ORIGINAL ARTICLE

An elevated Fibrosis-4 score is associated with poor clinical outcomes in patients with sepsis: an observational cohort study

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KEY WORDS

critical illness, hepatic fibrosis, liver fibrosis index, outcome, sepsis

ABSTRACT

INTRODUCTION So far, no study has investigated the association between subclinical hepatic fibrosis and sepsis, especially in terms of prognosis.

OBJECTIVES The purpose of our study was to explore the association of liver fibrosis indexes with the outcomes of septic patients without overt chronic liver disease.

PATIENTS AND METHODS We performed a cohort study using data extracted from the Medical Information Mart for Intensive Care III (version 1.4) database. External validation was obtained from the First Affiliated Hospital of Wenzhou Medical University, China. We calculated the Aspartate Aminotransferase–to–Platelet Ratio Index, the Fibrosis-4 (FIB-4) score, and the Nonalcoholic Fatty Liver Disease Fibrosis Score using the existing formulas. The primary outcome was 28-day mortality. We assessed the associations of these 3 indexes with patient outcomes using logistic regression analysis.

RESULTS In the FIB-4 sepsis cohort (n = 1560), there was a significant stepwise increase from quartile 1 to quartile 4 in the risk of 28-day mortality (quartile 1: reference; quartile 2: odds ratio [OR], 1.57, $P = 0.06$, 95% CI, 0.98−2.515; quartile 3: OR, 2.363, $P < 0.001$, 95% CI, 1.512−3.692; quartile 4: OR, 2.933, $P < 0.001$, 95% CI, 1.895−4.538). The results of multivariable regression, Kaplan–Meier, and Cox regression analyses as well as external validation exhibited good consistency.

CONCLUSIONS The FIB-4 index is associated with 28-day, 90-day, and in-hospital mortality as well as with renal replacement therapy in septic patients without overt chronic liver disease. In other words, an advanced stage of subclinical hepatic fibrosis as represented by the FIB-4 score indicates poor outcomes in patients with sepsis.

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Received: November 7, 2020.
Revision accepted: December 1, 2020.
Published online: December 4, 2020.
Pol Arch Intern Med. 2020; 130 (12): 1064-1073
doi:10.20452/pamw.15699

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INTRODUCTION Sepsis, a syndrome of pathophysiological abnormalities and severe organ dysfunction induced by infection, is associated with high incidence and mortality rates worldwide.[1-4] Several inflammatory markers and scoring models, such as procalcitonin, C-reactive protein, Simplified Acute Physiology Score II (SAPS II), and Sequential Organ Failure Assessment (SOFA), play important roles in evaluating the severity and prognosis of critical illness.[5-7]

Nonalcoholic fatty liver disease (NAFLD) is defined as a spectrum of liver diseases with lipid infiltration in hepatocytes, without alcohol abuse, ranging from simple steatosis through steatohepatitis to advanced fibrosis, cirrhosis, and ultimately hepatocellular carcinoma.[8] Nonalcoholic fatty liver disease, which is tightly linked to metabolic disorders, has been considered the hepatic manifestation of metabolic syndrome (MetS).[8,9] The liver fibrosis stage is strongly associated with long-term outcomes in patients with NAFLD.[10,11]

Notably, recent research showed that NAFLD-predisposing genes are also involved in the pathogenesis of sepsis phenotypes.[12] Moreover, biomedical and RNA sequencing–based analyses both highlighted significant associations among the acquired and inherited pathogenic, cardiac, and

WHAT'S NEW?

The Fibrosis-4 (FIB-4) index can be used as an independent short-term mortality scoring system to evaluate the outcomes of septic patients without overt chronic liver disease. An advanced stage of subclinical hepatic fibrosis as represented by the FIB-4 score can indicate poor outcomes in patients with sepsis. This significant association can also be observed in nonseptic patients, which suggests that the FIB-4 score may be used in all critically ill patients. The FIB-4 index, as an effective supplementary tool for the existing prognostic scoring system, improves the predictive performance regarding clinical outcomes to some extent. External validation with new data collected from our hospital yielded results similar to those of our primary analysis, which indicates that the FIB-4 score has good generalizability.

inflammatory traits of sepsis and MetS.[13] Of note, both advanced cirrhosis and MetS lead to poor prognosis in sepsis.[14,15]

However, no previous study has investigated the association between subclinical hepatic fibrosis and sepsis, especially regarding prognosis. Several noninvasive fibrosis scoring systems, such as the Aspartate Aminotransferase–to–Platelet Ratio Index (APRI), the Fibrosis-4 (FIB-4) score, and the NAFLD Fibrosis Score (NFS),[16-18] are widely used to evaluate the risk of poor prognosis in chronic liver disease,[19,20] cardiovascular and cerebrovascular diseases,[21,22] and malignant tumors.[23,24] Therefore, the purpose of our study was to explore the potential association of liver fibrosis indexes with the outcomes of septic patients without overt chronic liver disease.

PATIENTS AND METHODS

Data source We performed a cohort study using data extracted from the Medical Information Mart for Intensive Care III (MIMIC III) clinical database (version 1.4), which contained over 58 000 hospital admission data entries of adult patients and neonates admitted to various critical care units between 2001 and 2012.[25] One of the study investigators (WZ) was allowed to download data from the database, having completed the "Data or Specimens Only Research" course (record identity, 25222342). The requirement for individual patient consent was waived, as the project neither contained any protected health information nor impacted clinical care.[25]

Patient records for the external validation of our findings were obtained from the First Affiliated Hospital of Wenzhou Medical University (Wenzhou, Zhejiang, China) after approval from that institution's ethical committee. All study participants provided written informed consent and their data confidentiality was protected.

Study participants A flowchart of the inclusion and exclusion procedure for MIMIC III is presented in FIGURE 1. We adopted The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3; a diagnosis flowchart is available in Supplementary material, *Figure S1*) to extract septic patients from the database.[1] Based on the Sepsis-3 criteria, patients with suspected infection and evidence of organ dysfunction (SOFA score ≥2) were identified as septic patients.[1] Suspected infection was defined as the concomitant administration of antibiotics and sampling of body fluid cultures (eg, blood, urine, sputum).[1] In other words, if culture was obtained, we required that an antibiotic was administered within 72 hours, whereas if the antibiotic was administered first, culture was required within 24 hours.[1] Moreover, we defined the period of suspected infection as ranging between 24 hours before and 24 hours after admission to an intensive care unit (ICU). Patients in the CareVue and MetaVision information systems of MIMIC III were admitted before and after 2008, respectively. Only patient data stored in the MetaVision system were collected for analysis. Antibiotic prescription data were available only after 2002; thus, there was a fraction (1/7) of the CareVue patients who were missing data to meet our definition of suspected infection. It was the simplest option for us to limit the cohort to the MetaVision system, because the resulting sample size was sufficient.

To minimize the effect of potential confounding variables in our analysis, patients aged 16 years or younger and those with repeated admissions to the ICU, a history of alcohol abuse, overt chronic liver disease (including chronic viral hepatitis, autoimmune liver disease, alcoholic liver disease, overt liver cirrhosis, or liver transplant), hematologic or solid malignancies, or chronic kidney disease were excluded from the initial study cohort. Furthermore, the exclusion criteria for the sepsis cohort were as follows: current treatment relating to cardiac, vascular, or thoracic surgery. We assumed that these subpopulations had physiological abnormalities yet caused by factors unrelated to sepsis.

The data for external validation were prospectively collected between October 12, 2017 and January 16, 2020, according to the same inclusion and exclusion criteria. The clinical outcomes were followed up for 90 days after admission.

Data extraction The data were extracted from MIMIC III and our hospital system and included information on patients' sex, age, race, body mass index (BMI), laboratory investigations, ICU interventions, vital statistics, comorbidities, and length of hospital stay. Sores for the evaluation of illness severity, including SAPS II and SOFA scales, were calculated based on their predefined criteria.[6,7] The mean values of BMI, laboratory parameters, and vital statistics during the first 24 hours of ICU stay were regarded as baseline data. The SAPS II and SOFA scores as well as the necessity to perform interventions with vasopressors and mechanical ventilation were evaluated during the first 24 hours of ICU stay.

Exposures and outcomes We calculated 3 liver fibrosis indexes (APRI, FIB-4, and NFS) using their existing formulas (FIGURE 2).[16-18] These

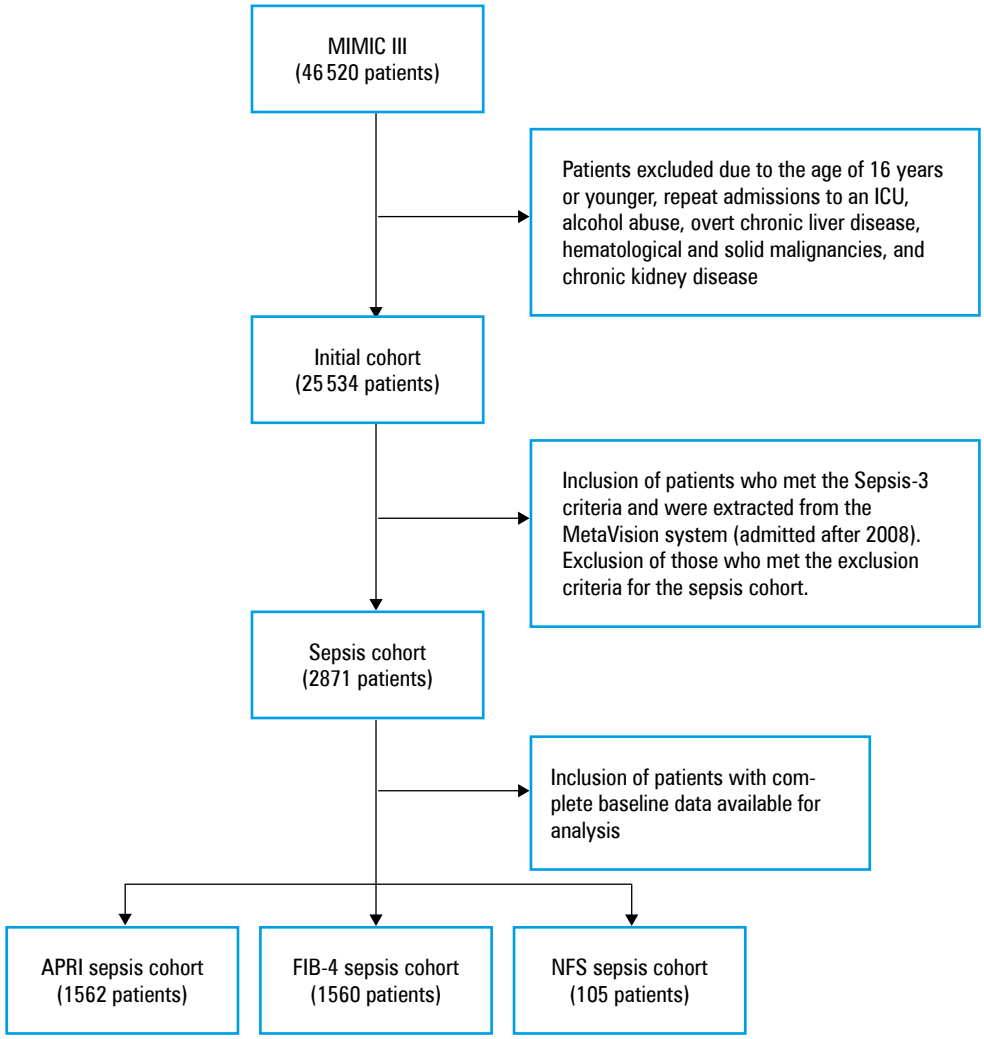

FIGURE 1 The flowchart of the inclusion and exclusion procedure for the Medical Information Mart for Intensive Care III (MIMIC III) database

Abbreviations: APRI, Aspartate Aminotransferase–to–Platelet Ratio Index; FIB-4, Fibrosis-4 score; ICU, intensive care unit; NFS, Nonalcoholic Fatty Liver Disease Fibrosis Score

$$\text{APRI} = \frac{\dfrac{\text{AST (IU/l)}}{\text{ULN}^{a}}}{\text{PLT } (10^{9}/\text{l})} \times 100$$

$$\text{FIB-4} = \frac{\text{age (years)} \times \text{AST (IU/l)}}{\text{PLT } (10^{9}/\text{l}) \times \sqrt{\text{AST (IU/l)}}}$$

$$\text{NFS} = -1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{prediabetes/diabetes}$$

$$(\text{yes} = 1;\ \text{no} = 0) + 0.99 \times \frac{\text{AST (IU/l)}}{\text{ALT (IU/l)}} - 0.013 \times \text{PLT } (10^{9}/\text{l}) - 0.66 \times \text{albumin (g/dl)}$$

FIGURE 2 Formulas of 3 liver fibrosis indexes

a 37 IU/l for men and 31 IU/l for women

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; PLT, platelets; ULN, upper limit of normal; others, see **FIGURE 1**

indexes were evaluated at baseline with factors assumed to reflect patients' initial condition on ICU admission, and we categorized the patients by the quartiles of their index values at baseline. Diabetes was defined according to the *International Classification of Diseases, Ninth Revision* codes or hemoglobin A_{1C} level of 6.5% or greater, and prediabetes, as a hemoglobin A_{1C} level ranging between 5.7% and 6.5%.

The primary endpoint of the present study was 28-day mortality. Secondary endpoints included 90-day mortality, in-hospital mortality, and renal replacement therapy (RRT). Mortality in MIMIC III was calculated based on the dates

of admission and death obtained from social security records.

Statistical analysis The Kolmogorov–Smirnov test was used to check the normality assumption for numerical variables. Normally and non-normally distributed variables were compared using the unpaired *t* test and the Wilcoxon rank sum test, respectively. Comparisons for categorical variables were performed using the Pearson χ^2 test and the Fisher exact test. Normally distributed data were expressed as mean (SD), and non-normally distributed data, as median (interquartile range [IQR]). Categorical variables were presented as frequency and percentage.

We assessed the associations of the 3 indexes with the primary and secondary outcomes using logistic regression analysis. The results were expressed as odds ratios (ORs) with 95% CIs. Septic patients were categorized according to the quartiles of their index values at baseline, and quartile 1 was considered the reference for all subsequent analyses.

A 2-tailed *P* value less than 0.05 was considered significant. Statistical analyses were performed using the SPSS software, version 20.0 (SPSS, Chicago, Illinois, United States), the MedCalc software, version 19.0.5 (MedCalc Software, Ostend, Belgium), and the MATLAB software, version R2018b (MathWorks, Natick, Massachusetts, United States).

Multivariable analysis, sensitivity analysis, and external validation Due to the influence of missing data and potentially relevant confounding factors, several additional analyses were performed to further verify the predictive ability of the liver fibrosis indexes.

First, we attempted to adjust the potential confounding variables through multivariable logistic regression analysis. The following variables were adjusted in the multivariable model: sex, race, laboratory parameters (white blood cell count, hemoglobin, lactate, creatinine, international normalized ratio, partial thromboplastin time, sodium, and potassium levels), vital statistics (heart rate, mean blood pressure, respiration rate, body temperature, and pulse oxygen saturation), comorbidities (congestive heart failure, cardiac arrhythmias, hypertension, chronic pulmonary disease, and diabetes), SOFA and SAPS II scores, and length of hospital stay. Forward likelihood ratio selection was used to filter the included variables.

Second, subset analyses based on 2 liver function indexes were performed to determine whether patients with abnormal baseline liver function distorted the results. Albumin and bilirubin, representing synthesis and metabolism in the liver, were used to divide the patients into groups with normal and abnormal levels according to reference ranges.

Third, we conducted a comparative analysis between the septic and nonseptic patients according to the indexes. Moreover, we performed an additional analysis to establish whether similar results also applied for nonseptic patients.

Fourth, some patients were excluded in the primary analysis, because their index data were not complete during the first 24 hours of ICU stay. Thus, sensitivity analysis was performed for patients in whom baseline index values could not be used, but data from their ICU stay were available.

Fifth, we conducted separate analyses to determine whether liver fibrosis indexes combined with SOFA or SAPS II scores could improve the predictive performance regarding patient outcomes. Performance discrimination was assessed by calculating the receiver operating characteristic (ROC) curve and the area under the ROC curve (AUROC). The DeLong test was used to assess differences in AUROC among the different models. Additionally, we calculated the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) to evaluate improvement associated with the liver fibrosis indexes relative to the SOFA or SAPS II score.

Sixth, we repeated the primary analysis using the Kaplan–Meier and Cox regression analyses instead of logistic regression analysis to evaluate the impact of various analytical methods. The results were presented in the form of a survival curve and the hazard ratio with 95% CI, respectively.

Finally, external validation was introduced to verify whether similar results can be observed in the East Asian population.

RESULTS

Baseline characteristics of the study cohort The baseline characteristics of the APRI, FIB-4, and NFS sepsis cohorts are summarized in TABLE 1. The median (IQR) APRI, FIB-4, and NFS values were 0.537 (0.296–1.339), 2.365 (1.305–4.837), and 0.791 (–0.198 to 1.858), respectively.

Associations of APRI, FIB-4, and NFS scores with primary and secondary outcomes As listed for the FIB-4 sepsis cohort in TABLE 2, there was a significant stepwise increase from quartile 1 to quartile 4 in the risk of 28-day mortality (quartile 1: reference; quartile 2: OR, 1.57, $P = 0.06$, 95% CI, 0.98–2.515; quartile 3: OR, 2.363, $P < 0.001$, 95% CI, 1.512–3.692; quartile 4: OR, 2.933, $P < 0.001$, 95% CI, 1.895–4.538). The rates of 28-day mortality according to the quartiles of the FIB-4 score were as follows: quartile 1, 8.2%; quartile 2, 12.3%; quartile 3, 17.4%; and quartile 4, 20.8%. Similarly, increasing trends in all secondary outcomes could be noted in the FIB-4 sepsis cohort. However, no significant trends were observed in the APRI and NFS sepsis groups.

Multivariable analysis, sensitivity analysis, and external validation In univariable analysis, the FIB-4 score was significantly correlated with the primary and secondary outcomes. Thus, multivariable analysis, sensitivity analysis, and additional external validation were performed to further explore

TABLE 1 Baseline characteristics of the study patients with sepsis stratified using the Aspartate Aminotransferase–to–Platelet Ratio Index, the Fibrosis-4 score, and the Nonalcoholic Fatty Liver Disease Fibrosis Score

Characteristics		APRI (n = 1562)	FIB-4 (n = 1560)	NFS (n = 105)
Sex (male/female)		769/793	768/792	69/36
Age, y, median (IQR)		67.56 (52.88–81.25)	67.54 (52.84–81.25)	64.65 (53.88–75.34)
Age group, y	≤40	181 (11.6)	181 (11.6)	9 (8.6)
	40–60	385 (24.6)	385 (24.7)	36 (34.3)
	60–80	561 (35.9)	560 (35.9)	43 (41)
	>80	435 (27.8)	434 (27.8)	17 (16.2)
Race or ethnicity	White	1128 (72.2)	1127 (72.2)	72 (68.6)
	Black	131 (8.4)	131 (8.4)	10 (9.5)
	Hispanic	52 (3.3)	52 (3.3)	1 (1)
	Other	251 (16.1)	250 (16)	22 (21)
Comorbidities				
Congestive heart failure		360 (23)	359 (23)	39 (37.1)
Cardiac arrhythmias		492 (31.5)	492 (31.5)	40 (38.1)
Hypertension		873 (55.9)	873 (56)	72 (68.6)
Chronic pulmonary disease		351 (22.5)	350 (22.4)	22 (21)
Diabetes		432 (27.7)	430 (27.6)	44 (41.9)
ICU interventions				
Vasopressor (first 24 hours)		449 (28.7)	448 (28.7)	43 (41)
Mechanical ventilation (first 24 hours)		696 (44.6)	695 (44.6)	57 (54.3)
Renal replacement therapy		33 (2.1)	33 (2.1)	3 (2.9)
Severity of illness (first 24 hours), median (IQR)				
SOFA score		4 (3–6)	4 (3–6)	4 (3–6)
SAPS II score		36 (29–44)	36 (29–44)	35 (29–40.5)
Length of stay, d, median (IQR)				
ICU		2.67 (1.61–5.13)	2.67 (1.61–5.13)	3.05 (1.97–5.12)
Hospital		6.94 (4.28–12.02)	6.94 (4.28–12.03)	6.81 (5.04–11.83)
Outcomes				
28-day mortality		229 (14.7)	229 (14.7)	9 (8.6)
90-day mortality		296 (19)	296 (19)	12 (11.4)
In-hospital mortality		189 (12.1)	189 (12.1)	9 (8.6)
Scoring items				
Platelets, × 10^9/l, median (IQR)		215 (159–285)	215 (159–284.92)	213.5 (167.33–264.08)
AST, IU/l, median (IQR)		36.5 (23–73.75)	36.5 (23–73.92)	39 (22.5–73.25)
ALT, IU/l, median (IQR)		–	28 (17.5–61.75)	27 (19.5–50.5)
BMI, kg/m^2, median (IQR)		–	–	27.98 (25.13–33.54)
Albumin, g/dl, mean (SD)		–	–	3.54 (0.52)
Prediabetes or diabetes		–	–	85 (81)

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: BMI, body mass index; IQR, interquartile range; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; others, see FIGURE 1

the association between the FIB-4 score and the outcomes. To assess the bias from the missing information due to incomplete baseline data, we compared the baseline characteristics of the final study cohort against those of the missing data cohort (Supplementary material, *Table S1*).

As shown in FIGURE 3, the stepwise increasing trends from quartile 1 to quartile 4 in the risk of death at 28 days, 90 days, and during hospital stay remained significant after multivariable adjustments.

The cutoff values of albumin and bilirubin levels were defined as 3.5 g/dl and 1 mg/dl, respectively. As presented in Supplementary material, *Table S2*, a stepwise increasing trend in 28-day mortality from quartile 1 to quartile 4 was observed in septic patients with low albumin levels (quartile 1: reference; quartile 2: OR, 1.821, P = 0.1, 95% CI, 0.893–3.714; quartile 3: OR,

TABLE 2 Association of the Aspartate Aminotransferase–to–Platelet Ratio Index, the Fibrosis-4 score, and the Nonalcoholic Fatty Liver Disease Fibrosis Score with primary and secondary study outcomes

Liver fibrosis index	28-day mortality			90-day mortality			In-hospital mortality			RRT		
	OR	*P* value	95% CI	OR	*P* value	95% CI	OR	*P* value	95% CI	OR	*P* value	95% CI
APRI												
Quartile 1	Reference			Reference			Reference			Reference		
Quartile 2	1.088	0.69	0.722–1.639	1.129	0.52	0.78–1.633	1.145	0.57	0.722–1.815	1.671	0.48	0.397–7.041
Quartile 3	1.305	0.19	0.876–1.943	1.373	0.08	0.958–1.966	1.521	0.06	0.980–2.361	1.675	0.48	0.398–7.059
Quartile 4	1.181	0.42	0.789–1.77	1.187	0.36	0.823–1.712	1.453	0.1	0.933–2.261	6.954	0.002	2.049–23.598
FIB-4												
Quartile 1	Reference			Reference			Reference			Reference		
Quartile 2	1.57	0.06	0.98–2.515	1.536	0.046	1.008–2.34	1.743	0.04	1.029–2.952	2.016	0.32	0.501–8.117
Quartile 3	2.363	<0.001	1.512–3.692	2.486	<0.001	1.67–3.699	2.664	<0.001	1.619–4.385	2.702	0.14	0.711–10.26
Quartile 4	2.933	<0.001	1.895–4.538	2.974	<0.001	2.011–4.398	3.163	<0.001	1.939–5.162	5.519	0.007	1.595–19.095
NFS												
Quartile 1	Reference			Reference			Reference			Reference		
Quartile 2	1	1	0.222–4.512	1	1	0.222–4.512	1.394	0.69	0.279–6.953	–	1	–
Quartile 3	<0.001	1	–	0.212	0.18	0.022–2.035	<0.001	1	–	1	1	–
Quartile 4	0.22	0.19	0.023–2.119	0.717	0.69	0.144–3.578	0.639	0.64	0.098–4.18	–	1	–

Abbreviations: OR, odds ratio; RRT, renal replacement therapy; others, see **FIGURE 1**

3.078, $P = 0.001$, 95% CI, 1.569–6.039; and quartile 4: OR, 3.77, $P < 0.001$, 95% CI, 1.956–7.269). However, the subset analysis of bilirubin yielded the opposite result. There was a significant increasing trend from quartile 1 to quartile 4 for the normal-bilirubin group regarding the risk of 28-day mortality (quartile 1: reference; quartile 2: OR, 1.624, $P = 0.07$, 95% CI, 0.965–2.736; quartile 3: OR, 2.419, $P = 0.001$, 95% CI, 1.471–3.979; and quartile 4: OR, 4.073, $P < 0.001$, 95% CI, 2.479–6.693). Moreover, similar trends were also found in all secondary outcomes.

Regarding the median (IQR) baseline FIB-4 value, there was a nonsignificant difference between the sepsis (n = 1560; 2.365 [1.305–4.837]) and nonsepsis cohorts (n = 7968; 2.193 [1.19–5.024]; $P = 0.08$). For nonseptic patients, the same trend in the risk of 28-day mortality from quartile 1 to quartile 4 was observed (quartile 1: reference; quartile 2: OR, 2.376, $P < 0.001$, 95% CI, 1.883–2.998; quartile 3: OR, 3.578, $P < 0.001$, 95% CI, 2.863–4.471; and quartile 4: OR, 6.386, $P < 0.001$, 95% CI, 5.153–7.914).

A total of 215 patients in whom baseline FIB-4 values were unavailable, but such values from their ICU stay could be used were included in the sensitivity analysis. However, no significant trend was observed between the FIB-4 score and 28-day mortality, unlike in the primary analysis (quartile 1: reference; quartile 2: OR, 2.174, $P = 0.23$, 95% CI, 0.613–7.704; quartile 3: OR, 0.75, $P = 0.72$, 95% CI, 0.16–3.524; and quartile 4: OR, 5.743, $P = 0.003$, 95% CI, 1.784–18.49).

The performance of the various prognostic models were summarized using ROC curves (Supplementary material, *Figure S2*). The mean AUROCs for identifying 28-day mortality when using the SOFA and FIB-4–SOFA models were 0.624 (SD, 0.02; 95% CI, 0.6–0.648) and 0.649 (SD, 0.019; 95% CI, 0.625–0.673), respectively, whereas the mean AUROCs for the SAPS II and FIB-4–SAPS II models were 0.762 (SD, 0.016; 95% CI, 0.74–0.783) and 0.765 (SD, 0.016; 95% CI, 0.743–0.785), respectively. Comparative analyses showed that the addition of FIB-4 to SOFA significantly improved the AUROC ($P = 0.046$), whereas the addition of FIB-4 to SAPS II was nonsignificant ($P = 0.45$). Furthermore, the addition of FIB-4 to SOFA was associated with a significant increase in both NRI (0.093, $P = 0.002$) and IDI (0.009, $P < 0.001$) for 28-day mortality. However, the addition of FIB-4 to SAPS II was associated with a significant increase in NRI only (0.032, $P = 0.005$).

Additionally, the results of repeated Kaplan–Meier (**FIGURE 4**) and Cox regression analyses (Supplementary material, *Table S3*) were consistent with those of logistic regression analysis, indicating that the conclusions were not affected by the analytical method used.

Finally, new data (n = 35) collected from our hospital for external validation also led to similar results (Supplementary material, *Table S4*) as in the primary analysis, indicating that the FIB-4

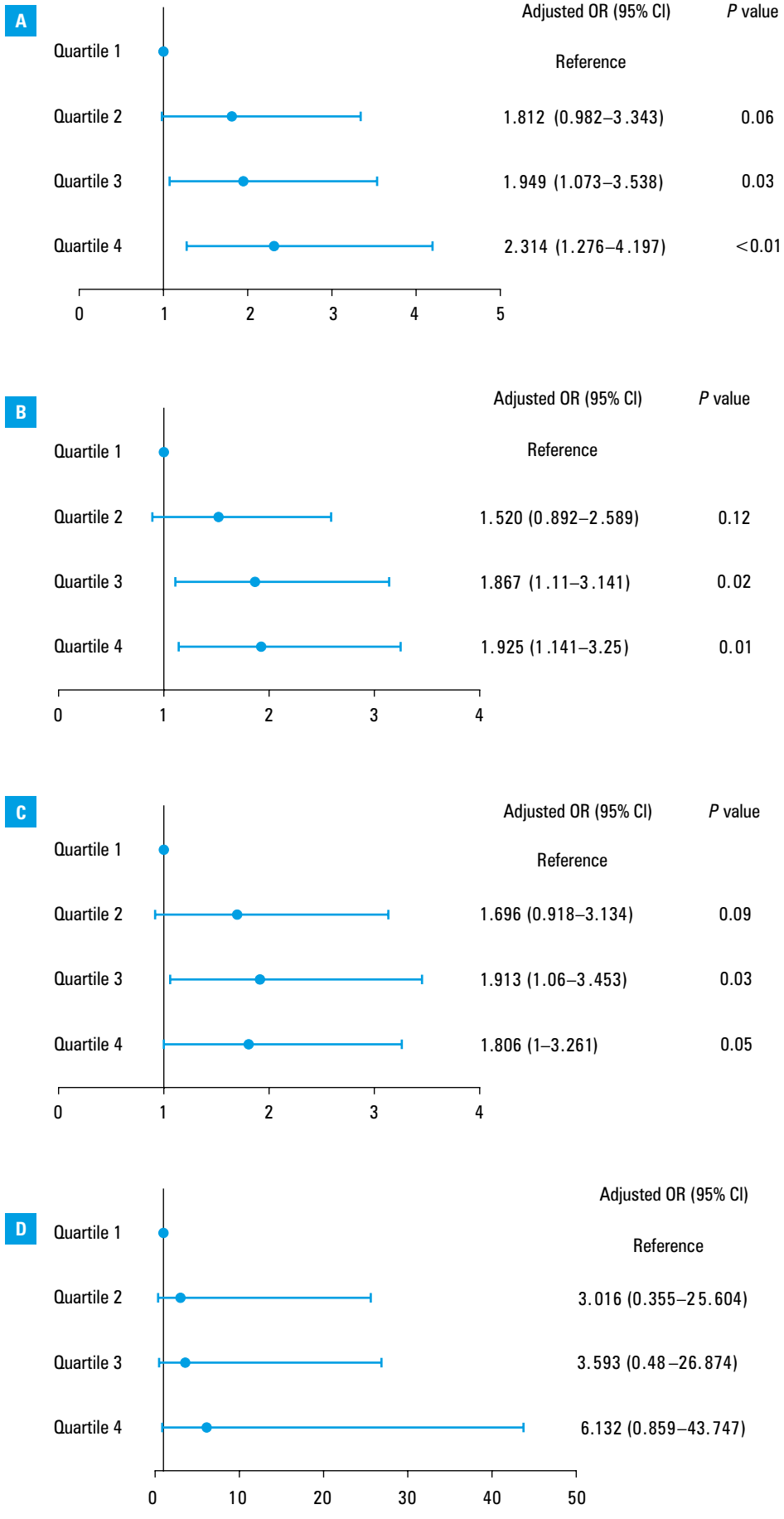

FIGURE 3 Multivariable logistic regression analysis of primary and secondary outcomes in the Fibrosis-4 sepsis cohort: **A** – 28-day mortality; **B** – 90-day mortality; **C** – in-hospital mortality; **D** – renal replacement therapy
Abbreviations: see **TABLE 2**

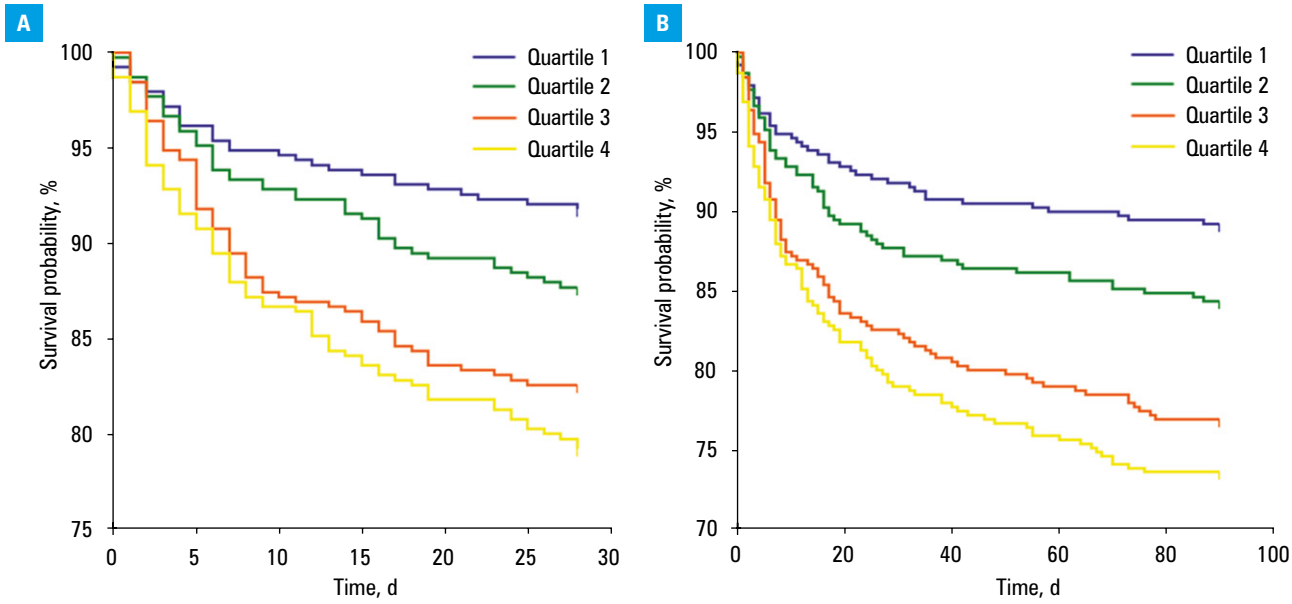

FIGURE 4 Kaplan–Meier survival analysis in the Fibrosis-4 sepsis cohort: **A** – 28-day survival curve; **B** – 90-day survival curve

score can be generally used to predict the outcomes of patients with sepsis to some extent.

DISCUSSION The present study revealed that the FIB-4 index can be used as an independent short-term mortality scoring system to evaluate the outcomes of septic patients without overt chronic liver disease. In other words, an advanced stage of subclinical hepatic fibrosis as represented by the FIB-4 score indicates poor outcomes in patients with sepsis. Similarly, a significant association was observed in nonseptic patients, which suggests that use of the FIB-4 index may be generalizable across all critically ill patients. Furthermore, the FIB-4 index, as a supplement to the existing prognostic scoring system, to some extent improved the prediction of outcomes. To assess the impact of confounding factors, we performed multivariable logistic regression, Kaplan–Meier, and Cox regression analyses, as well as external validation; all the results exhibited good consistency.

Sepsis, a syndrome of immense clinical importance, has been associated with high incidence, mortality, and ICU admission rates in recent years.[4,26,27] The latest Sepsis-3 definition, which is gradually replacing previous definitions of sepsis, denotes it as a life-threatening organ dysfunction caused by a dysregulated host response to infection.[1,28] Johnson et al[29] performed a comparative analysis of sepsis identification methods in MIMIC III (version 1.4) and concluded that the Sepsis-3 criteria had several advantages over previously used methods, including lower susceptibility to changes in coding practices, provision of a temporal context for extracting a sepsis cohort by suspected infection with associated organ failure at a certain time point rather than by the *International Classification of Diseases, Ninth Revision* codes, and better conformation to the contemporary understanding of the pathophysiology of sepsis. Therefore, it was appropriate to extract septic patients from the database according to the Sepsis-3 criteria.

Liver cirrhosis is the leading cause of death and disability worldwide, mainly caused by hepatitis B and C virus infection, and alcohol abuse.[30] Notably, NAFLD has been identified as another crucial risk factor for liver cirrhosis.[31] In a study using data from the National Health and Nutrition Examination Survey,[31] 7% of NAFLD patients progressed to cirrhosis within a median follow-up time of 178.27 months. Several studies have confirmed that liver cirrhosis is an independent risk factor for poor prognosis in patients with sepsis.[14,32,33] The mechanisms of increased mortality in cirrhotic patients with sepsis are likely to be multifactorial. In patients with cirrhosis, adrenal insufficiency during sepsis is associated with a higher rate of mortality.[34,35] The occurrence of sepsis aggravates adrenal insufficiency in patients with liver cirrhosis, which may be due to the inhibitory effect of increased cytokine release for the hypothalamus–pituitary–adrenal axis and glucocorticoid receptor function.[34,35] In addition, abnormalities in cell-mediated immunity, humoral immunity, and the release of cytokines (tumor necrosis factor α and interleukin 6) that mediate systemic inflammation may represent other major causes of increased mortality.[14,36,37] Liver fibrosis, an early manifestation of liver cirrhosis and mainly related to NAFLD, has a high prevalence in adults with unidentified liver diseases.[38] However, the association between the stage of subclinical hepatic fibrosis and the outcomes of sepsis remains unclear. Notably, in a longitudinal study of patients with NAFLD, the fibrosis stage was the only histologic feature independently associated with overall mortality, liver transplant, and liver-related events.[10] Recently, noninvasive fibrosis scoring systems have been

shown to identify histologic fibrosis with reasonable accuracy in retrospective cohort studies.[11,39] In addition, our baseline data used to calculate liver fibrosis indexes were obtained during the first 24 hours of ICU stay, which can indirectly reflect the initial stage of subclinical fibrosis in the septic patients. Of all the fibrosis scoring systems, APRI, FIB-4, and NFS are widely used in the prognostic evaluation of nonhepatic diseases.[21-24] However, little is known about the application of liver fibrosis indexes to infection and inflammation. Thus, further studies are warranted to explore the possible mechanisms of increased mortality in septic patients with an advanced stage of subclinical hepatic fibrosis. Obviously, the mechanisms described in patients with overt cirrhosis have significance as a reference.

Acute kidney injury (AKI) is frequent in patients with cirrhosis, in whom the incidence reaches approximately 20%.[40] The pathogenesis of sepsis-induced AKI in patients with cirrhosis is consistent with the so-called splanchnic arterial vasodilation hypothesis, which pertains to arterial vasodilation and reduction in cardiac output.[41] Moreover, in the context of sepsis, circulating endotoxins and proinflammatory cytokines impair portal hypertension and liver function, further producing synergistic negative effects in patients with cirrhosis.[41]

Acute kidney injury is the main reason for the use of RRT in an ICU. Patients with advanced AKI often need RRT; thus, the proportion of RRT can indirectly reflect the status of patients with severe AKI. Similarly, the FIB-4 score was also correlated with RRT during the ICU stay in our study. After excluding patients with chronic kidney disease, a late stage of subclinical hepatic fibrosis may indicate a high probability of severe AKI in patients with sepsis. In the subset analyses, results similar to those of the primary analysis were obtained for patients with normal bilirubin levels, but the results were opposite in individuals with normal albumin levels. The half-life of albumin in the body is as long as 21 days. A reduction in albumin levels after liver damage caused by sepsis is often evident after a week. Thus, the baseline albumin level was obtained during the first 24 hours of ICU stay, which may represent the basic condition that is not significantly affected by sepsis. However, baseline albumin levels are also affected by nutritional status, endocrine metabolism, kidney metabolism, and other factors, which cause deviations in the results of subset analysis. Additionally, the FIB-4 index is also applicable to nonseptic patients. Thus, we hypothesize that the fibrosis stage may be a risk factor for unfavorable outcomes in critically ill patients.

The NFS includes BMI, diabetes, and impaired fasting glucose levels, which reflect this score's usefulness primarily for the detection of advanced fibrosis among patients with NAFLD. Several components of the NFS, such as BMI, may in fact, paradoxically, have a protective role. Additionally, the limited sample size of our NFS cohort is of importance. The simpler APRI has been validated in a larger number of liver diseases and may be more useful in the general population. However, a few variables in this model may lead to bias, undermining the generalization of our sepsis cohort study. These factors may explain why the APRI and NFS scores failed to demonstrate any prognostic value in our study.

The FIB-4 index has potential strengths in clinical application. First, the formula for calculating it, simply composed of age, platelet count, and the levels of alanine aminotransferase and aspartate aminotransferase, may be more suitable for the rapid assessment of patients with sepsis, according to good repeatability, continuous monitoring, and graded management of patients, which can be carried out in an ICU. Second, even though there are several effective prognostic scoring models for sepsis, the FIB-4 model can be regarded as a supplementary tool for evaluating the stage of subclinical hepatic fibrosis, which is closely related to the outcomes of septic patients. Third, considering cost and safety, the FIB-4 index can be used as a feasible alternative to imaging and biopsy of the liver in assessing the stage of liver fibrosis.

Limitations Our study had several limitations. First, our main study, due to its retrospective design, was vulnerable to selection bias as a result of the inclusion of only a single-center sample and the exclusion of patients with missing data. Although the sample size of the external validation cohort was limited, it yielded results similar to those of the primary analysis. Second, there were some false-positives among the NRI and IDI results; however, it is still reasonable to assess performance discrimination based on the comprehensive analysis of AUROC, NRI, and IDI. Third, liver biopsy remains the gold standard method for assessing the severity of liver fibrosis. Over- or underestimation of the fibrosis stage, which could stem from any discrepancy in FIB-4 predictive accuracy, may contribute to estimation bias for the true strength of the association between the fibrosis stage and adverse outcomes. However, a significant estimation bias is unlikely, because the FIB-4 score has identified the fibrosis stage with a reasonable accuracy in recent studies.[15,39] Therefore, further prospective studies are needed to validate our findings by determining the fibrosis stage using liver imaging or biopsy.

Conclusions The present study for the first time revealed that the FIB-4 index is associated with 28-day, 90-day, and in-hospital mortality as well as RRT in septic patients without overt chronic liver disease. Namely, an advanced stage of subclinical hepatic fibrosis as represented by the FIB-4 score can indicate poor outcomes in patients with sepsis. The FIB-4 index, as an effective

supplement to the existing prognostic scoring systems, may help in the graded management of patients with different prognosis scores and remind physicians to pay more attention to patients with a high risk score.

ARTICLE INFORMATION

ACKNOWLEDGMENTS This work was supported by a grant from the Research Incubation Project of the First Affiliated Hospital of Wenzhou Medical University (grant no. FHY2019088; to WZ).

CONTRIBUTION STATEMENT XDZ and WZ conceived and designed this study. XYQ, XH, and WZ helped with the collection and assembly of data. All authors contributed to data analysis, drafted and critically revised the paper, and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

CONFLICT OF INTEREST None declared.

HOW TO CITE Zhu X, Hu X, Qin X, et al. An elevated Fibrosis-4 score is associated with poor clinical outcomes in patients with sepsis: an observational cohort study. Pol Arch Intern Med. 2020; 130: 1064-1073. doi:10.20452/pamw.15699

REFERENCES

1 Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315: 801-810.

2 Lagu T, Rothberg MB, Shieh MS, et al. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. Crit Care Med. 2012; 40: 754-761.

3 Kaukonen KM, Bailey M, Suzuki S, et al. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. JAMA. 2014; 311: 1308-1316.

4 Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001; 29: 1303-1310.

5 Jain S, Sinha S, Sharma SK, et al. Procalcitonin as a prognostic marker for sepsis: a prospective observational study. BMC Res Notes. 2014; 7: 458.

6 Auriant I, Vinatier I, Thaler F, et al. Simplified acute physiology score II for measuring severity of illness in intermediate care units. Crit Care Med. 1998; 26: 1368-1371.

7 Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001; 286: 1754-1758.

8 Yu Y, Cai J, She Z, Li H. Insights into the epidemiology, pathogenesis, and therapeutics of nonalcoholic fatty liver diseases. Adv Sci (Weinh). 2018; 6: 1801585.

9 Yki-Järvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol. 2014; 2: 901-910.

10 Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology. 2015; 149: 389-397. e10.

11 Marella HK, Reddy YK, Jiang Y, et al. Accuracy of noninvasive fibrosis scoring systems in African American and white patients with nonalcoholic fatty liver disease. Clin Transl Gastroenterol. 2020; 11: e00165.

12 Sookoian S, Pirola CJ. Genetics of nonalcoholic fatty liver disease: from pathogenesis to therapeutics. Semin Liver Dis. 2019; 39: 124-140.

13 Meydan C, Bekenstein U, Soreq H. Molecular regulatory pathways link sepsis with metabolic syndrome: non-coding RNA elements underlying the sepsis/metabolic cross-talk. Front Mol Neurosci. 2018; 11: 189.

14 Foreman MG, Mannino DM, Moss M. Cirrhosis as a risk factor for sepsis and death: analysis of the National Hospital Discharge Survey. Chest. 2003; 124: 1016-1020.

15 Tracy BM, Wilson JM, Staley C, et al. Metabolic Syndrome: major risk factor for morbidity and mortality in severely injured trauma patients. J Am Coll Surg. 2020; 230: 145-150.

16 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: 518-526.

17 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: 1317-1325.

18 Angulo P, Hui JM, Marchesini G, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007; 45: 846-854.

19 Kim D, Kim WR, Kim HJ, Therneau TM. Association between noninvasive fibrosis markers and mortality among adults with nonalcoholic fatty liver disease in the United States. Hepatology. 2013; 57: 1357-1365.

20 Barré T, Protopopescu C, Bani-Sadr F, et al. Elevated Fatty Liver Index as a Risk Factor for All-Cause Mortality in Human Immunodeficiency Virus-Hepatitis C Virus-Coinfected Patients (ANRS CO13 HEPAVIH cohort study). Hepatology. 2020; 71: 1182-1197.

21 Chen Q, Li Q, Li D, et al. Association between liver fibrosis scores and the risk of mortality among patients with coronary artery disease. Atherosclerosis. 2020; 299: 45-52.

22 Parikh NS, Kamel H, Navi BB, et al. Liver fibrosis indices and outcomes after primary intracerebral hemorrhage. Stroke. 2020; 51: 830-837.

23 Park JH, Choi IS, Han KD, et al. Association between fatty liver index and risk of breast cancer: a nationwide population-based study. Clin Breast Cancer. 2020; 20: e450-e457.

24 Ze EY, Kim BJ, Jun DH, et al. The fatty liver index: a simple and accurate predictor of colorectal adenoma in an average-risk population. Dis Colon Rectum. 2018; 61: 36-42.

25 Johnson AE, Pollard TJ, Shen L, et al. MIMIC-III, a freely accessible critical care database. Sci Data. 2016; 3: 160035.

26 Iwashyna TJ, Cooke CR, Wunsch H, Kahn JM. Population burden of long-term survivorship after severe sepsis in older Americans. J Am Geriatr Soc. 2012; 60: 1070-1077.

27 Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med. 2013; 41: 1167-1174.

28 Delano MJ, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. Immunol Rev. 2016; 274: 330-353.

29 Johnson AEW, Aboab J, Raffa JD, et al. A comparative analysis of sepsis identification methods in an electronic database. Crit Care Med. 2018; 46: 494-499.

30 GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015; 385: 117-171.

31 Younossi Z, Henry L. Contribution of alcoholic and nonalcoholic fatty liver disease to the burden of liver-related morbidity and mortality. Gastroenterology. 2016; 150: 1778-1785.

32 Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology. 2010; 139: 1246-1256, 1256.e1-5.

33 Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol. 2014; 60: 1310-1324.

34 McLaughlin D, Shellenback L. Sepsis in patients with cirrhosis. AACN Adv Crit Care. 2016; 27: 408-419.

35 Anastasiadis SN, Giouleme OI, Germanidis GS, Vasiliadis TG. Relative adrenal insufficiency in cirrhotic patients. Clin Med Insights Gastroenterol. 2015; 8: 13-17.

36 Byl B, Roucloux I, Crusiaux A, et al. Tumor necrosis factor alpha and interleukin 6 plasma levels in infected cirrhotic patients. Gastroenterology. 1993; 104: 1492-1497.

37 Albillos A, Hera Ad Ade L, Reyes E, et al. Tumour necrosis factor-alpha expression by activated monocytes and altered T-cell homeostasis in ascitic alcoholic cirrhosis: amelioration with norfloxacin. J Hepatol. 2004; 40: 624-631.

38 Caballería L, Pera G, Arteaga I, et al. High prevalence of liver fibrosis among European adults with unknown liver disease: a population-based study. Clin Gastroenterol Hepatol. 2018; 16: 1138-1145.e5.

39 Ben Ayed H, Koubaa M, Yaich S, et al. A new combined predicting model using a non-invasive score for the assessment of liver fibrosis in patients presenting with chronic hepatitis B virus infection. Med Mal Infect. 2019; 49: 607-615.

40 Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology. 2008; 48: 2064-2077.

41 Angeli P, Tonon M, Pilutti C, et al. Sepsis-induced acute kidney injury in patients with cirrhosis. Hepatol Int. 2016; 10: 115-123.