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

INTRODUCTION
Sepsis, a syndrome of pathophysiological abnormalities and severe organ dysfunction induced by infection, is associated with high incidence and mortality rates worldwide.\textsuperscript{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.\textsuperscript{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.\textsuperscript{8} Nonalcoholic fatty liver disease, which is tightly linked to metabolic disorders, has been considered the hepatic manifestation of metabolic syndrome (MetS).\textsuperscript{9,10} The liver fibrosis stage is strongly associated with long-term outcomes in patients with NAFLD.\textsuperscript{10,11}

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

### 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.
and prediabetes, as a hemoglobin A1C 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 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 A1C level of 6.5% or greater, and prediabetes, as a hemoglobin A1C level ranging between 5.7% and 6.5%.

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Liver fibrosis index in septic patients

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 χ² 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
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, 2.972, \( P = 0.03, 95\% \) CI, 1.487–5.951; quartile 4: OR, 4.301, \( P = 0.003, 95\% \) CI, 2.229–8.280).

**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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>APRI (n = 1562)</th>
<th>FIB-4 (n = 1560)</th>
<th>NFS (n = 105)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>769/793</td>
<td>768/792</td>
<td>69/36</td>
</tr>
<tr>
<td>Age, y, median (IQR)</td>
<td>67.56 (52.88–81.25)</td>
<td>67.54 (52.84–81.25)</td>
<td>64.65 (53.88–75.34)</td>
</tr>
<tr>
<td>Age group, y</td>
<td>≤40</td>
<td>181 (11.6)</td>
<td>181 (11.6)</td>
</tr>
<tr>
<td></td>
<td>40–60</td>
<td>385 (24.6)</td>
<td>385 (24.7)</td>
</tr>
<tr>
<td></td>
<td>60–80</td>
<td>561 (35.9)</td>
<td>560 (35.9)</td>
</tr>
<tr>
<td></td>
<td>&gt;80</td>
<td>435 (27.8)</td>
<td>434 (27.8)</td>
</tr>
<tr>
<td>Race or ethnicity</td>
<td>White</td>
<td>1128 (72.2)</td>
<td>1127 (72.2)</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>131 (8.4)</td>
<td>131 (8.4)</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>52 (3.3)</td>
<td>52 (3.3)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>251 (16.1)</td>
<td>250 (16)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Congestive heart failure</td>
<td>360 (23)</td>
<td>359 (23)</td>
</tr>
<tr>
<td></td>
<td>Cardiac arrhythmias</td>
<td>492 (31.5)</td>
<td>492 (31.5)</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>873 (55.9)</td>
<td>873 (56)</td>
</tr>
<tr>
<td></td>
<td>Chronic pulmonary disease</td>
<td>351 (22.5)</td>
<td>350 (22.4)</td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>432 (27.7)</td>
<td>430 (27.6)</td>
</tr>
<tr>
<td>ICU interventions</td>
<td>Vasopressor (first 24 hours)</td>
<td>449 (28.7)</td>
<td>448 (28.7)</td>
</tr>
<tr>
<td></td>
<td>Mechanical ventilation (first 24 hours)</td>
<td>696 (44.6)</td>
<td>695 (44.6)</td>
</tr>
<tr>
<td></td>
<td>Renal replacement therapy</td>
<td>33 (2.1)</td>
<td>33 (2.1)</td>
</tr>
<tr>
<td>Severity of illness (first 24 hours), median (IQR)</td>
<td>SOFA score</td>
<td>4 (3–6)</td>
<td>4 (3–6)</td>
</tr>
<tr>
<td></td>
<td>SAPS II score</td>
<td>36 (29–44)</td>
<td>36 (29–44)</td>
</tr>
<tr>
<td>Length of stay, d, median (IQR)</td>
<td>ICU</td>
<td>2.67 (1.61–5.13)</td>
<td>2.67 (1.61–5.13)</td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>6.94 (4.28–12.02)</td>
<td>6.94 (4.28–12.03)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>28-day mortality</td>
<td>229 (14.7)</td>
<td>229 (14.7)</td>
</tr>
<tr>
<td></td>
<td>90-day mortality</td>
<td>296 (19)</td>
<td>296 (19)</td>
</tr>
<tr>
<td></td>
<td>In-hospital mortality</td>
<td>189 (12.1)</td>
<td>189 (12.1)</td>
</tr>
<tr>
<td>Scoring items</td>
<td>Platelets, ( \times 10^9/\text{l} ), median (IQR)</td>
<td>215 (159–285)</td>
<td>215 (159–284.92)</td>
</tr>
<tr>
<td></td>
<td>AST, IU/l, median (IQR)</td>
<td>36.5 (23–73.75)</td>
<td>36.5 (23–73.92)</td>
</tr>
<tr>
<td></td>
<td>ALT, IU/l, median (IQR)</td>
<td>–</td>
<td>28 (17.5–61.75)</td>
</tr>
<tr>
<td></td>
<td>BMI, kg/m², median (IQR)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Albumin, g/dl, mean (SD)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Prediabetes or diabetes</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

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.
Liver fibrosis index in septic patients

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, 0.60–0.648) 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 non-significant (P = 0.45). Furthermore, the addition of FIB-4 to SOFA was associated with a significant increase in both NRI (0.032, P = 0.005) 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

**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

<table>
<thead>
<tr>
<th>Liver fibrosis index</th>
<th>28-day mortality</th>
<th>90-day mortality</th>
<th>In-hospital mortality</th>
<th>RRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
<td>P value</td>
<td>95% CI</td>
<td>OR</td>
<td>P value</td>
</tr>
<tr>
<td>Quartile 1</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>1.088</td>
<td>0.69</td>
<td>0.722–1.639</td>
<td>1.008–2.34</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>1.305</td>
<td>0.06</td>
<td>0.767–2.184</td>
<td>1.273</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>1.181</td>
<td>0.19</td>
<td>0.876–2.638</td>
<td>1.73</td>
</tr>
</tbody>
</table>

**Abbreviations:** OR, odds ratio; RRT, renal replacement therapy; others, see Figure 1.
**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
Liver fibrosis index in septic patients

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Liver fibrosis index in septic patients

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. Notably, NAFLD has been identified as another crucial risk factor for liver cirrhosis. In a study using data from the National Health and Nutrition Examination Survey, 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. 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. 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. 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. Liver fibrosis, an early manifestation of liver cirrhosis and mainly related to NAFLD, has a high prevalence in adults with unidentified liver diseases. Therefore, it was appropriate to extract septic patients from the database according to the Sepsis-3 criteria.

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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. 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. Johnson et al 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.

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shown to identify histologic fibrosis with reasonable accuracy in retrospective cohort studies.\textsuperscript{11,38} 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.\textsuperscript{21-23} 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%.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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**

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**REFERENCES**


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