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ORIGINAL ARTICLE

Prospective Study

Role of mac-2 binding protein glycosylation isomer in predicting fibrosis in patients with metabolic dysfunction-associated steatotic liver disease

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Abstract

BACKGROUND

Mac-2 binding protein glycosylation isomer (M2BPGi) serves as a marker of activated hepatic stellate cells and as such holds potential as a biomarker for liver fibrosis. In Viet Nam, metabolic dysfunction-associated steatotic liver disease (MASLD) is rising in prevalence and there is an urgent need for better clinical management, particularly in early detection methods that will improve overall prognosis.

AIM

To examine M2BPGi cut-off values for staging liver fibrosis in patients with MASLD and risk factors associated with disease progression.

METHODS

A total of 301 individuals with ultrasound-confirmed or FibroScan-confirmed diagnosis of fatty liver were enrolled in the study. The participants were stratified according to fibrosis stage, measured *via* magnetic resonance elastography. M2-

BPGi, Fibrosis-4 (FIB-4) Index score, and routine parameters of liver function were assessed to statistically investigate the correlation of M2BPGi levels in various fibrosis stages and to identify risk factors associated with fibrosis severity.

RESULTS

M2BPGi levels positively correlated with fibrosis stages, with cut-off indexes of 0.57 for F0-1, 0.68 for F2-3, and 0.78 for F4. M2BPGi levels in the F0-1 group were significantly different from those in both the F2-3 group (P = 0.038) and the F4 group (P = 0.0051); the F2-3 and F4 groups did not show a significant difference (P = 0.39). Females exhibited significantly higher M2BPGi levels than males for all fibrosis stages, particularly in the F2-3 group (P = 0.01) and F4 group (P = 0.0006). In the F4 (cirrhosis) group, individuals with diabetes had significantly higher M2BPGi levels than those without. M2BPGi, hemoglobin A1c, and FIB-4 score were identified as independent risk factors for greater fibrosis and cirrhosis.

CONCLUSION

M2BPGi levels varied significantly throughout fibrosis progression, from early MASLD to cirrhosis, with sex correlation. M2BPGi holds promise as an early biomarker for fibrosis characterization in MASLD adult patient populations.

Key Words: Metabolic dysfunction-associated steatotic liver disease; Liver fibrosis; Cirrhosis; Mac-2 binding protein glycosylation isomer; Magnetic resonance elastography; Diabetes

Core Tip: This study investigated the role of mac-2 binding protein glycosylation isomer (M2BPGi) as a novel biomarker for staging liver fibrosis in patients with metabolic dysfunction-associated steatotic liver disease in Viet Nam. It established the optimal cut-off values for M2BPGi across fibrosis stages (F0-F4), revealing a moderate correlation with FibroScan and magnetic resonance elastography findings. Ultimately, M2BPGi, Fibrosis-4 Index score, and hemoglobin A1c were identified as independent risk factors for greater fibrosis and cirrhosis (F4), emphasizing M2BPGi's potential in early detection and risk stratification.

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INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD) is the updated term for what was previously known as non-alcoholic fatty liver disease (or NAFLD, for short). This condition occurs in the presence of cardiometabolic factors and in the absence of other causes of hepatic steatosis, including viral infections such as hepatitis B virus (HBV) and hepatitis C virus (HCV)[1]. Globally, it affects over 30% of the general population, making it the most prominent liver disease, with an approximate 1.66 million people reported to be living with this condition[2]. In high-risk groups, such as individuals with type 2 diabetes mellitus (T2DM) and/or obesity, the reported prevalence increases to 60%[3]. In Southeast Asia, MASLD affects over 33% of the population with variations across the country's different regions, fitting with the general range of 25%-33% among nations worldwide[2]. However, Viet Nam is an exception, having relatively low MASLD prevalence overall. When considering high-risk groups of the overweight and obese among the Vietnamese, the prevalences of MASLD are still low, at 10.2%-1.7% respectively[4].

Complications associated with MASLD extend beyond liver-related issues and include cardiovascular diseases, chronic renal diseases, and new-onset diabetes. Pathologically, the accumulation of lipids in liver tissue triggers an inflammatory response, which can eventually lead to liver fibrosis and potentially hepatocellular carcinoma (HCC), highlighting the substantial consequences of delayed diagnosis and treatment. Evidence that fibrosis resulting from MASLD is linked to poor liver-related outcomes and increased mortality is well-documented[5]. Cirrhosis, the end stage of liver fibrosis, is a long-recognized risk factor for HCC progression in patients who have progressed from MAFLD to the functionally injurious state of metabolic dysfunction-associated steatohepatitis[6]. However, a study in France found that 35% of diagnosed HCC cases occurred in patients with MASLD without cirrhosis[7]. Additionally, a recent meta-analysis revealed that approximately half of HCC cases are attributable to MASLD, with MASLD-induced single-etiology HCC accounting for only 12% of these severe cases[8]. A recent report, in 2024, further indicated the danger of this etiological correlation, showing a 16% increase in mortality of HCC when associated with MASLD[9]. Previous studies had shown

that isolated steatosis is not associated with liver-related events or mortality; rather, the stage of fibrosis was identified as a key factor in predicting adverse liver events and worse overall survival[10]. As such, the staging of fibrosis is a crucial clinical step in the management of patients with MASLD according to its status as the most significant predictor of HCC, liver-related events, and mortality.

Liver biopsy has traditionally been the gold standard for staging fibrosis. However, this invasive technique has well-documented limitations, including complications from the procedure itself, potential for sampling errors that may not accurately represent the liver stiffness, and variability in interpretation of the findings[11,12]. Recently, the established imaging-based diagnostic technologies of ultrasound elastography and magnetic resonance elastography (MRE) have emerged as clinician-preferred and patient-preferred procedures for assessing liver fibrosis with both offering non-invasive assessment yielding highly accurate and reproducible results[13]. Unfortunately, accessibility to each is limited by high cost, need for skilled practitioners and logistical complications related to the clinical setting (*i.e.* time requirements for patient preparation, operator processes, and logistical workflow). The serum biomarker scoring systems aspartate aminotransferase (AST)-to-platelet ratio index (APRI) and Fibrosis-4 (FIB-4) Index thus remain the most commonly recommended tools for non-invasive assessment of fibrosis stages in clinical practice[14]. They too have limitations, including the known cofounding factors of age and other medical conditions which can reduce accuracy. Additionally, well-documented reports[15,16] have indicated that both APRI and FIB-4 have low sensitivity for detecting advanced stages of fibrosis.

Mac-2 binding protein glycosylation isomer (M2BPGi) is a glycoprotein primarily derived from hepatic stellate cells (HSCs) located in the liver. This protein plays a crucial role in mediating interactions between macrophages and HSCs during inflammation. The inflammation-induced activation of HSCs facilitates extracellular matrix progression to fibrosis [17] and consequent overproduction of M2BPGi. Given its defined signaling pathway, M2BPGi has potential as a biomarker for staging fibrosis[18]. Indeed, recent studies have demonstrated its usefulness in staging fibrosis as well as in predicting HCC among high-risk patients[19,20], particularly in patients with HBV, HCV, and HCC; studies focusing on MASLD are limited. In Viet Nam specifically, no comprehensive study has investigated the utility of M2BPGi for fibrosis assessment in patients with MASLD.

This study was designed to determine M2BPGi levels across various MRE-stratified fibrosis stages in a Vietnamese patient population in order to determine correlation between MRE and other markers in MASLD and association between M2BPGi levels and fibrosis progression.

MATERIALS AND METHODS

Patients

This observational cross-sectional study comprised 301 patients with MASLD (Figure 1) who had sought medical care at Medic Medical Center (Ho Chi Minh, Viet Nam) between October 2022 and August 2024. According to Delphi Consensus clinical guideline[1], patients who met the following criteria were recruited for inclusion in the study: (1) Age of 18 years or older; (2) Fatty liver diagnosis confirmed by ultrasound or FibroScan (*via* controlled attenuation parameter); (3) Treatment-naïve or > 6-month treatment-cessation status for the fatty liver disease; (4) Presence of any one of the metabolic disorder factors of body mass index ≥ 23 kg/m^2, fasting serum glucose ≥ 5.6 mmol/L or hemoglobin (Hb) A1c ≥ 5.7% or T2DM or treatment for T2DM, plasma triglyceride ≥ 1.7 mmol/L, or high density lipoprotein-cholesterol ≤ 1.0 mmol/L; and (5) Eligibility for the MRE procedure. Patients with any of the following criteria were excluded from study enrollment: (1) Infectious disease etiology of fibrosis, such as mono-infection with HBV or HCV or co-infection with HBV and HCV; (2) Pregnancy; (3) Cancer diagnosis; (4) Alcohol intake > 30 g/day (males) or 20 g/day (females); (5) End-stage renal disease; and (6) Improper/insufficient samples that would hinder immunoassay accuracy, such as those with hemolysis or high turbidity features.

Laboratory tests

Whole blood counts and routine biochemical tests were performed using the Sysmex XN-9000 automated hematology system (Sysmex Corporation, Kobe, Japan) and the Cobas-8000 Analyzer automated immunoassay and photometric system (Roche Diagnostics, Mannheim, Germany). The FIB□4 score was calculated using the standard formula[21] of [age (years) × AST (U/L)]/[platelet count (10^9/L) × alanine aminotransferase (ALT) (U/L)]. The APRI score was calculated using the standard formula of [(AST/upper limit of the normal AST range) × 100]/platelet count (10^9/L)].

MRE

MRE was performed using a GE Signa™ 1.5T magnetic resonance imaging scanner (GE Healthcare, Chicago, IL, United States) and interpreted according to the following measurement ranges per stage: (1) < 3.5 kPa (no or mild fibrosis) for F0-1; (2) 3.5–4 kPa (significant fibrosis) for F2; (3) 4–5 kPa (advanced fibrosis) for F3; and (4) > 5 kPa (cirrhosis) for F4.

M2BPGi immunoassay

Serum specimens were processed on the same day of collection using the M2BPGi immunoassay (Sysmex Corporation) and Sysmex HISCL-5000 automated system. The serum M2BPGi level measurement was based on the interaction between N-glycans and lectins and the resulting complex being identified through a reaction involving the CDP-Star™ chemiluminescent substrate (Thermo Fisher Scientific, Waltham, MA, United States) and alkaline phosphatase. Results were interpreted on a binary scale according to their detected cut-off index (COI) value as follows: (1) > 1 for a negative

result; and (2) 1 for a positive result.

Statistics analysis

Statistical analysis was carried out with PRISM GraphPad software, version 10.0 (La Jolla, CA, United States). Analysis of the area under the receiver operating characteristic (ROC) curve was conducted to establish the cut-off value of M2BPGi for determining fibrosis stages. The Kruskal-Wallis test was applied for intergroup comparisons, with a significance level set at $P < 0.05$. The two-way analysis of variance, Dunn's test and Sidak test were applied for multiple-group comparisons. Univariate and multivariate logistic regression analyses were performed to identify risk factors associated with fibrosis advancement.

RESULTS

Baseline characteristics of study participants

Table 1 shows the baseline characteristics of the total 301 study participants, all with MASLD. The median age of the participants was 52 years and most were diagnosed with more severe fibrosis. Specifically, 168 of the patients were classified as having significant or advanced fibrosis, while cirrhosis was observed in only 43 of the patients (14.3%). The comorbid factors of obesity and diabetes affected 13.6% and 27.6% respectively. Further analysis with the population stratified by liver fibrosis stage as determined by MRE revealed statistical differences across all variables among the different stages, with the exception of ALT and lipid panel (Table 2). Notably, FibroScan-determined fibrosis staging was the only variable that showed significant differences in each pairwise comparison through post-hoc analysis.

M2BPGi medians amongst fibrosis stage groups

The median M2BPGi levels were 0.57, 0.68, and 0.78 COI for liver fibrosis stages F0-1, F2-3, and F4 respectively (Figure 2A). The levels were significantly different between the F0-1 and F2-3 groups ($P = 0.04$) and the F0-1 and F4 (cirrhosis) groups ($P = 0.0051$). However, the difference between the F4 (cirrhosis) and F2-3 group did not meet the threshold for statistical significance ($P = 0.35$).

Overall, the female patients exhibited higher M2BPGi levels than their male counterparts ($P = 0.0001$). This sex-related difference was particularly evident in the F2-3 group ($P = 0.01$) and the F4 group ($P = 0.0006$) (Figure 2B).

Among mix-sex patients with underlying diabetes, those with cirrhosis showed significantly higher M2BPGi levels than those without diabetes (Figure 2C).

Correlation between M2BPGi and other parameters

M2BPGi levels showed a strong correlation with FibroScan findings ($r = 0.61$, 95%CI: 0.53–0.68) (Figure 3A). In contrast, the correlation between M2BPGi and MRE findings was moderate ($r = 0.3$, 95%CI: 0.19–0.4) (Figure 3C), similar to the correlation found between M2BPGi and the FIB-4 score (Figure 3B).

Diagnostic performance of M2BPGi

M2BPGi level was able to effectively distinguish significant fibrosis from mild fibrosis, achieving an area under the curve (AUC) of 0.61 (95%CI: 0.54–0.68). This performance was comparable to that of FIB-4 score, which had an AUC of 0.63 (95%CI: 0.57–0.70), at a cut-off of 0.63, with a sensitivity of 63% and a specificity of 57.8%. In terms of diagnosing cirrhosis, the ROC curve analysis resulted in an AUC of 0.65 at a cut-off of 0.7, with a sensitivity of 62.8% and a specificity of 55.4%.

Risk factors of significant fibrosis and cirrhosis in patients with MASLD

As shown in Table 3, M2BPGi level, FIB-4 score, HbA1c level, and sex were independent risk factors for predicting significant fibrosis and cirrhosis in the patients with MASLD. Particularly, sex was found to be strongest independent factor associated with cirrhosis [adjusted odds ratio (aOR) of 2.5, 95%CI: 1.1–5.78].

DISCUSSION

MASLD, previously known as NAFLD, has emerged as a significant liver-related concern globally, with an estimated prevalence of 25% worldwide[22]. Notably, liver fibrosis has been demonstrated as being more closely associated with long-term outcomes than with histological results[22-24], making early identification of fibrosis stages crucial for patients with MASLD. Angulo *et al*[10], Hagström *et al*[24] and Dulai *et al*[25] reported findings showing that the presence of steatohepatitis did not predict mortality nor survival in patients with similar fibrosis stage. The terminology change from NAFLD to MASLD reflects that most affected individuals also have comorbidities related to metabolic disorders, particularly diabetes, obesity, hypertension, and hyperglycemia; as such, these conditions are considered major risk factors the condition's development and progression.

The correlation we observed between M2BPGi and FibroScan was consistent with a previous study on viral hepatitis [14]. Previous studies have also shown good correlation between M2BPGi levels and FibroScan-determined fibrosis stage in patients with viral-related liver disease[16,26]. Our research demonstrated a consistent correlation, regardless of the etiology (non-viral or viral). We also employed MRE to classify the fibrosis stages in some of our patients diagnosed with

Table 1 Baseline characteristics of the total 301 study participants, *n* (%)

Variables	Median (interquartile range)[1]
Sex	
Male	177 (58.8)
Female	124 (41.2)
Age (years)	52 (42-59)
Body mass index (kg/m^2)	26.4 (24.5-28.4)
Aspartate aminotransferase (U/L)	30 (22-43)
Alanine aminotransferase (U/L)	40 (25-70.5)
Low density lipoprotein-cholesterol (mmol/L)	3.2 (2.5-4.2)
Triglycerides (mmol/L)	2.3 (1.7-3.5)
Total cholesterol (mmol/L)	5.4 (4.6-6.2)
Gamma glutamyl transferase (U/L)	68 (37.5-120.5)
White blood cell (10^9/L)	8 (6.9-9.4)
Hemoglobin (g/L)	14.6 (13.5-15.7)
Platelet count (10^9/L)	261 (224.5-300.5)
Hemoglobin A1c (National Glycohemoglobin Standardization Program)	5.9 (5.6-6.7)
Glucose (mmol/L)	6.2 (5.6-7.5)
Fasting plasma glucose (mg/Dl)	111.9 (101.4-134.3)
Estimated glomerular filtration rate (mL/min/1.73 m^2)	100 (89-108)
FibroScan (kPa)	7.7 (6.2-9.4)
Mac-2 binding protein glycosylation isomer level (cut-off index)	0.67 (0.5-0.9)
Aspartate aminotransferase-to-platelet ratio index	0.3 (0.2-0.4)
Fibrosis-4 Index	0.9 (0.6-1.3)
Controlled attenuation parameter	301 (274-327.5)
Fibrosis stage	
F0-1	90 (29.9)
F2-3	168 (55.8)
F4	43 (14.3)
Comorbidity	
Obesity	41 (13.6)
Diabetes	83 (27.6)

[1]Unless otherwise indicated.

MASLD, following the American Association for the Study of Liver Diseases criteria for application. M2BPGi showed a positive correlation with the MRE-determined fibrosis stages as well. The median M2BPGi level for each MRE-determined fibrosis stage group was remarkably lower than those reported by Alkhouri *et al*[27] using histological-based staging of invasively obtained biopsy specimens. A similar trend was observed when we compared our results with those reported by Abe *et al*[28], Ogawa *et al*[29], Nishikawa *et al*[30], and Atsukawa *et al*[31]. In particular, the mean M2BPGi value reported in the study by Ogawa *et al*[29] was higher than that in our study, even though both studies used MRE as the reference method for assessing liver fibrosis. This suggests that M2BPGi levels may vary among populations with MASLD. Interestingly, the sex-specific groups among our study population exhibited significant differences in circulating M2BPGi levels, being higher in women than in men. This finding was also observed in a previous study conducted with healthy controls and patients with MASLD[32]; specifically, the females showed significantly higher M2BPGi levels than the males in both groups, regardless of disease status. The underlying differentiating mechanisms of mac-2 binding protein production in the context of HSC activation and under normal conditions in males and females are unclear and warrant focused investigation in future studies.

Table 2 Variables according to fibrosis stages stratified by magnetic resonance elastography, *n* (%)

Variables	No or mild fibrosis (group 1) [Median (IQR)]	Significant fibrosis (group 2) [Median (IQR)]	Cirrhosis (group 3) [Median (IQR)]	*P* value[1]			
				Group 1 *vs* group 2	Group 2 *vs* group 3	Group 1 *vs* group 3	All
Age (years)	49 (40.75-56.00)	53 (42-61.75)	52 (43-62)	0.0604	0.9999	0.2393	0.06
Sex							
Male	55 (61.1)	94 (57)	29 (67.4)	ND	ND	ND	ND
Female	35 (38.9)	71 (43)	14 (32.6)	ND	ND	ND	ND
Aspartate aminotransferase (U/L)	27 (21.84-36.25)	31 (22-45)	34.5 (25.25-53)	0.0724	0.0075	0.341	0.0062
Alanine aminotransferase (U/L)	31 (22.75-64.5)	45.5 (25-72.25)	47.5 (29-73.75)	0.1252	> 0.9999	0.2029	0.0741
Gamma glutamyl transferase (U/L)	58.5 (34-110.5)	70.5 (37.25-119)	84 (54-151)	0.6769	0.0987	0.0144	0.0187
Body mass index (kg/m^2)	26.63 (24.4-28.9)	26.3 (24.4-28)	27 (24.8-31)	> 0.9999	0.1613	0.2832	0.1449
FibroScan (kPa)	6.3 (5.78-7.7)	8 (7.03-9.5)	11 (7.1-15.7)	< 0.0001	0.0018	< 0.0001	< 0.0001
Fibrosis-4 Index	0.76 (0.57-1.00)	0.95 (0.67-1.35)	1.18 (0.7-1.79)	0.0092	0.2237	0.0007	0.0004
Aspartate aminotransferase-to-platelet ratio index	0.26 (0.19-0.36)	0.32 (0.21-0.46)	0.33 (0.21-0.62)	0.023	> 0.9999	0.029	0.0073
Mac-2 binding protein glycosylation isomer (cut-off index)	0.57 (0.45-0.81)	0.68 (0.52-0.9)	0.78 (0.58-1.17)	0.038	0.39	0.005	0.0035
Hemoglobin A1c	5.78 (5.45-6.31)	6 (5.59-6.8)	5.92 (5.65-7.52)	0.0344	> 0.9999	0.1148	0.0241
Glucose (mmol/L)	5.85 (5.49-6.59)	6.42 (5.69-7.55)	6.42 (5.66-9.02)	0.0083	> 0.9999	0.0243	0.0041
Low density lipoprotein-cholesterol (mmol/L)	3.35 (2.61-4.19)	3.13 (2.45-4.1)	3.7 (2.62-4.59)	> 0.9999	0.2192	0.9231	0.1824
Triglycerides (mmol/L)	2.29 (1.62-3.22)	2.43 (1.75-3.68)	2.08 (1.73-3.28)	0.8688	> 0.9999	> 0.9999	0.4874
Total cholesterol (mmol/L)	5.3 (4.66-6.17)	5.24 (4.37-6.22)	5.57 (4.84-6.74)	> 0.9999	0.5871	> 0.9999	0.4242
Comorbidity							
Hyperglycemia	20 (22.2)	71 (42.3)	22 (51.2)	ND	ND	ND	ND
Diabetes	15 (16.7)	52 (31)	16 (37.2)	ND	ND	ND	ND
Obesity	12 (13.3)	20 (11.9)	12 (27.9)	ND	ND	ND	ND

[1]Dunn's test was performed to compare individual groups in post-hoc analysis, $P < 0.05$.
ND: Not done; IQR: Interquartile range.

A remarkable finding from our study was the statistically higher M2BPGi levels in patients with cirrhosis and those with significant fibrosis (*vs* mild fibrosis). Patients with significant fibrosis are at a higher risk of progression to cirrhosis, in general, and this status is associated with poor clinical outcomes owing to liver-related events as well as a higher mortality rate. Therefore, determining the stage of fibrosis is also crucial for initiating lifestyle interventions, providing proper and timely treatment, and conducting useful monitoring over time. Abe *et al*[28] conducted one of the first studies to examine the fibrosis performance of M2BPGi in patients with MASLD by liver biopsy. In that study, the optimal thresholds of M2BPGi for detecting significant fibrosis and cirrhosis were 0.9 COI and 1.46 COI respectively. About a decade later, Cheng and Wang[32] showed that M2BPGi could detect significant fibrosis at a cut-off of 0.71, with an AUC of 0.87 and higher sensitivity (85.3%). To the contrary, our study demonstrated that the optimal cut-offs for staging significant fibrosis and cirrhosis were remarkably lower, at 0.61 COI and 0.65 COI respectively. Additionally, our study's cut-off for diagnosing cirrhosis was consistent with that for significant fibrosis and notably lower than the thresholds reported by Abe *et al*[28] (1.46 COI), Ogawa *et al*[29] (1.26 COI), Nishikawa *et al*[30] (1.6 COI), and Atsukawa *et al*[31] (1.38 COI). Compared to other traditional markers, we found that M2BPGi had a diagnostic performance comparable to that of FIB-4 scoring for diagnosing F2 (and F4); this finding is consistent with the work of Cheng and Wang[32], and Jang *et al*[33]. In contrast, Nah *et al*[34] directly compared M2BPGi with FIB-4 scoring and found superior performance across all stages of assessment. These differences may arise from variability in the MRE results used in each to classify the liver fibrosis among the various patient populations under care of different hospital teams; unlike histological assessment of

Table 3 Univariate and multivariate logistic regression identification of risk factors of significant fibrosis and cirrhosis, *n* (%)

Condition	Variable	Univariate analysis		Multivariate analysis	
		OR	95%CI	Adjusted OR	95%CI
Significant fibrosis	Age	1.02	1-1.04	1	0.98-1.03
	Sex				
	Male	Reference		Reference	
	Female	1.15	0.69-1.91	0.72	0.4-1.3
	FIB-4	2.41	1.48-4.23	2.1	1.18-4.3
	M2BPGi (COI)	2.3	1.18-4.93	1.6	0.74-3.8
	HbA1c	1.43	1.13-1.86	1.4	1.08-1.81
Cirrhosis	Age	1	0.98-1.03	0.99	0.96-1.03
	Sex				
	Male	1.5	0.79-3.13	2.5	1.1-5.78
	Female	Reference		Reference	
	FIB-4	2.2	1.54-3.35	1.2	0.92-1.53
	M2BPGi (COI)	2.4	1.37-4.47	1.7	0.85-3.6
	HbA1c	1.2	0.95-1.45	1.2	0.92-1.53

COI: Cut-off index; FIB-4: Fibrosis-4 Index; HbA1c: Hemoglobin A1c; M2BPGi: Mac-2 binding protein glycosylation isomer; OR: Odds ratio.

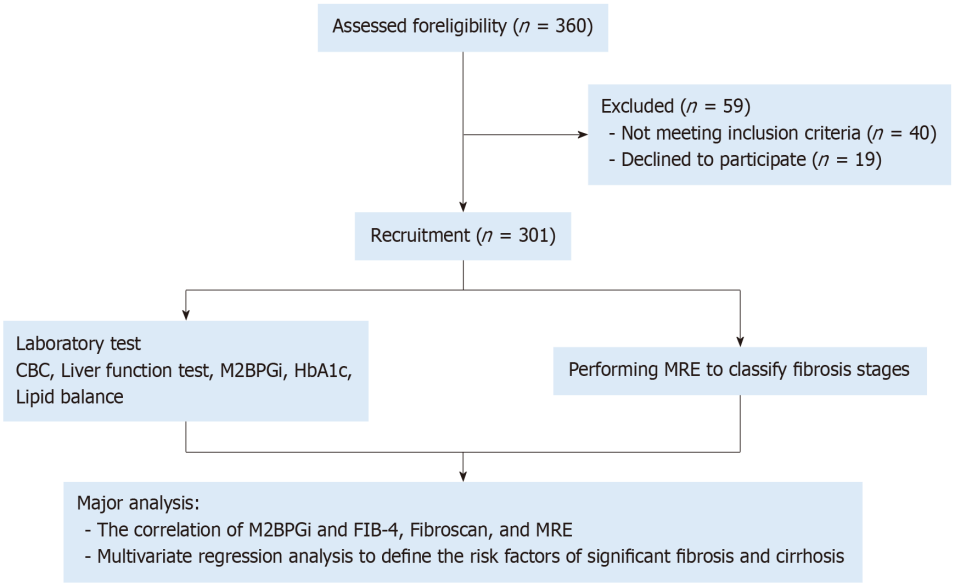

Figure 1 Study flow diagram. CBC: Complete blood count; FIB-4: Fibrosis-4 Index; HbA1c: Hemoglobin A1c; M2BPGi: Mac-2 binding protein glycosylated isomer; MRE: Magnetic resonance elastography.

liver biopsy, MRE is affected by patient-caused sampling errors such as inability to cooperate in breath-holding during a scan[35]. Finally, we believe that the comparatively low M2BPGi levels detected in our patients' various fibrosis stages and the insignificant difference between those in the F2-3 and F4 groups may have led to similarly low cut-off values for these stages.

MASLD's emergence as a major public health concern is closely linked to the rising incidence of metabolic irregularities, such as diabetes, obesity, and dyslipidemia. These conditions are significant risk factors for fibrosis progression [36,37]. Multivariate logistic regression was used in our study to identify risk factors associated with significant fibrosis and cirrhosis. The results clearly indicated that FIB-4 score, M2BPGi level, and HbA1c level could effectively predict significant fibrosis and cirrhosis. Notably, multivariate analysis revealed that male sex was a strongly significant risk factor for predicting cirrhosis. Moon *et al*[38] had also demonstrated that M2BPGi is the strongest predictor of advanced

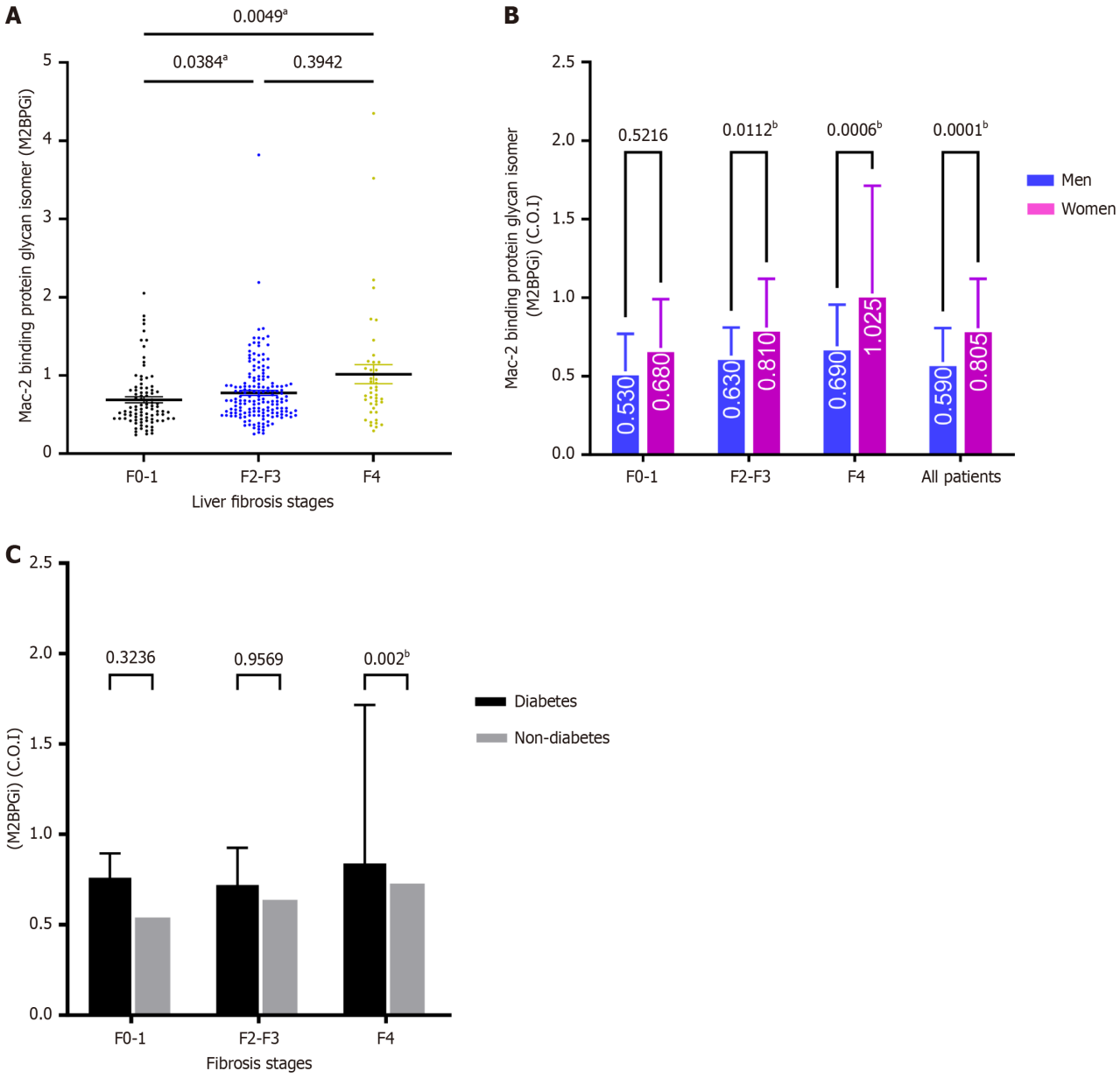

Figure 2 Median of mac-2 binding protein glycosylated isomer levels. A: Median of mac-2 binding protein glycosylated isomer (M2BPGi) levels between different fibrosis stages; B: M2BPGi distributed in various sex-subgrouped fibrosis stages; C: M2BPGi distribution through diabetes-subgroups fibrosis stages. COI: Cut-off index; M2BPGi: Mac-2 binding protein glycosylated isomer. [a]Kruskal-Wallis test, Dunn's test for post-hoc analysis. [b]Two-way analysis of variance, Sidak's test for multiple comparison, $P < 0.05$.

fibrosis in patients with MASLD, reporting an OR of 9.31 in univariate analysis and an aOR of 4.5. Given these findings, M2BPGi can serve as a valuable predictor of fibrosis severity, aiding in risk stratification for patients with MASLD, in addition to its established role in fibrosis assessment in viral liver diseases.

This study had several limitations. MRE was used as a reference method to assess liver fibrosis instead of liver biopsy. Notably, Kawamura *et al*[39] reported a discordance between MRE and liver biopsy results, which could lead to biased conclusions. To be more precise, one significant limitation of MRE is its susceptibility to technical failures, particularly in patients with high liver iron content, which affects the clarity and quality of images[33]. Similarly, issues such as biliary obstruction and congestive heart failure can artificially elevate stiffness readings[33], complicating the interpretation of results. MRE faces challenges in differentiating early fibrosis stages, as small differences in stiffness between these stages can lead to misclassification[40]. Additionally, patient-related factors, such as difficulty in holding breath during the exam, can yield inconsistent results, although techniques like free-breathing MRE attempt to address this issue[35]. Second, the study participants with normal or slightly elevated liver function test findings might not represent the entire population of patients with MASLD. Hence, a multicenter study needs to be conducted in Viet Nam to ensure the data maps the entire geo/demographical population. However, stringent inclusion and exclusion criteria were applied to select patients with MASLD without acute inflammation or necrosis, thereby minimizing bias in the M2BPGi results[41]. Additionally, to mitigate the irregular fibrosis resulting in inaccurate assessments, multiple regions of interest analysis was applied to provide a more comprehensive assessment of liver stiffness. Therefore, our results are of sufficient quality

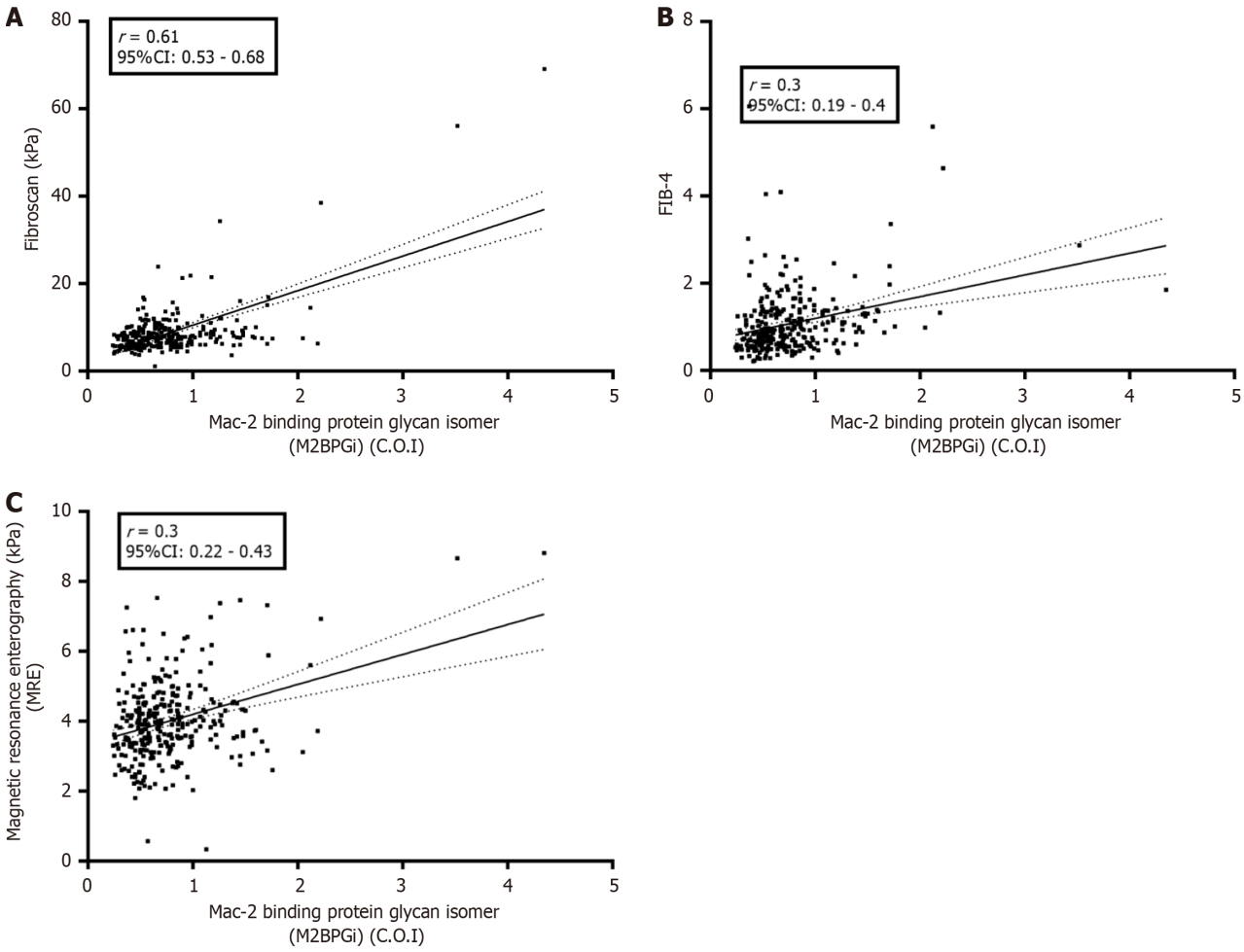

Figure 3 Correlation between mac-2 binding protein glycosylated isomer and major markers of liver fibrosis. A: The correlation with FibroScan; B: The correlation found between mac-2 binding protein glycosylated isomer (M2BPGi) and the Fibrosis-4 Index score; C: The correlation between M2BPGi and magnetic resonance elastography. COI: Cut-off index; FIB-4: Fibrosis-4 Index; M2BPGi: Mac-2 binding protein glycosylated isomer; MRE: Magnetic resonance elastography.

to form a strong foundation for multicenter study on MASLD in the future.

CONCLUSION

The promise held by M2BPGi as a biomarker for predicting liver fibrosis in patients with MASLD is warranted, particularly in settings without access to advanced imaging diagnostics, as it does not require additional calculations such as FIB-4 does. Additionally, this study revealed that both diabetes and M2BPGi level were significantly associated with cirrhosis in MASLD. Thus, M2BPGi level, alongside diabetes, is a risk factor for disease progression. It is important to note that M2BPGi level can vary depending on the underlying causes of MASLD, with our study revealing that the average M2BPGi level in MASLD patients was remarkably lower than that reported in HBV-infected and HCV-infected populations.

FOOTNOTES

Author contributions: Pham TTT, Ho DT, Pham C, Phan H and Phu B conducted the patients' recruitment; Pham TTT, Ho DT and Nguyen KM contributed equally in their efforts towards completion of the study, performed the conceptualization, design of the study, the materials' preparation, and data acquisition and analysis; Nguyen T managed the laboratory tests' performance and provided overall logistical administration of the study; Nguyen D and Phan HT managed the FibroScan performance and provided ultimate supervision of the study; Nguyen KM developed the original draft of the manuscript; all authors contributed to writing of the sequential revisions of the manuscript and approved the final version.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at minhkhuenguyen8888@gmail.com.

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