by the Institutional Ethics Committee of Hue University of Medicine and Pharmacy (Code: H2022/109). The research was conducted following the guidelines stipulated in the Helsinki Declaration (2013). In addition, for investigations involving human subjects, informed consent was obtained from the participants involved.

TRANSPARENCY STATEMENT

The lead author, Hai Nguyen Ngoc Dang, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

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