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ORIGINAL ARTICLE
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Prognostic implication of liver fibrosis scores in patients with non-ischemic dilated cardiomyopathy

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Aims Liver fibrosis was associated with adverse outcomes in various cardiovascular diseases. The current risk stratification of non-ischemic dilated cardiomyopathy (NIDCM) still largely depends on the left ventricular ejection fraction (LVEF). At present, the relationship between liver fibrosis and prognosis in patients with NIDCM remains blank.

Methods and results A total of 433 NIDCM patients were analysed in this study. Liver fibrosis was assessed by three liver fibrosis scores (LFS), including aspartate aminotransferase to platelet ratio index (APRI), aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT ratio), and gamma-glutamyltransferase to platelet ratio (GPR). The primary endpoint was defined as all-cause mortality or heart transplantation (ACM/HTx). During a median follow-up period of 1.7 years, 140 ACM/HTx events occurred. Positive associations were observed between LFS and ACM/HTx. Patients with elevated APRI, AST/ALT ratio, and GPR scores exhibited increased ACM/HTx (all $P < 0.05$). Intermediate-to-high APRI [hazard ratio (HR) 1.66, 95%CI 1.06–2.61, $P = 0.027$], AST/ALT ratio (HR 1.59, 95%CI 1.07–2.36, $P = 0.021$), and GPR (HR 1.64, 95%CI 1.11–2.42, $P = 0.013$) were independently associated with increased risk of ACM/HTx, even after adjusting for LVEF and other covariates. The positive relationship remains consistent across different subgroups, including those with diabetes and obesity.

Conclusions Elevated liver fibrosis scores were associated with a worse outcome beyond LVEF in patients with NIDCM, which may provide additional prognostic value in the management of NIDCM.

Keywords Non-ischemic dilated cardiomyopathy • Liver fibrosis scores • Risk factor

Introduction

Non-ischemic dilated cardiomyopathy (NIDCM) is a non-ischemic heart muscle disease of unknown cause and characterized by left ventricular or biventricular dilatation and systolic dysfunction.[1] NIDCM is the leading indication of heart transplantation in both adolescents and elders.[2,3] Despite advancements in pharmacological and device therapies in the past few decades, NIDCM remains a progressive disease with high mortality rates.[4] At present, the risk stratification of NIDCM largely depends on the left ventricular ejection fraction (LVEF), but its performance is unsatisfactory. Therefore, identifying potential risk factors is of great significance for the clinical management of NIDCM.

Liver fibrosis is a reversible pathological process. Without intervention, liver fibrosis could progress to irreversible cirrhosis and liver carcinoma eventually. It's estimated that 3.6–9% of the general population

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might have liver fibrosis.[5] The cardiovascular and hepatology systems have close associations, and moderate-to-severe hepatic fibrosis is an independent risk factor for cardiovascular events in patients with heart failure with preserved ejection fraction or coronary artery disease.[6–10] Liver cirrhosis could lead to cirrhotic cardiomyopathy, characterized by hyperdynamic circulation, myocardial systolic and diastolic dysfunction, and electrophysiological abnormalities.[11] However, the effect of liver fibrosis, which is considered a pre-stage of cirrhosis, on the prognosis of cardiomyopathy remains unknown. This study aims to investigate the association between liver fibrosis and the prognosis of NIDCM.

Studying liver fibrosis is challenging as it is often asymptomatic. Liver biopsy is the gold standard for diagnosing liver fibrosis and evaluating the severity of liver fibrosis.[12] However, it is an invasive procedure with potential complications, making it unsuitable for routine examination in all patients. In recent years, liver fibrosis scores (LFS) such as aspartate aminotransferase to platelet ratio index (APRI), aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT ratio), and gamma-glutamyltransferase to platelet ratio (GPR) have been reported as safe, effective, and non-invasive diagnostic methods for liver fibrosis.[13–15] Elevated LFS were associated with adverse outcomes in various cardiovascular diseases.[8,9] The present study aimed to investigate the relationship between LFS and the clinical outcomes in patients with NIDCM.

Methods

Study population

From January 2010 to October 2011, we recruited 572 consecutive NIDCM patients at the National Center for Cardiovascular Diseases (Fuwai Hospital, China). This study was a retrospective analysis of prospectively collected data. The inclusion criteria were patients who were diagnosed as NIDCM, which was based on the World Health Organization definition: (i) left ventricular end-diastolic diameter (LVEDD) more than 56 millimetres and LVEF less than 45% in echocardiography; (ii) no severe coronary artery disease in the last 6 months, including coronary artery stenosis >70%, history of myocardial infarction, or infarcted segments shown by single-photon emission computed tomography; (iii) not caused by hypertension, valvular disease or other aetiologies. The exclusion criteria were as follows: (i) patients with missing clinic data or lost to follow-up; (ii) patients treated with corticosteroids or antithyroid therapy within 1 month; (iii) patients who lack laboratory test; (iv) patients with a history of heart transplantation; (v) patients with hepatitis B/C virus infection. Finally, our study included 433 NIDCM patients. All included patients were Asian. This study complied with the Declaration of Helsinki. The study was approved by the Institutional Review Board Committee of Fuwai Hospital. All patients who participated in the study have provided written informed consent.

Study design

The primary endpoint was all-cause death or heart transplantation (ACM/HTx). Follow-up was conducted by professional staff by phone every 6 months according to the follow-up schedule. Mortality caused by accidents was considered censored data and the follow-up was censored at the time of death. Patients lost to follow-up were censored at last contact with them.

Parameters

Lipid profiles and biochemical indicators were assessed through blood chemical analysis. Liver functions were tested by liver blood tests. Blood samples were collected in the morning at a fasting state after admission by intravenous blood collection. LVEF and LVEDD were obtained via transthoracic echocardiography.

As shown in Supplementary material online, *Table S1*, this study calculated three LFS, including aspartate aminotransferase-platelet ratio index (APRI), AST/ALT ratio, and gamma-glutamyl transferase to platelet ratio (GPR). These scores were calculated from clinical variables and blood markers. According to the cut-off value in previous studies, LFS were divided into low and intermediate-to-high scores, corresponding to the low, and intermediate-to-high risk.

Statistical analysis

Continuous variables were presented as mean and standard deviation, and comparisons were conducted using Students' *t*-tests. Categorical variables were presented as counts and percentages, and comparisons were conducted using the χ^2 test. The correlation between LFS and echocardiographic parameters were examined using Spearman or Pearson rank correlations. The predictive ability was evaluated using the area under the receiver operating characteristic curves. Cumulative event rates during follow-up were analysed using Kaplan–Meier analysis. The association between LFS and outcomes was assessed using the Cox proportional hazard regression model. To examine the relationship between continuous LFS and outcomes, a restricted cubic spline analysis was performed. Subgroup analysis was conducted to further evaluate the relationship between LFS and the endpoint. The adjusted variables were based on independent predictors for the primary endpoint and clinically relevant variables. Stepwise regression analysis was used to identify independent risk predictors by including variables with $P < 0.1$ in univariable Cox analysis (see Supplementary material online, *Table S2*). The final adjusted variables were shown as the following: old age, male sex, body mass index (BMI), New York Heart Association (NYHA) heart function class III-IV, diabetes mellitus, smoking, drinking, LVEF, LVEDD, high-sensitive C reactive protein, total cholesterol, total thyroxine, and low-density lipoprotein (LDL)-C. Statistical analysis was performed using R 4.0.3 software (R foundation). $P < 0.05$ was considered statistically significant.

Results

Study patients

A total of 433 patients with NIDCM were enrolled in this study. the average age was 51.1 years old and 72.3% were males. The baseline characteristics of patients were shown in *Table 1*. Compared to patients without ACM/HTx, patients with ACM/HTx had higher scores of APRI, AST/ALT ratio, and GPR. Patients with ACM/HTx are younger and more likely to have NYHA class IV, but less likely to have diabetes mellitus. Meanwhile, patients with ACM/HTx had higher levels of LVEDD, thyroid-stimulating hormone, total thyroxine, and gamma-glutamyl transpeptidase, but lower levels of LVEF, free triiodothyronine, high-density lipoprotein (HDL)-C, uric acid, high-sensitivity C-reactive protein, and albumin.

Liver fibrosis scores and outcomes

During a median follow-up of 1.7 years, the incidence of ACM/HTx was 32.3% (140 events). As shown in *Table 2*, compared with patients in the low-score group, intermediate-to-high scores of APRI, AST/ALT ratio, and GPR exhibited increased rates of ACM/HTx (all $P < 0.05$). Similarly, in the Kaplan–Meier analysis (*Figure 1*), compared with patients in the low-score group, the event-free survival rates of patients with an intermediate-to-high score of APRI, AST/ALT ratio, and GPR decreased significantly (all $P < 0.05$).

In unadjusted Cox regression analysis (*Table 3*), compared to patients with low scores, patients with intermediate-to-high scores of APRI (HR 2.04, 95%CI 1.43–2.92, $P < 0.001$), AST/ALT ratio (HR 1.44, 95%CI 1.02–2.02, $P = 0.039$), and GPR (HR 2.23, 95%CI 1.60–3.12, $P = 0.001$) had significantly increased risk of ACM/HTx. In adjusted Cox regression analysis, the relationships between LFS and ACM/HTx were consistent. Compared with patients with low scores, patients with intermediate-to-high scores of APRI (HR 1.66, 95%CI 1.06–2.61, $P = 0.027$), AST/ALT ratio (HR 1.59, 95%CI 1.07–2.36, $P = 0.021$), and GPR (HR 1.64, 95%CI 1.11–2.42, $P = 0.013$) exhibited significantly elevated ACM/HTx.

In further analysis of restricted cubic spline analysis (*Figure 2*), as continuous variables, APRI and GPR were positively and nonlinearly associated with ACM/HTx. Besides, in the subgroup analysis divided by age,

Table 1 Baseline characteristics

Variables	Overall cohort ($n = 433$)	With ACM/HTx ($n = 140$)	Without ACM/HTx ($n = 293$)	*P*-value
Demographic characteristics				
Age	51.1 (14.0)	48.0 (13.0)	52.6 (14.2)	0.001
Male	313 (72.3)	97 (69.3)	216 (73.7)	0.396
BMI	24.5 (7.4)	23.5 (4.2)	25.0 (8.4)	0.059
New York Heart Association function class				<0.001
I	11 (2.5)	0 (0.0)	11 (3.8)	
II	84 (19.4)	8 (5.7)	76 (25.9)	
III	179 (41.3)	50 (35.7)	129 (44.0)	
IV	159 (36.7)	82 (58.6)	77 (26.3)	
Diabetes mellitus	80 (18.5)	17 (12.1)	63 (21.5)	0.027
Smokers	202 (46.7)	62 (44.3)	140 (47.8)	0.563
Echocardiography parameters				
Left ventricular ejection fraction	32.0 (9.7)	27.7 (8.0)	34.0 (9.8)	<0.001
Left ventricular end-diastolic diameter	68.8 (10.9)	74.7 (11.6)	66.0 (9.3)	<0.001
Laboratory test				
Thyroid-stimulating hormone	3.6 (9.9)	5.5 (11.6)	2.7 (8.9)	0.006
Free triiodothyronine	2.7 (0.5)	2.5 (0.5)	2.8 (0.5)	<0.001
Free thyroxine	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	0.181
Total triiodothyronine	1.0 (0.3)	1.0 (0.3)	0.9 (0.4)	0.084
Total thyroxine	7.9 (2.1)	8.2 (2.0)	7.4 (2.3)	<0.001
Triglyceride	1.6 (1.1)	1.5 (0.7)	1.7 (1.3)	0.066
Total cholesterol	4.4 (1.1)	4.3 (1.1)	4.4 (1.1)	0.172
Low-density lipoprotein cholesterol	2.6 (0.8)	2.6 (0.9)	2.6 (0.8)	0.904
High-density lipoprotein cholesterol	1.0 (0.3)	0.9 (0.3)	1.0 (0.3)	<0.001
Blood glucose	5.5 (1.6)	5.4 (1.7)	5.6 (1.6)	0.113
Creatine	95.9 (32.3)	99.1 (37.2)	94.4 (29.6)	0.163
Platelet	195.0 (60.2)	189.3 (62.6)	197.7 (58.9)	0.179
White blood cell count	25.7 (385.2)	7.7 (2.3)	34.3 (468.3)	0.501
Lymphocyte count	2.0 (1.9)	1.8 (0.7)	2.0 (2.3)	0.271
Monocytes count	0.7 (1.0)	0.7 (1.2)	0.6 (0.2)	0.171
Uric acid	468.3 (170.6)	454.5 (152.4)	497.1 (201.1)	0.015
High sensitivity C-reactive protein	5.4 (4.4)	4.8 (4.2)	6.7 (4.5)	<0.001
AST	31.9 (46.3)	37.8 (62.9)	29.0 (35.5)	0.063
ALT	43.5 (78.8)	51.9 (104.3)	39.5 (62.9)	0.124
γ-glutamyl transferase	77.6 (92.7)	97.2 (112.8)	68.3 (79.8)	0.002
Albumin	40.8 (4.0)	40.2 (4.3)	41.1 (3.8)	0.03
Liver fibrosis scores				
APRI	0.5 (0.6)	0.6 (0.7)	0.4 (0.6)	0.026
AST/ALT ratio	1.0 (0.5)	1.0 (0.5)	0.9 (0.5)	0.049
GPR	0.4 (0.6)	0.6 (0.7)	0.4 (0.5)	0.002

BMI, body mass index; NYHA classification, New York Heart Association class; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine transaminase; APRI, aspartate aminotransferase to platelet ratio index; AST/ALT ratio, aspartate aminotransferase to alanine aminotransferase ratio; GPR, γ-Glutamyl transferase to platelet ratio.

sex, BMI, diabetes mellitus, smoking, LDL-C, LVEDD, and LVEF, compared to patients with low scores, patients with intermediate and high scores of APRI, aspartate transaminase (ASLT)/ALT ratio, and GPR were positively correlated with ACM/HTx as well (see Supplementary material online, *Figures S1–S3*). To investigate the predictive ability of the LFS, we performed the receiver operating characteristic curve (ROC) analysis of 1-year ACM/HTx-free survival. APRI, AST/ALT ratio, and GPR had the area under the ROC (AUC) of 0.590 (95%CI 0.527–0.654), 0.550 (95%CI 0.487–0.614), and 0.642 (95%CI 0.581–0.703), respectively (*Figure 3*).

Liver fibrosis scores and echocardiographic parameters

As shown in *Table 4*, GPR is strongly and significantly correlated with LVEF ($R = -0.157$, $P = 0.001$). Correlations were weaker between

Table 2 Incidence of ACM/HTx

Variables	Events	Percentage	*P*-value
APRI			<0.001
Low ($n = 345$)	96	27.8	
Intermediate-to-high ($n = 88$)	44	50.0	
AST/ALT ratio			0.025
Low ($n = 196$)	52	26.5	
Intermediate-to-high ($n = 237$)	88	37.1	
GPR			<0.001
Low ($n = 255$)	60	23.5	
Intermediate-to-high ($n = 178$)	80	44.9	

APRI, aspartate aminotransferase to platelet ratio index; AST/ALT ratio, aspartate aminotransferase to alanine aminotransferase ratio; GPR, γ-glutamyl transferase and platelet ratio; ACM/HTx, all-cause death or heart transplantation.

APRI and LVEDD (R = 0.106, $P = 0.027$) as well as between GPR and LVEDD (R = 0.109, $P = 0.023$).

Discussion

This study demonstrated that the elevated LFS, including APRI, AST/ALT ratio, and GPR, were associated with the elevated risk of ACM/HTx in NIDCM patients. These findings remained consistent after multivariable adjustment and the positive relationship were observed across various subgroups based on age, sex, diabetes mellitus status, BMI, smoking status, LDL-C, LVEDD, and LVEF. Compared to patients with low scores, those with intermediate-to-high APRI, AST/ALT ratio, and GPR had a significantly higher risk of ACM/HTx, ranging from 1.59 to 1.66 times. These results suggest that LFS could independently predict adverse outcomes in NIDCM patients.

Despite advancements in therapeutic drugs and devices, the prognosis of NIDCM remains poor.[16] Therefore, identifying high-risk individuals is crucial for clinical management. At present, the risk stratification of patients with NIDCM largely depends on LVEF, which has limited value in clinical practice a because a great amount of mortality also occurs in patients without severely reduced ejection fraction.

The liver disease has the potential to impact cardiac function. Mechanistically, liver cirrhosis could lead to a state of hyperdynamic circulation, characterized by an increased in cardiac output and heart rate, as well as decreased peripheral resistance and arterial pressure. This condition could contribute to the development of heart failure and is closely linked to adverse outcomes. Additionally, it is known that cardiac dysfunction could be severe enough to result in liver dysfunction. Elevated LFS have been found to predict adverse outcomes in various cardiovascular diseases,[7,8,17,18] including coronary artery disease, ischaemic stroke, and heart failure with preserved ejection fraction.[9,19–22] Liver fibrosis is considered to serve as crucial link between chronic liver injury and liver cirrhosis.

However, no prior studies have investigated whether liver fibrosis is associated with adverse outcomes in NIDCM. Given the estimated global prevalence of liver fibrosis in up to 9% of patients, it is important to assess its relationship with the prognosis of NIDCM. NIDCM, along with systolic and diastolic cardiac dysfunction, may contribute to liver fibrosis through potential mechanisms. In NIDCM, the heart muscle weakens and enlarges, which could lead to congestive heart failure and increased blood pressure in the hepatic veins. This, in turn, could cause liver congestion and increased pressure within the liver, activating the hepatic stellate cells, and resulting in the development of liver fibrosis.[23,24]

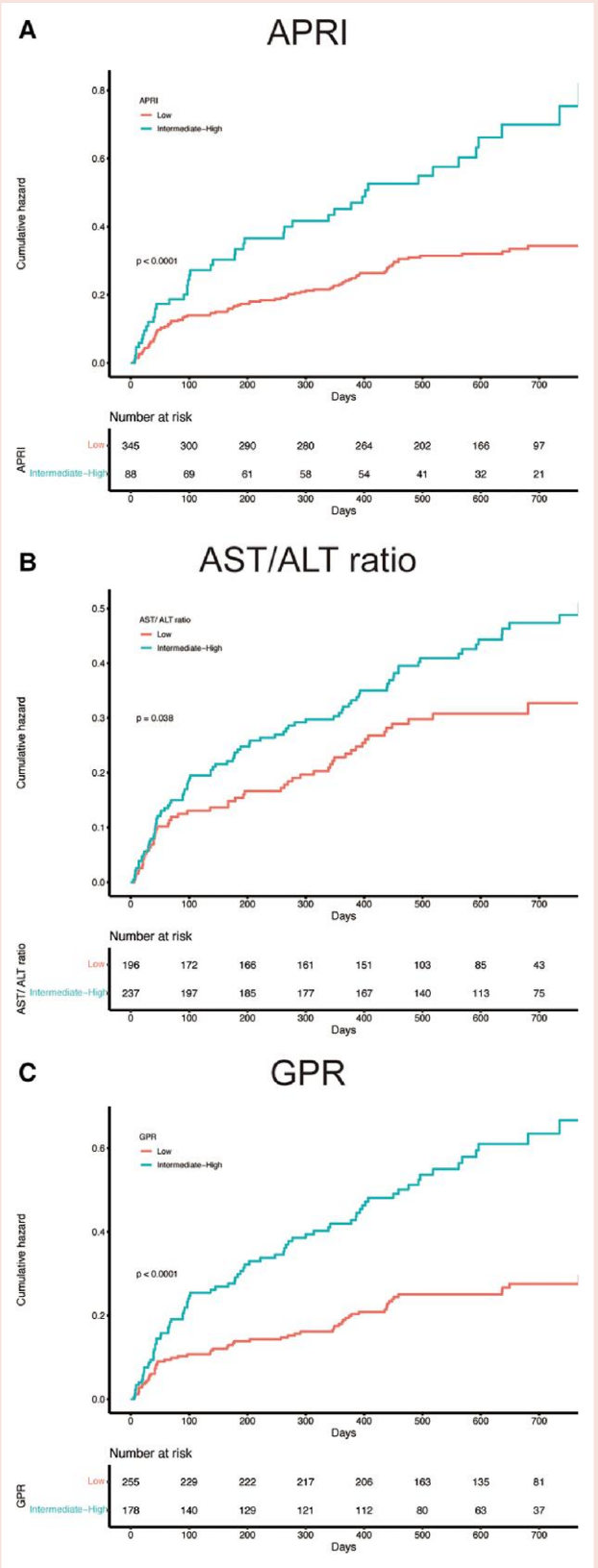

Figure 1 The Kaplan–Meier analysis for ACM/HTx according to liver fibrosis scores. APRI, aspartate aminotransferase to platelet ratio index; AST/ALT ratio, aspartate aminotransferase to alanine aminotransferase ratio; GPR, gamma-glutamyl transpeptidase to platelet ratio.

Table 3 Univariable and multivariable Cox regression analysis of ACM/HTx according to liver fibrosis scores.

Variables	HR	95%CI
Univariable Cox regression		
APRI		
Low ($n = 345$)	1	
Intermediate-to-high ($n = 88$)	2.04 (1.43–2.92)	<0.001
AST/ALT ratio		
Low ($n = 196$)	1	
Intermediate-to-high ($n = 237$)	1.44 (1.02–2.02)	0.039
GPR		
Low ($n = 255$)	1	
Intermediate-to-high ($n = 178$)	2.23 (1.60–3.12)	0.001
Multivariable Cox regression		
APRI		
Low ($n = 345$)	1	
Intermediate-to-high ($n = 88$)	1.66 (1.06–2.61)	0.027
AST/ALT ratio		
Low ($n = 196$)	1	
Intermediate-to-high ($n = 237$)	1.59 (1.07–2.36)	0.021
GPR		
Low ($n = 255$)	1	
Intermediate-to-high ($n = 178$)	1.64 (1.11–2.42)	0.013

HR, hazard ratio; 95% CI, 95% confidential interval; APRI, aspartate aminotransferase to platelet ratio index; AST/ALT ratio, aspartate aminotransferase to alanine aminotransferase ratio; GPR, γ-glutamyl transferase to platelet ratio; ACM/HTx, all-cause death or heart transplantation.

Taking the role of right atrial pressure (RAP), systolic pulmonary artery pressure (sPAP), and tricuspid regurgitation pressure gradient (TRPG) as an example. Elevated RAP, sPAP, and TRPG are examples of factors that reflect increased pressure in the right atrium. These factors could increase inferior cava pressure on the sinusoidal liver bed due to a lack of valves in hepatic veins,[25,26] facilitating liver fibrosis. Additionally, systolic and diastolic cardiac dysfunction could lead to decreased cardiac output, which can activate the renin–angiotensin–aldosterone system and sympathetic nervous system.[27] These systems could promote inflammation and oxidative stress, activating hepatic stellate cells and contributing to liver fibrosis. Moreover, decreased cardiac output can result in reduced oxygen delivery to the liver, leading to increased angiogenesis, a contributing factor to liver fibrosis.[28]

In our study, we observed a significant correlation between increased LFS (including APRI, AST/ALT ratio, and GPR) and an elevated risk of ACM/HTx in patients with NIDCM even beyond LVEF. This finding expands our understanding of the relationship between liver fibrosis and cardiomyopathy. On the other hand, elevated LFS might indicate more severe cardiac disease, as supported by the lower LVEF in this group. However, after adjusting for traditional risk factors, including LVEF and NYHA class, we found that elevated liver markers are associated with worse outcomes beyond LVEF in patients with NIDCM. This study suggests the importance of assessing liver fibrosis status when evaluating the prognosis of NIDCM. In the future, markers of hepatic fibrosis or inflammation, such as fibro scan, may be routinely performed in these patients. Our study emphasizes the need for screening the severity of liver fibrosis among patients with NIDCM.

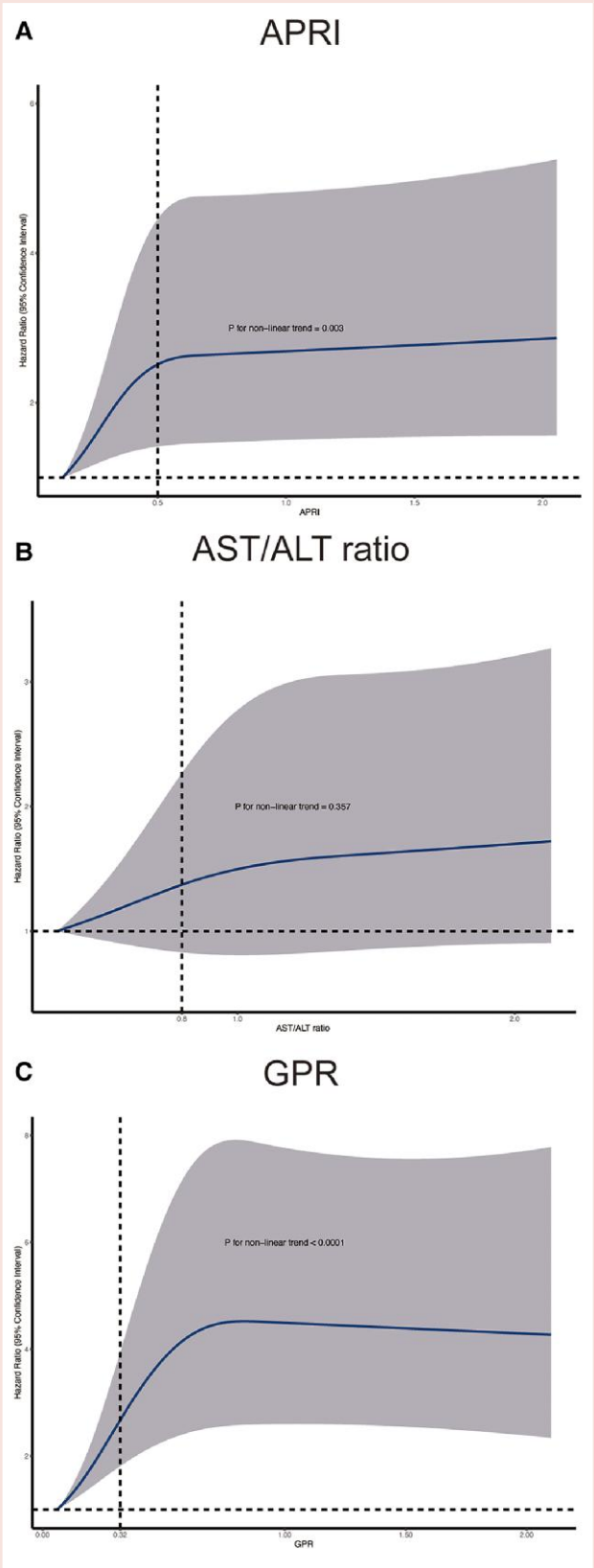

Figure 2 Restricted cubic spline analysis for ACM/HTx according to liver fibrosis scores. APRI, aspartate aminotransferase to platelet ratio index; AST/ALT ratio, aspartate aminotransferase to alanine aminotransferase ratio; GPR, gamma-glutamyl transpeptidase to platelet ratio.

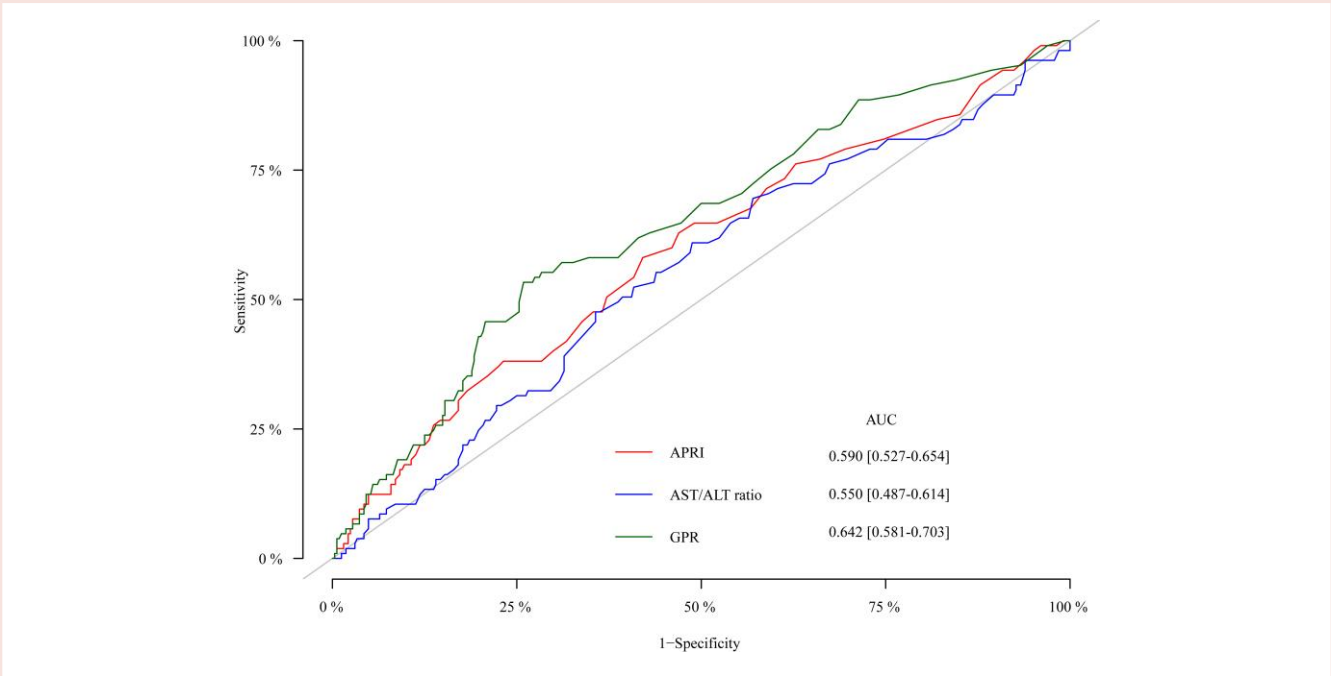

Figure 3 Receiver operating characteristic curve analysis for 2-year ACM/HTx according to liver fibrosis scores. APRI, aspartate aminotransferase to platelet ratio index; AST/ALT ratio, aspartate aminotransferase to alanine aminotransferase ratio; GPR, gamma-glutamyl transpeptidase to platelet ratio.

Table 4 Correlation between liver fibrosis scores and echocardiographic parameters

	Correlation coefficient	*P*-value
APRI		
Left ventricular ejection fraction	−0.035	0.464
Left ventricular end-diastolic diameter	0.106	0.027
AST/ALT ratio		
Left ventricular ejection fraction	−0.034	0.478
Left ventricular end-diastolic diameter	−0.022	0.646
GPR		
Left ventricular ejection fraction	−0.157	0.001
Left ventricular end-diastolic diameter	0.109	0.023

APRI, aspartate aminotransferase to platelet ratio index; AST/ALT ratio, aspartate aminotransferase to alanine aminotransferase ratio; GPR, γ-glutamyl transferase to platelet ratio.

Limitation

First, the patients have been recruited from January 2010 to October 2011. Since then, certain advances have been made in the treatment of patients with non-ischaemic dilated cardiomyopathy and the results have to be interpreted in this context. Second, due to limited echocardiographic reports in our centre, certain echocardiographic parameters, such as inferior vena cava diameter, right-ventricular systolic dysfunction, and pulmonary hypertension were not included in this study. Third, this study was conducted at a single centre, and it would be valuable to validate the findings in a multicenter setting. Fourth, the absence of liver sonography and elastography imaging limits the ability to rule out structural hepatic alterations in the included patients. Fifth, adjustment for natriuretic peptide levels, which could be a potential confounding factor, was not performed in this study. Finally, congestive hepatopathy could impact liver enzymes and subsequently LFS. While we adjustments were made for LVEDD and NYHA functional classification, which could indirectly adjust for congestion, direct adjustments for congestion in general and hepatic congestion in particular are lacking in this study.

Conclusions

This study demonstrates that elevated LFS, such as APRI, AST/ALT ratio, and GPR, were associated with a higher risk of adverse outcomes in NIDCM patients, independent of LVEF. These LFS can be utilized for risk stratification in NIDCM to identify patients who have a poorer prognosis.

Data availability

Data are available from the corresponding author upon reasonable request.

Lead author biography

Yupeng Liu, MD, PhD, is a cardiologist at Guangdong Provincial People's Hospital in Guangzhou, China, where he conducts research in the fields of metabolic disorders, with a particular focus on hepatic metabolic disorders and cardiovascular disease.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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Conflict of interest: None declared.

Consent

All patients who participated in the study have provided the written informed consent.

Author contributions

Y.L., J.S., W.W., and Y.T. contributed to the conception and design of the work. All contributed to the acquisition, analysis, or interpretation of data for the work. Y.L. and J.S. drafted the manuscript. W.W. and Y.T. critically revised the manuscript.

References

1. Schultheiss H-P, Fairweather D, Caforio ALP, Escher F, Hershberger RE, Lipshultz SE, Liu PP, Matsumori A, Mazzanti A, McMurray J, Priori SG. Dilated cardiomyopathy. *Nat Rev Dis Primers* 2019;**5**:32.
2. Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. *N Engl J Med* 1994;**331**:1564–1575.
3. Weintraub RG, Semsarian C, Macdonald P. Dilated cardiomyopathy. *Lancet* 2017;**390**:400–414.
4. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000;**342**:1077–1084.
5. Caballería L, Pera G, Arteaga I, Rodríguez L, Alumà A, Morillas RM, de la Ossa N, Díaz A, Expósito C, Miranda D, Sánchez C, Prats RM, Urquizu M, Salgado A, Alemany M, Martinez A, Majeed I, Fabrellas N, Graupera I, Planas R, Ojanguren I, Serra M, Torán P, Caballería J, Ginès P. High prevalence of liver fibrosis among European adults with unknown liver disease: a population-based study. *Clin Gastroenterol Hepatol* 2018;**16**:1138–1145.e5.
6. Peters AE, Pandey A, Ayers C, Wegermann K, McGarrah RW, Grodin JL, Abdelmalek MF, Bekfani T, Blumer V, Diehl AM, Moylan CA, Fudim M. Association of liver fibrosis risk scores with clinical outcomes in patients with heart failure with preserved ejection fraction: findings from TOPCAT. *ESC Heart Fail* 2021;**8**:842–848.
7. So-Armah KA, Lim JK, Lo Re V, Tate JP, Chang C-CH, Butt AA, Gibert CL, Rimland D, Marconi VC, Goetz MB, Ramachandran V, Brittain E, Long M, Nguyen K-L, Rodriguez-Barradas MC, Budoff MJ, Tindle HA, Samet JH, Justice AC, Freiberg MS. FIB-4 stage of liver fibrosis is associated with incident heart failure with preserved, but not reduced, ejection fraction among people with and without HIV or hepatitis C. *Prog Cardiovasc Dis* 2020;**63**:184–191.
8. Yoshihisa A, Sato Y, Yokokawa T, Sato T, Suzuki S, Oikawa M, Kobayashi A, Yamaki T, Kunii H, Nakazato K, Saitoh S, Takeishi Y. Liver fibrosis score predicts mortality in heart failure patients with preserved ejection fraction. *ESC Heart Fail* 2018;**5**:262–270.
9. Chen Q, Li Q, Li D, Chen X, Liu Z, Hu G, Wang J, Ling W. Association between liver fibrosis scores and the risk of mortality among patients with coronary artery disease. *Atherosclerosis* 2020;**299**:45–52.
10. Jin J-L, Zhang H-W, Cao Y-X, Liu H-H, Hua Q, Li Y-F, Zhang Y, Guo Y-L, Wu N-Q, Zhu C-G, Xu R-X, Gao Y, Cui C-J, Liu G, Sun J, Dong Q, Li J-J. Liver fibrosis scores and coronary atherosclerosis: novel findings in patients with stable coronary artery disease. *Hepatol Int* 2021;**15**:413–423.
11. Møller S, Bernardi M. Interactions of the heart and the liver. *Eur Heart J* 2013;**34**:2804–2811.
12. Bravo AA, Sheth SG, Chopra S. Liver biopsy. *N Engl J Med* 2001;**344**:495–500.
13. Wai C. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003;**38**:518–526.
14. Lemoine M, Shimakawa Y, Nayagam S, Khalil M, Suso P, Lloyd J, Goldin R, Njai H-F, Ndow G, Taal M, Cooke G, D'Alessandro U, Vray M, Mbaye PS, Njie R, Mallet V, Thursz M. The gamma-glutamyl transpeptidase to platelet ratio (GPR) predicts significant liver fibrosis and cirrhosis in patients with chronic HBV infection in West Africa. *Gut* 2016;**65**:1369–1376.
15. Sheth SG, Flamm SL, Gordon FD, Chopra S. AST/ALT ratio predicts cirrhosis in patients with chronic hepatitis C virus infection. *Am J Gastroenterol* 1998;**93**:44–48.
16. Merlo M, Pivetta A, Pinamonti B, Stolfo D, Zecchin M, Barbati G, Di Lenarda A, Sinagra G. Long-term prognostic impact of therapeutic strategies in patients with idiopathic dilated cardiomyopathy: changing mortality over the last 30 years: prognosis of idiopathic dilated cardiomyopathy. *Eur J Heart Fail* 2014;**16**:317–324.
17. Unalp-Arida A, Ruhl CE. Noninvasive fatty liver markers predict liver disease mortality in the U.S. Population: unalp-Arida and ruhl. *Hepatology* 2016;**63**:1170–1183.
18. Maeda D, Kagiyama N, Jujo K, Saito K, Kamiya K, Saito H, Ogasahara Y, Maekawa E, Konishi M, Kitai T, Iwata K, Wada H, Hiki M, Dotare T, Sunayama T, Kasai T, Nagamatsu H, Ozawa T, Izawa K, Yamamoto S, Aizawa N, Yonezawa R, Oka K, Momomura S-I, Matsue Y. Aspartate aminotransferase to alanine aminotransferase ratio is associated with frailty and mortality in older patients with heart failure. *Sci Rep* 2021;**11**:11957.
19. Iwasaki Y, Tomiyama H, Shiina K, Matsumoto C, Kimura K, Fujii M, Takata Y, Yamashina A, Chikamori T. Liver stiffness and arterial stiffness/abnormal central hemodynamics in the early stage of heart failure. *Int J Cardiol Heart Vasc* 2018;**20**:32–37.
20. Takahashi T, Watanabe T, Shishido T, Watanabe K, Sugai T, Toshima T, Kinoshita D, Yokoyama M, Tamura H, Nishiyama S, Arimoto T, Takahashi H, Yamanaka T, Miyamoto T, Kubota I. The impact of non-alcoholic fatty liver disease fibrosis score on cardiac prognosis in patients with chronic heart failure. *Heart Vessels* 2018;**33**:733–739.
21. Laribi S, Mebazaa A. Cardiohepatic syndrome: liver injury in decompensated heart failure. *Curr Heart Fail Rep* 2014;**11**:236–240.
22. Fandler-Höfler S, Stauber RE, Kneihsl M, Wünsch G, Haidegger M, Poltrum B, Pichler A, Deutschmann H, Enzinger C, Fickert P, Gattringer T. Non-invasive markers of liver fibrosis and outcome in large vessel occlusion stroke. *Ther Adv Neurol Disord* 2021;**14**:17562864211037239.
23. Louie CY, Pham MX, Daugherty TJ, Kambham N, Higgins JPT. The liver in heart failure: a biopsy and explant series of the histopathologic and laboratory findings with a particular focus on pre-cardiac transplant evaluation. *Mod Pathol* 2015;**28**:932–943.
24. Samsky MD, Patel CB, DeWald TA, Smith AD, Felker GM, Rogers JG, Hernandez AF. Cardiohepatic interactions in heart failure: an overview and clinical implications. *J Am Coll Cardiol* 2013;**61**:2397–2405.
25. Je N GS, Rj L EZ, Y D. Heart diseases affecting the liver and liver diseases affecting the heart. *Am Heart J* 2000;**140;**111–120.
26. Dunn GD, Hayes P, Breen KJ, Schenker S. The liver in congestive heart failure: a review. *Am J Med Sci* 1973;**265**:174–189.
27. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. *Nat Rev Cardiol* 2017;**14**:30–38.
28. Li H. Angiogenesis in the progression from liver fibrosis to cirrhosis and hepatocelluar carcinoma. *Expert Rev Gastroenterol Hepatol* 2021;**15**:217–233.