BMC Infectious Diseases

RESEARCH

Open Access

The predictive value of fibrosis profiles for hepatitis E virus-related liver failure among hospitalized patients with acute hepatitis E: a retrospective cohort study

Rui Dong[1†], Lili Huang[2†], Lin Chen[3], Hong Xue[4], Jianguo Shao[3], Chunyan Ye[5], Yonglin Yang[6], Ke Xu[7], Zhenghan Luo[8*] and Jie Wang[1*]

Abstract

Background Hepatitis E virus (HEV) infection is an important etiology of liver failure. This study aimed to explore the associations of blood fibrosis profiles with HEV-related liver failure (HEV-LF) onset and evaluate their prediction performance in hospitalized patients with acute hepatitis E.

Methods Participants were obtained from two tertiary medical centers in Jiangsu, China, between January 2018 and November 2024. Cox proportional hazards regression, restricted cubic splines, and threshold effect analysis were used to examine associations between fibrosis markers and HEV-LF risk. The predictive value of these markers was evaluated for importance ranking, discrimination, calibration, and net benefit.

Results Among 504 included participants, 59 developed HEV-LF during hospitalization. After adjusting for covariates, elevated baseline laminin (HR = 1.432, 95% CI: 1.080–1.900), fibrosis-4 score (HR = 1.865, 95% CI: 1.375–2.530), and aspartate aminotransferase to platelet ratio index (APRI) (HR = 1.603, 95% CI: 1.315–1.954) were associated with a higher HEV-LF risk in a dose-dependent manner. Hyaluronic acid (≤ 740 ng/mL: HR = 1.797, 95% CI: 1.177–2.744) and type IV collagen (≤ 137 ng/mL: HR = 3.075, 95% CI: 1.709–5.533) showed nonlinear associations. APRI was ranked the highest in importance, and its combination with the other two top important markers provided good discrimination (7-day HEV-LF: AUROC = 84.98%, 95% CI: 78.55–91.41; 14-day HEV-LF: AUROC = 80.11%, 95% CI: 73.49–86.73), calibration, and clinical utility for predicting HEV-LF onset.

Conclusions Several blood fibrosis markers are closely associated with HEV-LF risk and have promising predictive value. These findings may inform clinical risk stratification in patients with AHE.

Trial registration Not applicable.

Keywords Chronic liver disease, Noninvasive, Association, Risk stratification, Nonlinear, Discrimination, Calibration, Net benefit

†Rui Dong and Lili Huang contributed equally to this manuscript.

*Correspondence:
Zhenghan Luo
IrvingHan@126.com
Jie Wang
wangjienjmu@126.com
Full list of author information is available at the end of the article

Background

Hepatitis E virus (HEV) is a leading etiology of acute viral hepatitis globally [1, 2]. Although HEV infection is generally considered asymptomatic or self-limiting in the general population, it remains a major contributor to liver failure, accounting for approximately 40% of acute liver failure cases in developing countries [3]. Hospitalized patients with acute hepatitis E (AHE) are usually symptomatic and at risk of developing acute liver failure [4]. Patients with preexisting chronic liver diseases (CLD) are at higher risk of developing acute-on-chronic liver failure if infected by this virus [4–7]. The mechanisms driving HEV-related liver failure (HEV-LF) onset remain inadequately understood. The treatments for HEV-LF mainly include intensive nursing care, artificial liver support, and liver transplantation, which often result in high medical expenditures and are usually unavailable in resource-limited settings [8]. Moreover, despite that a recombinant HEV vaccine is currently licensed and publicly available in China, vaccination coverage remains limited [9]. Although several useful diagnostic and prognostic tools have been constructed, the rapid disease progression and limited time for effective treatments highlight the importance of moving the strategic indication for intervention to the earlier onset of liver failure [10]. Thus, identifying effective predictors for the early warning of HEV-LF is critical for risk stratification, proactive monitoring, and optimizing management among hospitalized patients with AHE [10].

Fibrosis, characterized by the excessive deposition of extracellular matrix, represents a highly conserved and coordinated response to both acute and chronic tissue injury [11]. Acute liver failure is associated with extensive and rapid hepatocellular death, while chronic liver injury is characterized by ongoing cell death over a protracted period [12]. Liver fibrosis is closely correlated with the prognosis in patients with liver diseases of various etiologies [13, 14]. While liver biopsy is considered the gold standard for the diagnosis and staging of hepatic fibrosis, it is invasive and has several limitations, including sampling variability, subjective interpretation, risk of complications, and high cost, which hinder its clinical application [13]. Noninvasive fibrosis scores (such as fibrosis-4 score [FIB-4] and aspartate aminotransferase [AST] to platelet ratio index [APRI]) and blood fibrosis markers (such as laminin [LN], hyaluronic acid [HA], type IV collagen [IV-C], and N-terminal propeptide of type III collagen [PIIINP]) are acceptable alternatives for fibrosis assessment and have been widely used in both prior literature and clinical practice [13, 15–18]. Although acute HEV infection can affect the prediction accuracy of the FIB-4 and APRI when predicting liver fibrosis, the key components of these scores (such as platelet count) have been reported to have high prognostic value in patients with HEV-LF [13, 19]. Prior studies have demonstrated that FIB-4 and APRI are valuable in predicting postoperative liver failure and hepatitis B virus-related acute-on-chronic liver failure [15–18]. Additionally, blood fibrosis markers have been shown to enhance outcome prediction in patients with non-acetaminophen-related acute liver failure [20]. However, limited studies have explored the associations of these markers with HEV-LF or evaluated their potential as early warning markers. Therefore, this study aimed to explore the associations of blood fibrosis profiles with the risk of HEV-LF and further evaluate their predictive value among hospitalized patients with AHE.

Methods

Study design and participants

This study was conducted based on a retrospective cohort design. Study participants were obtained from two tertiary medical centers in Jiangsu, China, between January 2018 and November 2024, including The Third Affiliated Hospital of Nantong University and The Third People's Hospital of Changzhou. Adult hospitalized patients with AHE and available data on fibrosis profiles were included in the current study. Pregnant females, patients < 18 years old, patients who received baseline treatments for HEV infection, artificial liver support, or liver transplantation, patients with baseline organ failure, hepatitis A virus infection, recent excessive alcohol intake (within 2 weeks before admission), drug-induced liver injury, extrahepatic malignancies, immunosuppression, chronic hepatitis E or chronic liver failure development, hospitalization time < 24 h, or missingness on any required data were excluded. All the included participants received integrative treatments based on the consensus on prevention and treatment of hepatitis E during hospitalization. The baseline and follow-up data were collected from the electronic medical records (EMR) using automatic data capture systems for analysis. The follow-up time was calculated from the admission date to the date of HEV-LF onset or discharge [21]. All study procedures were identical among all medical centers. This study was conducted in line with the Declarations of Helsinki and Istanbul and approved by the Institutional Review Board of The Third Affiliated Hospital of Nantong University (EK2023108) and The Third People's Hospital of Changzhou (02A-A2024021). Due to the retrospective design and the use of anonymous clinical data, informed consent was waived by the Institutional Review Board of The Third Affiliated Hospital of Nantong University and The Third People's Hospital of Changzhou.

Study definitions

Acute Hepatitis E

AHE was defined based on the presence of acute viral hepatitis manifestations and at least one of the following laboratory results: positive serum anti-HEV IgM, more than twofold increased titers in serum anti-HEV IgG, or detectable HEV RNA. Acute viral hepatitis manifestations included jaundice, elevated liver enzymes, and nonspecific clinical presentations (e.g., fatigue, itching, and nausea).

HEV-related liver failure

According to the Chinese diagnostic and treatment guidelines for liver failure, liver failure was diagnosed based on jaundice, coagulopathy (international normalized ratio [INR] ≥ 1.5 or prothrombin activity $< 40\%$), and encephalopathy [4, 22]. In this study, liver failure included (sub) acute (in patients without CLDs) and acute-on-chronic liver failure (in patients with CLDs). CLDs were ascertained using the admission diagnosis and medical history modules in the EMR, including chronic hepatitis B (CHB), chronic hepatitis C (CHC), metabolic dysfunction-associated steatotic liver disease, alcoholic liver disease, autoimmune liver disease, hepatocellular carcinoma, and cirrhosis (known or unknown etiologies).

Blood fibrosis profiles

The blood fibrosis profiles included four blood fibrosis markers and two widely used noninvasive fibrosis scores. Blood LN, HA, IV-C, and PIIINP were determined using automatic analyzers in the standard laboratories in each medical center, and the results were obtained from the laboratory test module of EMR. FIB-4 and APRI were calculated based on established methodologies [23, 24].

Covariates

Sex (male/female), age, self-reported alcohol intake (never drink/alcohol drinker), and type 2 diabetes (yes/no) were obtained from the inpatient record module of EMR. The results of complete blood cell count, coagulation function, and blood biochemistry indicators were extracted from the laboratory test module of EMR. In addition, the systemic inflammation response index (SIRI) was computed using the established formula to reflect the overall balance between the inflammatory response and immune status [25]. Based on clinical knowledge and data availability, sex, age, alcohol use, type 2 diabetes, SIRI, INR, total bilirubin, and cirrhosis were defined as covariates in this study.

Statistical analyses

All statistical analyses were performed using statistical packages in R (Version: 4.4.0) and Python (Version: 3.11.0). Continuous variables were demonstrated as medians (inter-quartile ranges [IQR]) and compared using the Wilcoxon rank sum test. Categorical variables were demonstrated as frequencies (percentages) and compared using the chi-square test or Fisher's exact test. Spearman's correlation analysis was conducted to assess pairwise correlations among fibrosis markers and their correlations with disease severity indicators. The participants were stratified into two groups based on the medians of the fibrosis markers (Low: $\leq$ median; High: $>$ median), and the Kaplan–Meier cumulative event curves were visualized to initially evaluate the associations between fibrosis markers and HEV-LF risk. Univariate and multivariate Cox proportional hazards regression models were subsequently constructed to scrutinize the associations. The fibrosis markers were ln-transformed before being introduced into the continuous models. Based on the tertiles, categorical models were constructed by introducing the fibrosis markers as categorical variables. Model 1 was the crude model without any adjustment, while models 2 and 3 were adjusted for a range of potential covariates. The proportional hazards assumption was examined using the Schoenfeld residual test. The variance inflation factor was calculated to examine the issue of collinearity for multivariate models. The restricted cubic spline regression (RCS) analysis was applied to explore the possible nonlinear associations of fibrosis profiles with the risk of HEV-LF. Threshold effect analysis was conducted utilizing the maximum likelihood method for inflection point ascertainment, piecewise regression models for threshold effect exploration, and log-likelihood ratio test for model comparison [26]. Moreover, considering the potential nonlinear associations, a random survival forest model was constructed to assess the predictive value. The Shapley additive explanation (SHAP) technique was applied to rank the importance of the fibrosis markers in predicting HEV-LF onset. The time-dependent area under the receiver-operating-characteristic curve (AUROC) was calculated to evaluate the discrimination ability of the markers. The calibration performance was visualized using calibration plots and tested using the Greenwood-Nam-D'Agostino test. The decision curve analysis was used to assess the net benefit of applying the identified markers for HEV-LF prediction. The predictive value of the markers was tentatively validated using 1000 bootstrap samples. All statistical analyses were two-sided, with statistical significance defined as $P < 0.050$.

Results

Baseline characteristics of the included participants

A total of 504 eligible participants were included in this study (Table S1). The median baseline age was 55 (IQR: 48–65) years and 70.44% ($n=355$) of them were males. During a median follow-up time of 18 (IQR: 10–24) days, 59 (11.71%, 59/504) HEV-LF cases were observed. Compared to participants without HEV-LF onset, participants who progressed to HEV-LF during follow-up were more likely to be males ($P=0.035$) and had higher baseline levels of inflammation (monocyte count and SIRI), coagulation impairment (prothrombin time and INR), liver injury (AST, alanine aminotransferase, total bilirubin, and direct bilirubin) indicators, and prolonged hospital stays (all P values <0.050).

Fibrosis markers and their correlations with severity indicators

The characteristics of the fibrosis profiles among the included participants are demonstrated in Table S2. Spearman's correlation analysis indicated significant positive correlations within most pairs of the fibrosis markers, with correlation coefficients ranging from 0.25 (IV-C and APRI) to 0.86 (FIB-4 and APRI) (all P values <0.050 except for IV-C and APRI) (Fig. 1A). Compared to participants without HEV-LF onset during hospitalization, participants who progressed to HEV-LF had significantly higher baseline levels of LN, HA, IV-C, PIIINP, FIB-4, and APRI (all P values <0.001) (Fig. 1B). As shown in Fig. 2 and Fig. 3, the baseline blood LN, HA, IV-C, and PIIINP were significantly correlated to worse liver injury (AST and TBIL) (Fig. 2A-B), anabolic capacity (albumin) (Fig. 2C), coagulation (INR) (Fig. 3A), inflammation indicators (SIRI) (Fig. 3B), and longer hospital stays (Fig. 3C) (all P values <0.050).

Associations between fibrosis markers and HEV-LF risk

As presented in Figure S1 (A-F), participants with high levels of fibrosis markers or noninvasive scores (> median) had a significantly higher cumulative event rate of HEV-LF compared to those with low levels (≤ median). The log-rank test indicated a significant difference between each of the two groups (all P values <0.050). Univariate and multivariate Cox proportional hazards regression models were utilized to investigate the associations between fibrosis markers and the risk of HEV-LF onset during hospitalization, with results being summarized in Table 1. In the crude model without any adjustment (Model 1), LN (HR = 2.144, 95% CI: 1.658–2.772, $P<0.001$), HA (HR = 1.993, 95% CI: 1.534–2.588, $P<0.001$), IV-C (HR = 2.396, 95% CI: 1.784–3.220, $P<0.001$), PIIINP (HR = 1.686, 95% CI: 1.367–2.079, $P<0.001$), FIB-4 (HR = 2.301, 95% CI: 1.773–2.985, $P<0.001$), APRI (HR = 1.888, 95% CI: 1.550–2.300, $P<0.001$) were associated with an elevated risk of HEV-LF onset. After adjusting for all potential covariates (Model 3), the risk of developing HEV-LF was significantly increased by

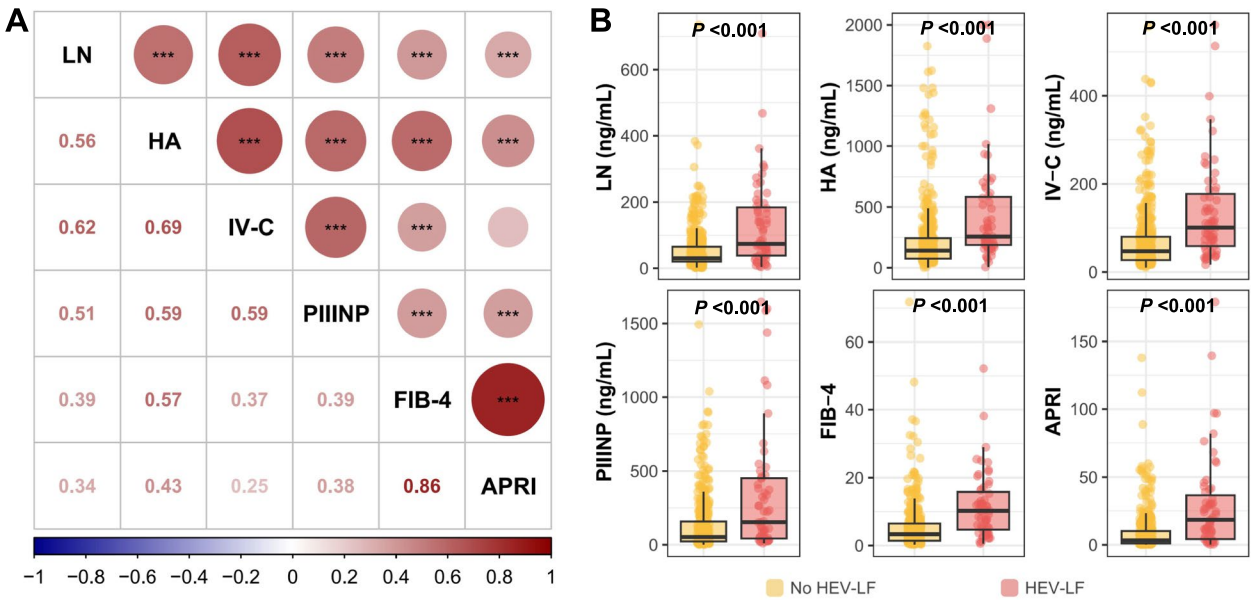

Fig. 1 Pairwise correlations of fibrosis markers (**A**) and group comparisons by HEV-LF onset (**B**). *Notes:* ***, $P<0.001$. *Abbreviations:* LN, laminin; HA, hyaluronic acid; IV-C, type IV collagen; PIIINP, N-terminal propeptide of type III collagen; FIB-4, fibrosis-4 score; APRI, aspartate aminotransferase to platelet ratio index

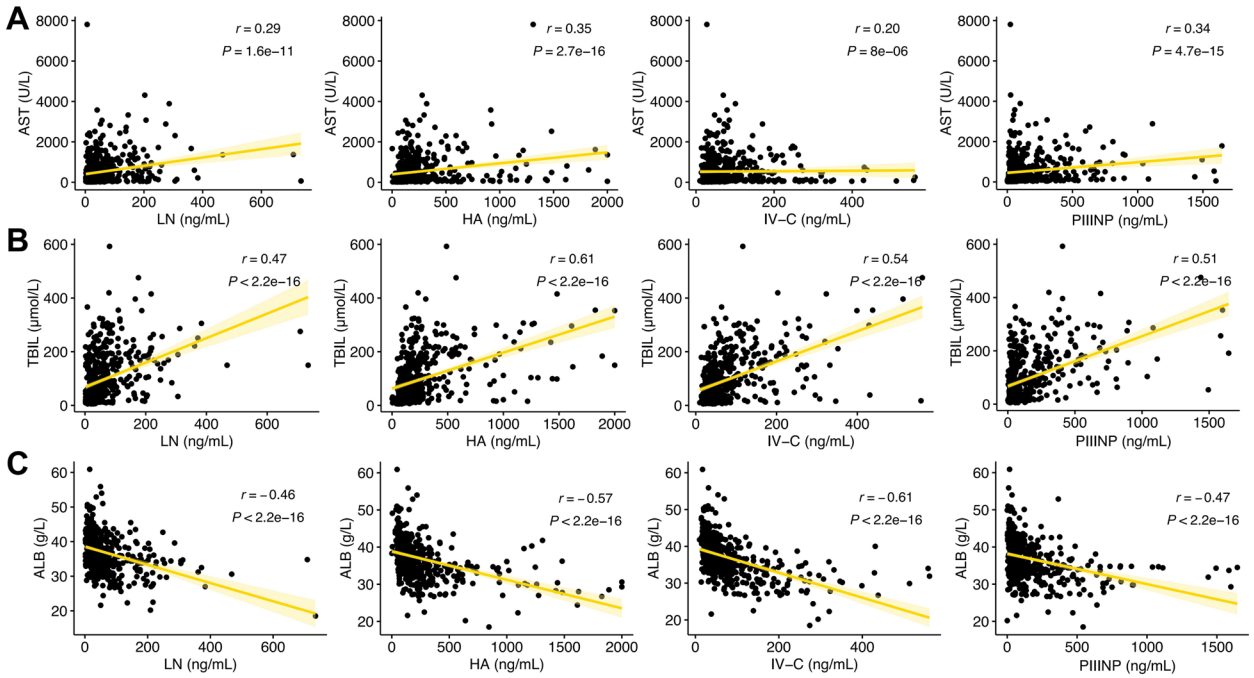

Fig. 2 Correlations of fibrosis profiles with liver injury (**A**-**B**) and anabolic capacity (**C**) indicators. *Abbreviations:* AST, aspartate aminotransferase; ALB, albumin; TBIL, total bilirubin; LN, laminin; HA, hyaluronic acid; IV-C, type IV collagen; PIIINP, N-terminal propeptide of type III collagen

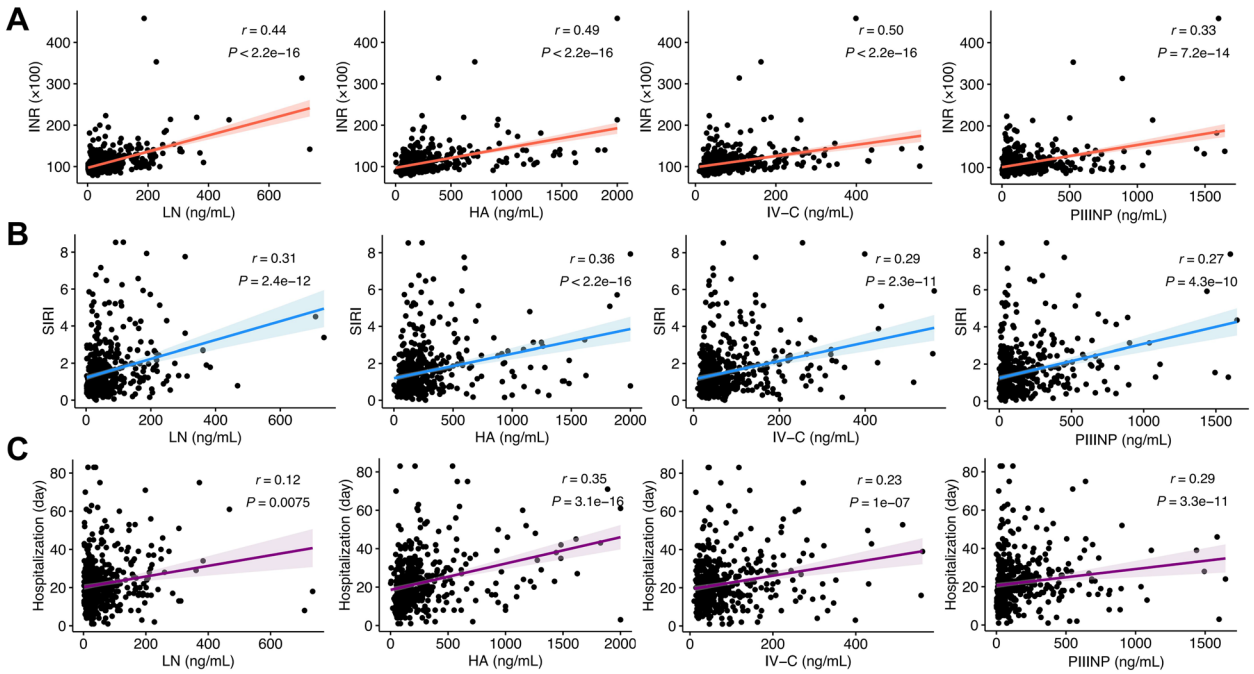

Fig. 3 Correlations of fibrosis profiles with coagulopathy (**A**), inflammation (**B**) indicators, and hospital stays (**C**). *Abbreviations:* INR, international normalized ratio; SIRI, systemic inflammation response index; LN, laminin; HA, hyaluronic acid; IV-C, type IV collagen; PIIINP, N-terminal propeptide of type III collagen

Table 1 Associations between fibrosis profiles and HEV-LF risk during hospitalization ($n=504$)

Models	ln-transformed continuous[a]		Tertile1[b]	Tertile2[b]		Tertile3[b]		*P* for trend[c]
	HR (95% CI)	*P* value		HR (95% CI)	*P* value	HR (95% CI)	*P* value	
Model 1[d]								
LN	2.144 (1.658, 2.772)	**< 0.001**	1.00 (Reference)	1.241 (0.514, 2.994)	0.631	4.621 (2.238, 9.543)	**< 0.001**	**< 0.001**
HA	1.993 (1.534, 2.588)	**< 0.001**	1.00 (Reference)	3.727 (1.391, 9.985)	**0.009**	7.056 (2.760, 18.035)	**< 0.001**	**< 0.001**
IV-C	2.396 (1.784, 3.220)	**< 0.001**	1.00 (Reference)	1.904 (0.768, 4.719)	0.164	5.668 (2.529, 12.701)	**< 0.001**	**< 0.001**
PIIINP	1.686 (1.367, 2.079)	**< 0.001**	1.00 (Reference)	1.940 (0.871, 4.321)	0.105	3.551 (1.692, 7.450)	**0.001**	**< 0.001**
FIB-4	2.301 (1.773, 2.985)	**< 0.001**	1.00 (Reference)	2.948 (1.071, 8.114)	**0.036**	7.862 (3.096, 19.970)	**< 0.001**	**< 0.001**
APRI	1.888 (1.550, 2.300)	**< 0.001**	1.00 (Reference)	4.808 (1.391, 16.613)	**0.013**	13.969 (4.322, 45.152)	**< 0.001**	**< 0.001**
Model 2[d]								
LN	2.187 (1.678, 2.850)	**< 0.001**	1.00 (Reference)	1.441 (0.593, 3.501)	0.420	5.075 (2.416, 10.661)	**< 0.001**	**< 0.001**
HA	2.081 (1.586, 2.730)	**< 0.001**	1.00 (Reference)	4.230 (1.560, 11.473)	**0.005**	8.741 (3.336, 22.903)	**< 0.001**	**< 0.001**
IV-C	2.552 (1.870, 3.485)	**< 0.001**	1.00 (Reference)	2.041 (0.818, 5.097)	0.126	6.714 (2.893, 15.580)	**< 0.001**	**< 0.001**
PIIINP	1.667 (1.351, 2.056)	**< 0.001**	1.00 (Reference)	1.893 (0.848, 4.225)	0.119	3.485 (1.650, 7.360)	**0.001**	**0.001**
FIB-4	2.501 (1.901, 3.289)	**< 0.001**	1.00 (Reference)	3.248 (1.170, 9.013)	**0.024**	9.276 (3.573, 24.079)	**< 0.001**	**< 0.001**
APRI	1.883 (1.538, 2.305)	**< 0.001**	1.00 (Reference)	4.395 (1.267, 15.250)	**0.020**	13.213 (4.071, 42.889)	**< 0.001**	**< 0.001**
Model 3[d]								
LN	1.432 (1.080, 1.900)	**0.013**	1.00 (Reference)	1.346 (0.552, 3.286)	0.513	3.004 (1.331, 6.779)	**0.008**	**0.003**
HA	1.263 (0.893, 1.787)	0.187	1.00 (Reference)	3.655 (1.333, 10.023)	**0.012**	4.447 (1.576, 12.552)	**0.005**	**0.020**
IV-C	1.748 (1.175, 2.599)	**0.006**	1.00 (Reference)	1.798 (0.717, 4.508)	0.211	4.021 (1.614, 10.018)	**0.003**	**0.001**
PIIINP	1.229 (0.952, 1.586)	0.114	1.00 (Reference)	1.512 (0.671, 3.407)	0.318	1.849 (0.803, 4.255)	0.149	0.229
FIB-4	1.865 (1.375, 2.530)	**< 0.001**	1.00 (Reference)	2.557 (0.914, 7.150)	0.074	5.067 (1.890, 13.583)	**0.001**	**< 0.001**
APRI	1.603 (1.315, 1.954)	**< 0.001**	1.00 (Reference)	2.619 (0.726, 9.450)	0.141	8.202 (2.471, 27.224)	**0.001**	**< 0.001**

Abbreviations: LN laminin, *HA* hyaluronic acid, *IV-C* type IV collagen, *PIIINP* N-terminal propeptide of type III collagen, *FIB-4* fibrosis-4 score, *APRI* aspartate aminotransferase to platelet ratio index

[a] The fibrosis markers were ln-transformed and subsequently introduced into models as continuous variables

[b] The fibrosis markers were categorized based on tertiles and introduced into models as categorical variables

[c] *P* for trend was computed by entering the median value of each tertile of fibrosis markers as continuous variables in the models

[d] Model 1 was the crude model without any adjustment. Model 2 was adjusted for sex, age, alcohol intake, and type 2 diabetes. On the basis of Model 2, Model 3 extended the adjustment by further including SIRI, INR, total bilirubin, and cirrhosis

43.20% (95% CI: 1.080–1.900, $P=0.013$), 74.80% (95% CI: 1.175–2.599, $P=0.006$), 86.50% (95% CI: 1.375–2.530, $P<0.001$), and 60.30% (95% CI: 1.315–1.954, $P<0.001$) in response to one ln-transformed unit elevation of baseline LN, IV-C, FIB-4, and APRI levels, respectively. However, HA and PIIINP were not associated with the HEV-LF risk in the fully adjusted continuous models (all *P* values > 0.050). The fully adjusted categorical model showed that the highest tertiles of LN (HR = 3.004, 95% CI: 1.331–6.779, $P=0.008$), HA (HR = 4.447, 95% CI: 1.576–12.552, $P=0.005$), IV-C (HR = 4.021, 95% CI: 1.614–10.018, $P=0.003$), FIB-4 (HR = 5.067, 95% CI: 1.890–13.583, $P=0.001$), and APRI (HR = 8.202, 95% CI: 2.471–27.224, $P=0.001$) were associated with a higher risk of HEV-LF development when compared to their lowest tertiles. Linear trends were observed across the tertiles of the above-mentioned fibrosis markers in the categorical model (all *P* values < 0.050). No evidence of proportional hazard assumption violation (all *P* values for Schoenfeld residual test > 0.050) or collinearity (maximum variance inflation factor in the fully adjusted models = 2.840) was observed.

The RCS models were fitted with 3 knots at the 10th, 50th, and 90th percentiles of the fibrosis markers with the median as the reference (Fig. 4A-F). The results showed that LN, FIB-4, and APRI elevated the risk of HEV-LF onset in a dose-dependent manner (all *P* for overall < 0.050 and *P* for nonlinear > 0.050), while HA and IV-C showed nonlinear associations (all *P* for overall < 0.050 and *P* for nonlinear < 0.050). Threshold effect analysis further indicated that two-piecewise linear regression models were significantly better fitted than the standard linear regression models (all *P* for log-likelihood ratio test < 0.050), and 6.607 (740 ng/mL) and 4.920 (137 ng/mL) were inflection points for HA and IV-C, respectively (Table 2). The positive connections of HA and IV-C with HEV-LF risk only existed when their values were less than the above inflection points.

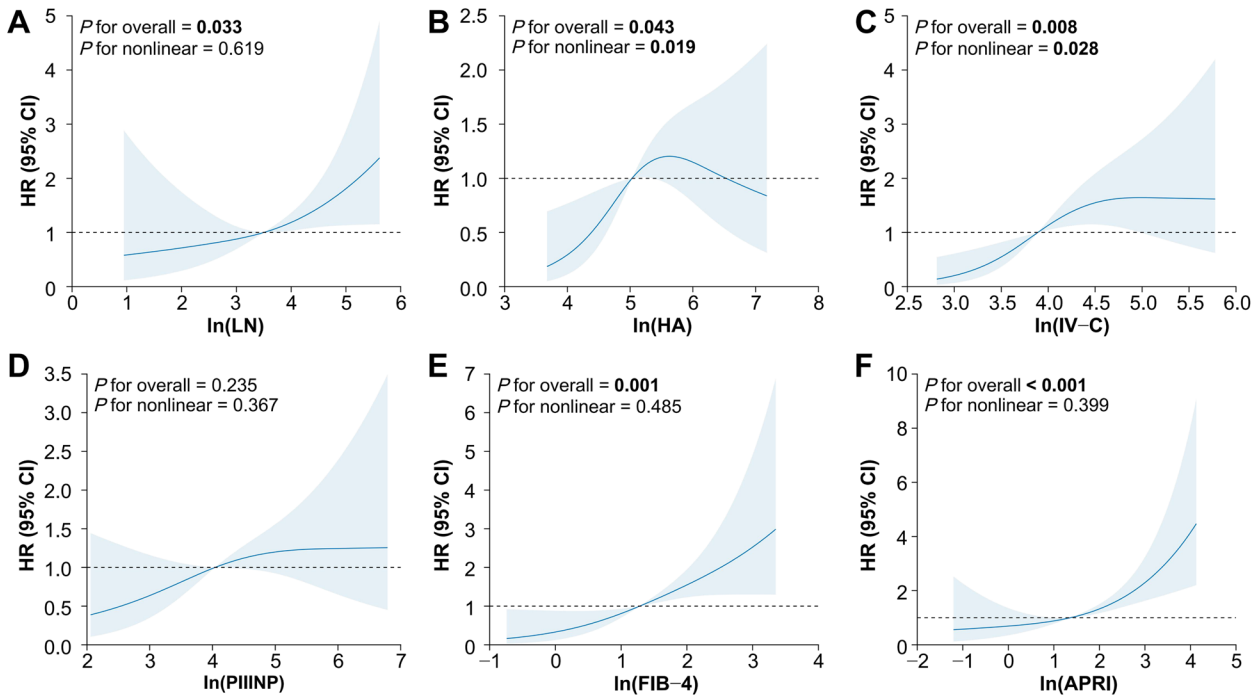

Fig. 4 The restricted cubic spline regression analysis for LN (**A**), HA (**B**), IV-C (**C**), PIIINP (**D**), FIB-4 (**E**), and APRI (**F**). ***Notes:*** The models were adjusted for sex, age, alcohol intake, type 2 diabetes, SIRI, INR, total bilirubin, and cirrhosis. *Abbreviations:* LN, laminin; HA, hyaluronic acid; IV-C, type IV collagen; PIIINP, N-terminal propeptide of type III collagen; FIB-4, fibrosis-4 score; APRI, aspartate aminotransferase to platelet ratio index

Table 2 Threshold effect analysis of HA and IV-C with HEV-LF risk ($n = 504$)

	HA[a]		IV-C[a]	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Model 1 (standard linear regression)	1.263 (0.893–1.787)	0.187	1.748 (1.175–2.599)	**0.006**
Model 2 (two-piecewise linear regression)				
Inflection point	6.607 (740 ng/mL)		4.920 (137 ng/mL)	
≤ Inflection point	1.797 (1.177–2.744)	**0.007**	3.075 (1.709–5.533)	**< 0.001**
> Inflection point	0.114 (0.029–0.451)	**0.002**	0.469 (0.166–1.331)	0.155
***P* for log-likelihood ratio test**		**< 0.001**		**0.004**

[a] The models were adjusted for sex, age, alcohol intake, type 2 diabetes, SIRI, INR, total bilirubin, and cirrhosis

Abbreviations: HA hyaluronic acid, *IV-C* type IV collagen

Early warning value of fibrosis profiles for HEV-LF onset

The SHAP summary plot visualized the importance of the blood fibrosis markers for predicting the risk of HEV-LF onset by evaluating the mean SHAP values and exhibiting them in descending order. APRI was ranked the most important marker, followed by IV-C, LN, FIB-4, and PIIINP, while HA contributed the least to the prediction of the HEV-LF risk (Fig. 5A). The AUROC values were calculated to evaluate the discrimination power of each marker for predicting 7-day and 14-day HEV-LF onset (Fig. 5B-C). APRI had the best discrimination ability among the fibrosis markers, as indicated by the highest 7-day (AUROC = 75.30%, 95% CI: 67.36–83.24) and 14-day (AUROC = 71.32, 95% CI: 63.19–79.45) AUROC values. Based on the SHAP results, the top three important markers were combined, reaching AUROC values of 84.98% (95% CI: 78.55–91.41) and 80.11% (95% CI: 73.49–86.73) for predicting 7-day and 14-day HEV-LF onset. The optimism-corrected values were generally similar to the apparent values, which further validated their prediction value (Table S3). Across participants with different CLD statuses, the AUROC values for 7-day

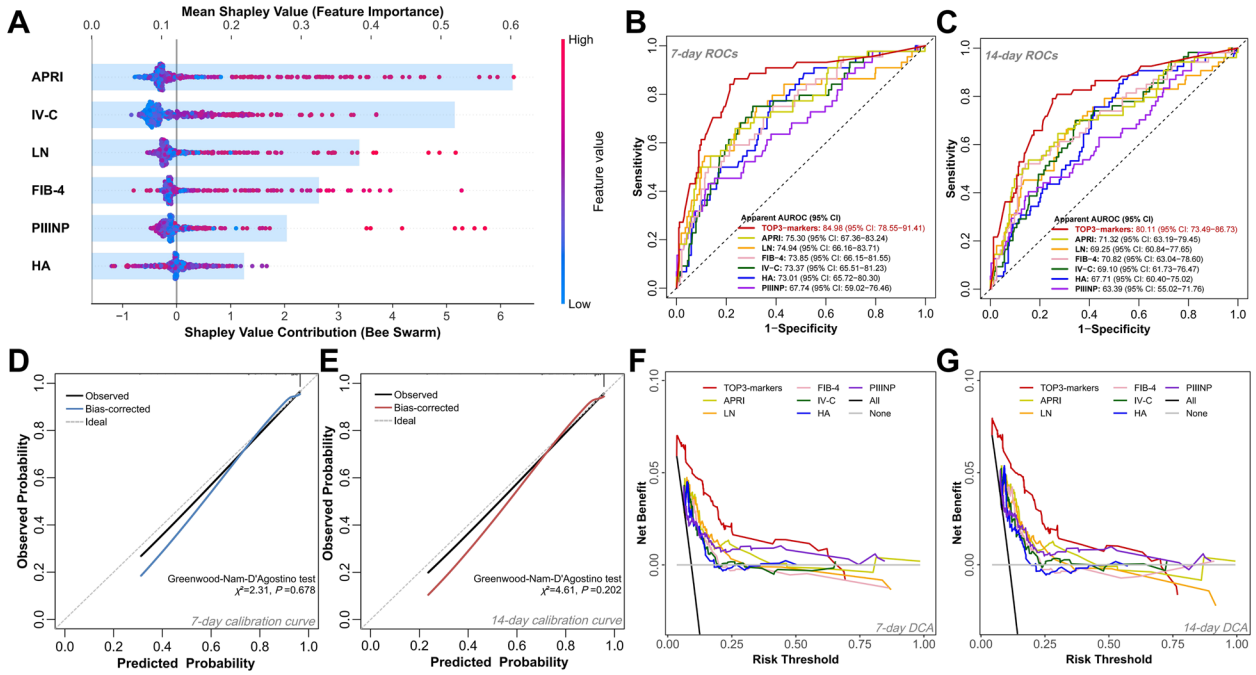

Fig. 5 Summary plot for the importance ranking (**A**), discrimination (**B**-**C**), calibration (**D**-**E**), and net benefit (**F**-**G**) assessments. Bootstrap resampling method (iterations = 1000) was applied to plot the bias-corrected calibration curves. *Abbreviations:* LN, laminin; HA, hyaluronic acid; IV-C, type IV collagen; PIIINP, N-terminal propeptide of type III collagen; FIB-4, fibrosis-4 score; APRI, aspartate aminotransferase to platelet ratio index. AUROC, area under the receiver-operating-characteristic curve; DCA, decision curve analysis

and 14-day HEV-LF predictions were the highest in participants without any CLD, followed by those with CHB or CHC (Table S4). As shown in Fig. 5(D-E), the combination of the top three markers had sufficient calibration performance, as indicated by the calibration curves and Greenwood-Nam-D'Agostino tests (all P values > 0.050). In addition, the decision curve analysis further demonstrated the net benefit of using the top three fibrosis markers to predict the 7-day and 14-day HEV-LF onset under certain risk thresholds (Fig. 5F-G).

Discussion

This retrospective cohort study was performed to explore the associations between fibrosis profiles and the risk of HEV-LF onset and further assess their early warning value among hospitalized patients with AHE. Three major findings were reported in the current study. First, the baseline levels of fibrosis markers were correlated with worse liver injury and anabolic capacity, coagulation impairment, inflammation, and longer hospitalization. Second, higher baseline levels of LN, FIB-4, APRI, HA, and IV-C significantly elevated the risk of HEV-LF onset, with the former three markers in a dose-dependent manner, while the latter two showed nonlinear relationships. Third, APRI and its combination with the other two top important fibrosis markers (LN and IV-C) exhibited promising predictive value for the risk of HEV-LF onset regarding discrimination, calibration, and net benefit. The above findings supported the use of fibrosis profiles for monitoring the disease progression and early warning of HEV-LF in hospitalized patients with AHE.

FIB-4 and APRI are two widely used noninvasive scores for the prediction of liver fibrosis [8, 13–18, 23, 24]. The current study found that participants with higher FIB-4 and APRI exhibited baseline worse disease severity indicators and had elevated risk of HEV-LF onset during hospitalization. It should be noted that the observed associations and high predictive value of the above noninvasive scores may not be simply interpreted as a contribution of their reflection of liver fibrosis. In the background of this study, the acute infection of HEV can elevate the aminotransferase levels in their algorithms, and thereby produce false positive results when predicting liver fibrosis [13]. The key components of APRI and FIB-4 include platelet count and AST. The HEV-induced direct impairment and systemic inflammation may influence platelet count in patients with HEV infection [19]. Significantly decreased levels of platelet count were observed in patients with HEV-related liver failure, and the prognostic value of platelet count for mortality among patients of this disease has been previously reported [19, 27]. Moreover, the association between

elevated AST and hepatic inflammation has been well recognized, and it is also commonly used in the outcome prediction among patients with viral hepatitis. The above evidence supported the findings of this study.

LN, HA, IV-C, and PIIINP are four regular commercial blood fibrosis markers in clinical practice, and their diagnostic performance for liver fibrosis has been confirmed by numerous studies [28, 29]. Similar to the noninvasive scores, LN, HA, and IV-C were closely correlated with the disease severity, and higher baseline levels of the above three markers independently elevated the risk of HEV-LF onset. Liver fibrosis refers to the excessive accumulation of extracellular matrix following both acute or chronic liver injury [11, 12]. In chronic liver injury, it is well-known that the progression of fibrosis can impair the architecture and function of the underlying organ or tissue, leading to adverse hepatic-related events, such as acute-on-chronic liver failure [11, 12]. By contrast, acute liver failure is characterized by massive and rapid hepatic injury and cell death in patients without underlying CLDs [22]. Prior studies found histological, imaging (increased liver stiffness measured by transient elastography), and serological (elevation of fibrosis markers) fibrosis evidence in patients with acute liver failure [11, 12]. To compensate for extensive cellular loss, hepatic stellate cells (HSCs) and the subsequent fibrogenesis may be activated and serve as a structural framework to maintain the architecture of the liver, representing a possibly beneficial response that attempts to repair tissue in acute liver damage [11, 12]. During this process, profibrogenic cells (e.g., HSCs and myofibroblasts) are activated early after liver injury to produce extracellular matrix components and HA [12]. LN, HA, and IV-C are three direct markers that are fragments of the liver matrix components produced during the process of fibrosis [29, 30]. Therefore, the elevation of fibrosis markers may be the markers of baseline severe liver damage in patients who had eventually progressed to acute liver failure, which may explain the associations observed in the current study. It is interesting that HA and IV-C showed nonlinear associations with the risk of HEV-LF, and further analysis indicated that they induced an HEV-LF risk increase within certain thresholds. Although degrees of fibrosis were shown to have significant correlations with serum HA and IV-C levels, little change over time as related to the change in fibrosis was noted in prior studies [29], which may contribute to the observed nonlinear associations. Due to the lack of direct evidence, these nonlinear associations deserve further verification and explanation in future studies.

Among the two noninvasive scores, APRI showed promising predictive value for early warning of the HEV-LF onset, as indicated by the highest AUROC and SHAP values among the markers. The calculation of APRI only requires routine laboratory parameters, further strengthening its applicability in real-world clinical practice. Previous studies also found that FIB-4 and APRI were independent risk factors and had sufficient predictive accuracy for postoperative liver failure and hepatitis B virus-related acute-on-chronic liver failure [15–18, 31, 32]. Previous studies reported that IV-C and LN were reliable biomarkers of disease progression and liver decompensation in patients with compensated cirrhosis of varying etiologies [30]. Additionally, blood fibrosis markers have been shown to enhance outcome prediction in patients with non-acetaminophen-related acute liver failure [20]. Similarly, by utilizing the SHAP technique, IV-C and LN were also ranked the second and third important fibrosis markers in the present study, respectively. The above evidence supported the findings of the current study. The top three important markers and their combination showed promising early warning value for HEV-LF onset among hospitalized patients with AHE regarding discrimination, calibration, and net benefit. The optimism-corrected metrics were similar to the apparent ones, tentatively validating its predictive value. The above results suggested that designing an early warning model based on these important fibrosis markers or incorporating them in the existing prognosis algorithms may be helpful for the early risk classification and assignment of intensified monitoring and treatment. Although HEV is well-recognized as a trigger of liver failure, evidence on early warning of HEV-LF remains scarce. The present study added further evidence on the associations of noninvasive fibrosis scores and blood fibrosis markers with the risk of HEV-LF and their promising value for risk prediction in this context.

Several important limitations of this study should be acknowledged. First, the relatively small sample size prevented the possibility of external validation. External validation in a multicenter cohort is crucial to assess the generalizability of our findings. Additionally, variations in the discrimination ability of fibrosis markers across subgroups of different CLD statuses were observed. However, due to the limited sample size within each subgroup, these findings should be regarded as exploratory. The prediction fairness of the fibrosis markers across these subgroups warrants further investigation and should be carefully considered when constructing future models using these markers. Second, the retrospective study design determined that only available data could be analyzed, which may introduce potential selection, misclassification biases, and residual confounding. Last, blood fibrosis markers were usually measured only once at baseline, longitudinal alterations of these markers during hospitalization could not be studied, which may

overestimate or underestimate the associations or correlations of interest.

Conclusions

In conclusion, baseline fibrosis profiles were associated with the risk of developing HEV-LF among hospitalized patients with AHE. APRI and its combination with certain blood fibrosis markers exhibited promising prediction value for the early warning of HEV-LF onset.

Abbreviations

HEV	Hepatitis E virus
AHE	Acute hepatitis E
CLD	Chronic liver disease
HEV-LF	Hepatitis E virus-related liver failure
FIB-4	Fibrosis-4 score
AST	Aspartate aminotransferase
APRI	Aspartate aminotransferase to platelet ratio index
LN	Laminin
HA	Hyaluronic acid
IV-C	Type IV collagen
PIIINP	N-terminal propeptide of type III collagen
EMR	Electronic medical record
CHB	Chronic hepatitis B
CHC	Chronic hepatitis C
SIRI	Systemic inflammation response index
IQR	Inter-quartile range
RCS	Restricted cubic spline regression
SHAP	Shapley additive explanation
AUROC	Area under the receiver-operating-characteristic curve
GND	Greenwood-Nam-D'Agostino
HSC	Hepatic stellate cell

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10632-z.

Supplementary Material 1.

Acknowledgements

Not applicable.

Authors' contributions

Rui Dong: conceptualization, data collection, formal analysis, and original draft preparation. Lili Huang: data collection, original draft preparation, and funding acquisition. Lin Chen: data collection. Hong Xue: data collection. Jianguo Shao: data collection and funding acquisition. Chunyan Ye: data collection. Yonglin Yang: data collection. Ke Xu: data collection. Zhenghan Luo: data collection, review and editing the manuscript, supervision, and funding acquisition. Jie Wang: conceptualization, review and editing the manuscript, supervision, and funding acquisition. All authors approved the final draft submitted.

Funding

This work was supported by the Nantong Social Livelihood Science and Technology Project (MS2023080), Open project of Jiangsu Health Development Research Center (JSHD2022046), Center for Disease Control and Prevention "Yiqi" Independent Innovation Incubation Fund (2023YQZL02), and Project of "Nursing Science" Funded by the 4th Priority Discipline Development Program of Jiangsu Higher Education Institutions (Jiangsu Education Department [2023] No.11).

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was conducted in line with the Declarations of Helsinki and Istanbul and approved by the Institutional Review Board of The Third Affiliated Hospital of Nantong University (Identification: EK2023108) and The Third People's Hospital of Changzhou (Identification: 02A-A2024021). Informed consent was waived by the Institutional Review Board of The Third Affiliated Hospital of Nantong University and The Third People's Hospital of Changzhou.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Fundamental and Community Nursing, School of Nursing, Nanjing Medical University, Jiangning District, Nanjing 211166, Jiangsu, China. [2]NHC Key Laboratory of Contraceptives Vigilance and Fertility Surveillance/ Jiangsu Health Development Research Center, Nanjing, China. [3]Nantong Institute of Liver Disease, the Third Affiliated Hospital of Nantong University, Nantong, China. [4]Department of Liver Disease, The Third Affiliated Hospital of Nantong University, Nantong, China. [5]Department of Liver Diseases, The Third People's Hospital of Changzhou, Changzhou, China. [6]Department of Infectious Diseases, The Affiliated Taizhou People's Hospital of Nanjing Medical University, Taizhou, China. [7]Department of Acute Infectious Diseases Control and Prevention, Jiangsu Provincial Center for Disease Control and Prevention, Nanjing, China. [8]Department of Infectious Disease Prevention and Control, Huadong Research Institute for Medicine and Biotechniques, Xuanwu District, Nanjing 210018, Jiangsu, China.

Received: 5 January 2025 Accepted: 12 February 2025
Published online: 24 February 2025

References

1. Kamar N, Izopet J, Pavio N, et al. Hepatitis E virus infection. Nat Rev Dis Primers. 2017;3:17086. https://doi.org/10.1038/nrdp.2017.86.
2. European Association for the Study of the Liver. EASL clinical practice guidelines on hepatitis E virus infection. J Hepatol. 2018;68(6):1256–71. https://doi.org/10.1016/j.jhep.2018.03.005.
3. Sedhom D, D'Souza M, John E, Rustgi V. Viral hepatitis and acute liver failure: still a problem. Clin Liver Dis. 2018;22(2):289–300. https://doi.org/10.1016/j.cld.2018.01.005.
4. Wang Y, Liu H, Liu S, et al. Incidence, predictors and prognosis of genotype 4 hepatitis E related liver failure: a tertiary nested case-control study. Liver Int. 2019;39(12):2291–300. https://doi.org/10.1111/liv.14221.
5. Li Q, Chen C, Huang C, Xu W, Hu Q, Chen L. Noninvasive models for predicting poor prognosis of chronic HBV infection patients precipitating acute HEV infection. Sci Rep. 2020;10(1):2753. https://doi.org/10.1038/s41598-020-59670-4.
6. Zhao H, Ye W, Yu X, et al. Hepatitis E virus superinfection impairs long-term outcome in hospitalized patients with hepatitis B virus-related decompensated liver cirrhosis. Ann Hepatol. 2023;28(2):100878. https://doi.org/10.1016/j.aohep.2022.100878.
7. Chen C, Zhu A, Ye S, et al. A new dyslipidemia-based scoring model to predict transplant-free survival in patients with hepatitis E-triggered acute-on-chronic liver failure. Lipids Health Dis. 2023;22(1):80. https://doi.org/10.1186/s12944-023-01826-y.
8. Watanabe Y, Osaki A, Waguri N, Tsuchiya A, Terai S. Prognostic study of acute-on-chronic liver failure patients: Usefulness of the fibrosis-4 index. Medicine (Baltimore). 2022;101(44):e31328. https://doi.org/10.1097/MD.0000000000031328.
9. Dong R, Luo Z, Shao J, et al. Understanding hepatitis E vaccination intention among women of childbearing-age: A theory-based cross-sectional study. Vaccine. 2024;42(24):126258. https://doi.org/10.1016/j.vaccine.2024.126258.

10. Luo J, Liang X, Xin J, et al. Predicting the onset of hepatitis B virus-related acute-on-chronic liver failure. Clin Gastroenterol Hepatol. 2023;21(3):681–93. https://doi.org/10.1016/j.cgh.2022.03.016.
11. He Y, Jin L, Wang J, Yan Z, Chen T, Zhao Y. Mechanisms of fibrosis in acute liver failure. Liver Int. 2015;35(7):1877–85. https://doi.org/10.1111/liv.12731.
12. Dechêne A, Sowa JP, Gieseler RK, et al. Acute liver failure is associated with elevated liver stiffness and hepatic stellate cell activation. Hepatology. 2010;52(3):1008–16. https://doi.org/10.1002/hep.23754.
13. European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol. 2021;75(3):659–89. https://doi.org/10.1016/j.jhep.2021.05.025.
14. Dong R, Zhang R, Shen C, et al. Urinary caffeine and its metabolites in association with advanced liver fibrosis and liver steatosis: a nationwide cross-sectional study. Food Funct. 2024;15(4):2064–77. https://doi.org/10.1039/d3fo04957d.
15. Yang F, Liu Y, Zeng B, et al. Noninvasive assessment of liver fibrosis for predicting acute-on-chronic liver failure in patients with chronic hepatitis B. Hepatol Int. 2021;15(3):593–601. https://doi.org/10.1007/s12072-020-10106-1.
16. Wang H, Li L, Bo W, et al. Immediate postoperative Fibrosis-4 predicts postoperative liver failure for patients with hepatocellular carcinoma undergoing curative surgery. Dig Liver Dis. 2018;50(1):61–7. https://doi.org/10.1016/j.dld.2017.09.127.
17. Feng JW, Qu Z, Wu BQ, Sun DL, Jiang Y. The preoperative fibrosis score 4 predicts posthepatectomy liver failure in patients with hepatocellular carcinoma. Ann Hepatol. 2019;18(5):701–7. https://doi.org/10.1016/j.aohep.2019.04.017.
18. Zhong W, Zhang F, Huang K, Zou Y, Liu Y. Development and validation of a nomogram based on noninvasive liver reserve and fibrosis (PALBI and FIB-4) model to predict posthepatectomy liver failure grade B-C in patients with hepatocellular carcinoma. J Oncol. 2021;2021:6665267. https://doi.org/10.1155/2021/6665267.
19. Mu X, Zou J, Chen J, et al. Low platelets: a new and simple prognostic marker for patients with hepatitis E virus-related acute liver failure. Hepatol Int. 2022;16(5):1116–26. https://doi.org/10.1007/s12072-022-10302-1.
20. Ugamura A, Chu PS, Nakamoto N, et al. Liver fibrosis markers improve prediction of outcome in non-acetaminophen-associated acute liver failure. Hepatol Commun. 2018;2(11):1331–43. https://doi.org/10.1002/hep4.1233.
21. Yi G, de Kraker MEA, Buetti N, et al. Risk factors for in-hospital mortality and secondary bacterial pneumonia among hospitalized adult patients with community-acquired influenza: a large retrospective cohort study. Antimicrob Resist Infect Control. 2023;12(1):25. https://doi.org/10.1186/s13756-023-01234-y.
22. Liver Failure and Artificial Liver Group, Chinese Society of Infectious Diseases, Chinese Medical Association; Severe Liver Diseases and Artificial Liver Group, Chinese Society of Hepatology, Chinese Medical Association. Diagnostic and treatment guidelines for liver failure. Zhonghua Gan Zang Bing Za Zhi. 2013;21(3):177–83.
23. Sterling RK, Lissen E, Clumeck N, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317–25. https://doi.org/10.1002/hep.21178.
24. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38(2):518–26. https://doi.org/10.1053/jhep.2003.50346.
25. Cao Y, Wang W, Xie S, Xu Y, Lin Z. Joint association of the inflammatory marker and cardiovascular-kidney-metabolic syndrome stages with all-cause and cardiovascular disease mortality: a national prospective study. BMC Public Health. 2025;25(1):10. https://doi.org/10.1186/s12889-024-21131-2.
26. Xiao Q, Cai B, Yin A, et al. L-shaped association of serum 25-hydroxyvitamin D concentrations with cardiovascular and all-cause mortality in individuals with osteoarthritis: results from the NHANES database prospective cohort study. BMC Med. 2022;20(1):308. https://doi.org/10.1186/s12916-022-02510-1.
27. Hoan NX, Tong HV, Hecht N, et al. Hepatitis E Virus Superinfection and Clinical Progression in Hepatitis B Patients. EBioMedicine. 2015;2(12):2080–6. https://doi.org/10.1016/j.ebiom.2015.11.020.
28. Qi X, Liu X, Zhang Y, et al. Serum liver fibrosis markers in the prognosis of liver cirrhosis: a prospective observational study. Med Sci Monit. 2016;22:2720–30. https://doi.org/10.12659/msm.900441.
29. Mak KM, Mei R. Basement membrane type IV collagen and laminin: an overview of their biology and value as fibrosis biomarkers of liver disease. Anat Rec (Hoboken). 2017;300(8):1371–90. https://doi.org/10.1002/ar.23567.
30. Chen Q, Mei L, Zhong R, et al. Serum liver fibrosis markers predict hepatic decompensation in compensated cirrhosis. BMC Gastroenterol. 2023;23(1):317. https://doi.org/10.1186/s12876-023-02877-2.
31. Kuang TZ, Xiao M, Liu YF. Predictive value of NLR, Fib4, and APRI in the occurrence of liver failure after hepatectomy in patients with hepatocellular carcinoma. World J Gastrointest Surg. 2024;16(1):155–65. https://doi.org/10.4240/wjgs.v16.i1.155.
32. Li C, Hu H, Bai C, Xu H, Liu L, Tang S. Alpha-fetoprotein and APRI as predictive markers for patients with Type C hepatitis B-related acute-on-chronic liver failure: a retrospective study. BMC Gastroenterol. 2024;24(1):191. https://doi.org/10.1186/s12876-024-03276-x.

Publisher's Note