Elevated liver fibrosis index FIB-4 is associated with poor clinical outcomes in patients with sepsis, an observational cohort study

Xiaodan Zhu
Wenzhou Medical University First Affiliated Hospital
Xiaoyi Qin
Wenzhou Medical University First Affiliated Hospital
Jingye Pan
Wenzhou Medical University First Affiliated Hospital
Xiang Hu
Wenzhou Medical University First Affiliated Hospital
Wei Zhou (wyyyzw@yahoo.com)
Wenzhou Medical University First Affiliated Hospital https://orcid.org/0000-0003-1268-1950

Research

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

Posted Date: August 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-56712/v1

Abstract

Background: No study for investigating the association between sub-clinical hepatic fibrosis and the outcomes of sepsis was performed before. Therefore, the purpose is to explore the association of liver fibrosis indexes with the outcomes of septic patients without overt chronic liver disease.

Methods: We performed a cohort study using data extracted from the Medical Information Mart for Intensive Care database (v1.4). The patient records of additional external validation were obtained from the First Affiliated Hospital of Wenzhou Medical University. Aspartate aminotransferase-platelet ratio index (APRI), fibrosis-4 (FIB-4) score and non-alcoholic fatty liver disease fibrosis score (NFS) were calculated with previous formulas. The primary outcome was 28-day mortality. The secondary outcomes were 90-day mortality, in-hospital mortality and renal replacement therapy (RRT). We assessed the associations of three indexes with primary and secondary outcomes using logistic regression analysis. Furthermore, we performed multivariable analysis, sensitivity analysis and additional external validation to verify the true strength of the results.

Results: In the FIB-4-sepsis cohort (N = 1560), there was a statistically significant stepwise increase from Quartile 1 to Quartile 4 in the risk of 28-day mortality (Quartile 1: reference; Quartile 2: OR = 1.570, P = 0.061, 95%CI = 0.980–2.515; 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). Similarly, the increased trends could also be found in all secondary outcomes for the FIB-4-sepsis cohort. However, no significant trends were observed in the APRI-sepsis and NFS-sepsis cohorts. The results of multivariable logistic regression analysis, Kaplan-Meier analysis, Cox regression analysis and additional external validation showed good consistency.

Conclusions: FIB-4 index was associated with 28-day mortality, 90-day mortality, in-hospital mortality and RRT in the septic patients without overt chronic liver disease. In other words, the high stage of sub-clinical hepatic fibrosis represented by FIB-4 could reflect the poor outcomes of patients with sepsis.

Introduction

Sepsis, a syndrome of pathophysiological abnormalities and severe organ dysfunction induced by infection, lead to high incidence and high mortality rates worldwide [1,2,3,4]. Several inflammatory markers and scoring models, such as procalcitonin, C-reactive protein, Simplified Acute Physiology Score (SAPS) and Sequential Organ Failure Assessment (SOFA), play important roles in evaluating the severity and prognosis of critical illness [5,6,7].

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

Notably, recent research found that NAFLD predisposing genes were also involved in the pathogenesis of phenotypes of sepsis [12]. Moreover, biomedical and RNA-sequencing based analyses both highlighted significant connections between the acquired and inherited pathogenic, cardiac and inflammatory traits of sepsis and MetS [13]. Then, we also noted that both advanced cirrhosis and MetS lead to poor prognosis of sepsis [14,15].

However, no study for investigating the association between sub-clinical hepatic fibrosis and the outcomes of sepsis was performed before. Several non-invasive fibrosis scoring systems, such as aspartate aminotransferase-platelet ratio index (APRI), fibrosis-4 (FIB-4) score and non-alcoholic fatty liver disease fibrosis score (NFS) [16,17,18], were widely used to evaluate the risk of poor prognosis in chronic liver diseases [19,20], cardiovascular and cerebrovascular diseases [21,22], and malignant tumors [23,24]. Therefore, the purpose of our study is to explore the potential association of liver fibrosis indexes with the outcomes of septic patients without overt chronic liver disease.

Methods

Data source

We performed a cohort study using data extracted from the Medical Information Mart for Intensive Care (MIMIC) clinical database (v1.4) which integrated deidentified and comprehensive clinical data of patients admitted to the Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts [25]. MIMIC III database contains over 58000 hospital admissions data for adult patients and neonates admitted to various critical care units between 2001 and 2012. The Institutional Review Board of the BIDMC (Boston, MA, USA) and Massachusetts Institute of Technology (Cambridge, MA, USA) have approved the use of the MIMIC III database for authorized users. Wei Zhou has been allowed to download the database after completed the "Data or Specimens Only Research" course (Record ID: 25222342). Requirement for individual patient consent was waived for the reason that the project neither contained the protected health information nor impacted clinical care [25].

The patient records of additional external validation were obtained from the First Affiliated Hospital of Wenzhou Medical University (Wenzhou, Zhejiang, China) after approval from the Ethical Committee. All study participants provided written informed consent, and their data confidentiality were protected.

Study participants

A flowchart of the inclusion and exclusion procedure for the MIMIC III database was depicted in Figure 1. We adopted the third international consensus definitions for sepsis (Sepsis-3, diagnosis flowchart was presented in Figure S1) to extract the 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 (blood, urine, sputum, etc) [1]. In other words, if the culture was obtained, the antibiotic was required to be administered within 72 hours, whereas if the antibiotic was first, the culture was required within 24 hours [1]. Moreover, we set a suspected infection period during 24 hours before and after intensive care unit (ICU) admission. Patients in the CareVue and MetaVision information systems of MIMIC were admitted before and after 2008, respectively. Only patient data stored in the MetaVision system were collected for future analysis. The antibiotic prescription data were only available after 2002, thus, there was a fraction (1/7) of the CareVue patients who had missing data for the suspected infection definition. It was easiest to limit the cohort to the MetaVision system, as the sample size was sufficient.

To minimize the contribution of potential confounding for future analysis, patients with aged 16 years or younger, repeat admissions to the ICU, alcohol abuse, overt chronic liver disease, haematological and solid malignancies, and chronic kidney disease were excluded from initial cohort. Furthermore, the exclusion criteria for sepsis cohort were as follows: current service related with (1) cardiac surgery, (2) vascular surgical and (3) thoracic surgical. Because we believed that these sub-populations were physiologically abnormal but due to non-sepsis reasons.

The data of 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 to 90 days after admission.

Data extraction

The data were extracted from the MIMIC III database and our hospital including gender, age, race, body mass index (BMI), laboratory data, ICU interventions, vital statistics data, comorbidities and length of stay (LOS). Severity of illness scores including SAPS and SOFA were computed on the basis of prescribed criteria [6,7]. The averages of BMI, laboratory data and vital statistics data during the first 24 hours of ICU admission were regarded as baseline data. The scores of SAPS and SOFA, as well as interventions of vasopressor and mechanical ventilation were evaluated during the first 24 hours of ICU stay.

Exposures and outcomes

Three liver fibrosis indexes (APRI, FIB-4 and NFS) were calculated with previous formulas (Figure 2) [16,17,18]. These indexes were evaluated at baseline on factors believed to reflect the initial condition of ICU admission, and patients were categorized by quartile of index values at baseline. Diabetes was defined as diagnosis of International Classification of Diseases-9 (ICD-9) codes or hemoglobin A1c (HbA1c) ≥ 6.5%, and prediabetes as HbA1c 5.7% – 6.5%. As HbA1c represented the blood glucose of patients for 2 to 3 months, the value of HbA1c within 7 days after ICU admission can be regarded as baseline data.

The primary end point for the present study was 28-day mortality. The secondary end points were 90-day mortality, in-hospital mortality and renal replacement therapy (RRT). Mortality information of MIMIC III database was calculated based on dates of

admission and death from the Social Security Death records.

Statistical analysis

Kolmogorov-Smirnov normality test was used to check the normality assumption for numerical variables. Differences in the normally and non-normally distributed variables were compared using the unpaired Student's t test and Wilcoxon rank-sum test, respectively. Comparisons for categorical variables were performed by Pearson $\chi 2$ test and Fisher exact test. Normally distributed data were expressed as mean ± standard deviation, and non-normally distributed data were expressed as median with inter-quartile range. Categorical variables were expressed as frequency with percentage.

We assessed the associations of three indexes with primary and secondary outcomes using logistic regression analysis. The results were presented in form of odds ratio (OR) with 95% confidence interval (CI). The septic patients were categorized according to quartile of index values at baseline, and Quartile 1 was considered as the reference group for all subsequent analyses.

A two-sided P-value < 0.05 was regarded as representing statistical significance. Statistical analyses were performed using SPSS software 20.0 (SPSS, Chicago, IL, USA), MedCalc software 19.0.5 (MedCalc Software, Ostend, Belgium) and MATLAB software R2018b (MathWorks, Natick, MA, USA).

Multivariable analysis, sensitivity analysis and external validation

Due to the influences of missing data and potentially relevant confounding factors, several additional analyses were performed to further verify the predictive abilities of liver fibrosis indexes.

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

Second, subset analyses on the basis of two different liver function indexes were performed to determine whether patients with abnormal baseline liver function distorted the results. Albumin and bilirubin, representing synthesis and metabolism of liver, were divided to normal and abnormal groups according to their normal ranges.

Third, we did a comparative analysis between sepsis and non-sepsis patients with index values. Moreover, we performed an additional analysis to see whether the similar results also existed in non-sepsis patients.

Fourth, a number of patients in the primary analysis were excluded because of no complete index data during the first 24 hours of ICU admission. Thus, a sensitivity analysis was performed for patients who did not have baseline index values but had available values during ICU stay.

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

Sixth, we repeated the primary analysis using Kaplan-Meier (K-M) and Cox regression analysis instead of logistic regression analysis to evaluate the impact of different analytical methods. The results were presented in form of survival curve and hazard ratio (HR) with 95% CI, respectively.

Finally, additional external validation was introduced to further verify whether the similar results also existed in the East Asian population.

Results

Baseline characteristics of study cohort

Baseline characteristic distributions of APRI-sepsis, FIB-4-sepsis and NFS-sepsis cohorts were summarized in Table 1. The median APRI, FIB-4 and NFS scores were 0.537 (inter-quartile range, 0.296 to 1.339), 2.365 (inter-quartile range, 1.305 to 4.837) and 0.791 (inter-quartile range, −0.198 to 1.858), respectively.

Association of APRI, FIB-4 and NFS with primary and secondary outcomes

As shown in the FIB-4-sepsis cohort of Table 2, there was a statistically significant stepwise increase from Quartile 1 to Quartile 4 in the risk of 28-day mortality (Quartile 1: reference; Quartile 2: OR = 1.570, P = 0.061, 95%CI = 0.980–2.515; 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 by increasing quartile of FIB-4 were as follows: Quartile 1: 8.2%, Quartile 2: 12.3%, Quartile 3: 17.4%, Quartile 4: 20.8%. Similarly, the increased trends could also be found in all secondary outcomes for the FIB-4-sepsis cohort. However, no significant trends were observed in the APRI-sepsis and NFS-sepsis cohorts.

Multivariable analysis, sensitivity analysis and external validation

In the univariate analysis, FIB-4 was significantly correlated with primary and secondary outcomes. Thus, multivariable analysis, sensitivity analysis and additional external validation were preformed to further explore the effect of FIB-4 on outcomes. To assess bias from missing data due to incomplete baseline data, comparison of baseline characteristics of final study cohort vs. missing data cohort was presented in Table S1.

As presented in Figure 3, the stepwise increase trends from Quartile 1 to Quartile 4 in the risk of death at 28 days, 90 days and in-hospital remained statistically significant after multivariable adjustments.

The cut-off values of albumin and bilirubin were defined as 3.5 g/dL and 1 mg/dL, respectively. As presented in Table S2, the stepwise increase trend of 28-day mortality from Quartile 1 to Quartile 4 was observed in the septic patients with low albumin (Quartile 1: reference; Quartile 2: OR = 1.821, P = 0.099, 95%CI = 0.893–3.714; Quartile 3: OR = 3.078, P = 0.001, 95%CI = 1.569–6.039; Quartile 4: OR = 3.770, P < 0.001, 95%CI = 1.956–7.269) instead of high albumin. However, subset analysis of bilirubin reached the opposite results. There was a statistically significant increase trend from Quartile 1 to Quartile 4 for normal bilirubin group in the risk of 28-day mortality (Quartile 1: reference; Quartile 2: OR = 1.624, P = 0.068, 95%CI = 0.965–2.736; Quartile 3: OR = 2.419, P = 0.001, 95%CI = 1.471–3.979; Quartile 4: OR = 4.073, P < 0.001, 95%CI = 2.479–6.693). Moreover, these similar trends could also be found in all secondary outcomes.

For the baseline FIB-4 value, there was a numerical difference but no statistical difference between sepsis cohort [N =1560, 2.365 (inter-quartile range, 1.305 to 4.837)] and non-sepsis cohort [N = 7968, 2.193 (inter-quartile range, 1.190 to 5.024)] (P = 0.076). For the analysis of non-sepsis patients, the same trend from Quartile 1 to Quartile 4 remained in the risk of 28-day mortality (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; Quartile 4: OR = 6.386, P < 0.001, 95%CI = 5.153–7.914).

A total of 215 patients who did not have baseline FIB-4 values but had available values during ICU stay were included in a sensitivity analysis. However, no significant trend was observed between FIB-4 and 28-day mortality as similar as the primary analysis (Quartile 1: reference; Quartile 2: OR = 2.174, P = 0.229, 95%CI = 0.613–7.704; Quartile 3: OR = 0.750, P = 0.716, 95%CI = 0.160–3.524; Quartile 4: OR = 5.743, P = 0.003, 95%CI = 1.784–18.490).

Performance comparisons of different prognostic models were summarized in Figure S2 via ROC curve. The AUROC for identifying 28-day mortality when using SOFA model and FIB-4-SOFA model were 0.624 ± 0.020 (95% CI: 0.600–0.648) and 0.649 ± 0.019 (95% CI: 0.625–0.673), respectively. Meanwhile, the AUROC were 0.762 ± 0.016 (95% CI: 0.740–0.783) and 0.765 ± 0.016 (95% CI: 0.743–0.785) for SAPS Ⅱ model and FIB-4-SAPS Ⅱ model, respectively. Comparative analyses showed that the addition of FIB-4 to SOFA improved the AUROC with statistical significance (P = 0.046), whereas no statistical significance for the addition of FIB-4 to SAPS Ⅱ (P = 0.447). Furthermore, the addition of FIB-4 to SOFA was associated with significant increases 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 significant increase in NRI only (0.032, P = 0.005).

Additionally, the results of repeated K-M (Figure 4) and Cox regression analysis (Table S3) were consistent with logistic regression analysis, which indicated that the conclusion was not interfered by different analytical methods.

Finally, a new data (N = 35) collected from our hospital as additional external validation also showed a similar result (Table S4) with the primary analysis, which indicated that FIB-4 score had good generalization for predicting the outcomes of patients with sepsis to some extent.

Discussion

The present study revealed that FIB-4 index could be used as an independent short-term mortality scoring system to evaluate the outcomes of the septic patients without overt chronic liver disease. In other words, the high stage of sub-clinical hepatic fibrosis represented by FIB-4 could reflect the poor outcomes of patients with sepsis. Similarly, the significant association could also be observed in non-sepsis patients, which suggested that the role of FIB-4 may be generalized to all critically ill patients. Furthermore, FIB-4 index, as an effective supplement to the existing prognostic scoring system, improved the predictive performance of outcomes to some extent. To assess the impact of confounding factors, we performed multivariable logistic regression analysis, K-M analysis, Cox regression analysis and additional external validation, and all the results showed good consistency.

Sepsis, a syndrome of immense clinical importance, accounts for high incidence, high mortality and high ICU admission rates in recent years [4,26,27]. The latest Sepsis-3 definition, replacing previous definitions of sepsis gradually, is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection [1,28]. Johnson AEW et al. performed a comparative analysis of sepsis identification methods in MIMIC □ database (v1.4), and indicated that Sepsis-3 criteria had several advantages over previous methods as follows: (1) less susceptibility to coding practices changes, (2) provision of temporal context because of extracting sepsis cohort by suspected of infection with associated organ failure at a time point not by ICD-9 codes, and (3) more conform to the contemporary understanding of the pathophysiology of sepsis [29]. Therefore, it is appropriate to extract the septic patients from database via the Sepsis-3 criteria.

Liver cirrhosis is one of the leading causes of death and disability worldwide, mainly caused by hepatitis B, C and alcohol abuse [30]. Notably, NAFLD has become another important factor for liver cirrhosis [31]. In a study using the National Health and Nutrition Examination Survey data, 7% of NAFLD patients progressed to cirrhosis in a median follow up time of 178.27 months [31]. Several studies have confirmed that liver cirrhosis was identified as an independent poor prognostic factor in patients with sepsis [14,32,33]. The mechanisms for increased mortality in cirrhotic patients with sepsis is 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 cytokines release for the hypothalamus-pituitary-adrenal axis and glucocorticoid receptor function [34,35]. In addition, abnormalities in cell-mediated immunity, humoral immunity and cytokines release (tumor necrosis factor-alpha and interleukin-6) that mediate systemic inflammation may be another major causes for 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 unknown liver disease [38]. However, the association between the stage of sub-clinical hepatic fibrosis and the outcomes of sepsis remains unclear. Notably, in a longitudinal study of patients with NAFLD, fibrosis stage was the only histologic feature independently associated with overall mortality, liver transplantation, and liver-related events [10]. Recently, non-invasive fibrosis scoring systems have been shown to identify histologic fibrosis with reasonable accuracy in the retrospective cohort studies [11,39]. Of all the fibrosis scoring systems, the APRI, FIB-4 score and NFS are widely used in prognostic evaluation of non-liver diseases [21,22,23,24], however, little is known about the application of liver fibrosis indexes in infection and inflammation. Thus, further studies are warranted to explore the possible mechanisms on increased mortality in septic patients with high stage of sub-clinical hepatic fibrosis. Obviously, the mechanisms described in patients with overt cirrhosis have certain reference significance.

The previous studies have shown that acute kidney injury (AKI) was frequent in patients with cirrhosis, whose incidence of AKI reached approximately 20% [40]. The pathogenesis of sepsis-induced AKI in patients with cirrhosis is well in keep with the “splanchnic arterial vasodilation hypothesis”, which involves arterial vasodilation and reduction in cardiac output [41]. Moreover, in the context of sepsis, circulating endotoxins and pro-inflammatory cytokines impair portal hypertension and liver function, further producing synergistic negative effects on patients with cirrhosis [41]. Similar, FIB-4 score also has a certain correlation with RRT during ICU stay in our study. After excluding patients with chronic kidney disease, the high stage of sub-clinical hepatic fibrosis could

reflect the high probability of severe AKI in patients with sepsis. Additionally, it is worth noting that FIB-4 index is also applicable to non-sepsis patients. Thus, we hypothesize that fibrosis stage may be a risk factor for the outcomes of critically ill patients.

FIB-4 index have potential strengths for clinical application. First, FIB-4 formula, simply composed of age, platelet, alanine aminotransferase and aspartate aminotransferase, may be more suitable for rapid assessment of patients with sepsis. Second, even though there are several effective prognostic scoring models for sepsis, FIB-4 model could also be regarded as a supplementary tool in clinical practice. Third, considering for cost and safety, FIB-4 index can be used as a feasible alternative for liver imaging and liver biopsy in evaluating the stage of liver fibrosis.

Our study also has several limitations. First, our main study with the retrospective design is vulnerable to selection bias as the result of inclusion of a single-center samples only and exclusion of patients with missing data. Although the sample size of additional external validation is limited, results similar to the primary analysis are also observed. Second, liver biopsy is still the gold standard method for assessing the severity of liver fibrosis. Over-estimation or under-estimation for fibrosis stage, which could have stemmed from the discrepancy of FIB-4 prediction accuracy, may contribute to estimation bias for the true strength of association of fibrosis stage with adverse outcomes. However, significant estimation bias is unlikely because FIB-4 score has been shown to identify fibrosis stage with reasonable accuracy in the recent studies [15, 39]. Therefore, further prospective studies are warranted to validate our findings with methods of fibrosis stage by liver imaging or liver biopsy.

Conclusions

The present study uncovered for the first time that FIB-4 index was associated with 28-day mortality, 90-day mortality, in-hospital mortality and RRT in the septic patients without overt chronic liver disease. In other words, the high stage of sub-clinical hepatic fibrosis represented by FIB-4 could reflect the poor outcomes of patients with sepsis. FIB-4 index, as an effective supplement to the existing prognostic scoring systems, might help the graded management of patients with different prognosis scores and remind physicians to pay more attention to patients with high risk score.

Abbreviations

AKI, acute kidney injury; APRI, aspartate aminotransferase-platelet ratio index; AUROC, area under the receiver operating characteristic curve; BIDMC, Beth Israel Deaconess Medical Center; BMI, body mass index; CI, confidence interval; FIB-4, fibrosis-4; HbA1c, hemoglobin A1c; HR, hazard ratio; ICD-9, International Classification of Diseases-9; ICU, intensive care unit; IDI, integrated discrimination improvement; K-M, Kaplan-Meier; LOS, length of stay; MetS, metabolic syndrome; MIMIC Ⅲ, Medical Information Mart for Intensive Care Ⅲ; NAFLD, non-alcoholic fatty liver disease; NFS, non-alcoholic fatty liver disease fibrosis score; NRI, net reclassification improvement; OR, odds ratio; ROC, receiver operating characteristic; RRT, renal replacement therapy; SAPS Ⅱ, Simplified Acute Physiology Score Ⅱ; SOFA, Sequential Organ Failure Assessment.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of the Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology have approved the use of the MIMIC III database. Requirement for individual patient consent was waived because the project did not impact clinical care and all protected health information was deidentified. The study of external validation was approved by the Ethical Committee of the First Affiliated Hospital of Wenzhou Medical University. All study participants provided written informed consent, and their data confidentiality were protected.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

This work was supported by a grant from Research Incubation Project of the First Affiliated Hospital of Wenzhou Medical University (Grant NO. FHY2019088).

Authors' contributions

XDZ and WZ conceived and designed this study; XYQ, XH and WZ helped with the collection and assembly of data. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315(8):801–10.
2. Lagu T, Rothberg MB, Shieh MS, Pekow PS, Steingrub JS, Lindenauer PK. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. Crit Care Med. 2012;40(3):754–61.
3. Kaukonen KM, Bailey M, Suzuki S, Pilcher D, Bellomo R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000-2012. JAMA. 2014;311(13):1308–16.
4. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med. 2001;29(7):1303–10.
5. Jain S, Sinha S, Sharma SK, Samantaray JC, Aggrawal P, Vikram NK, 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, Tourneur M, Loirat P. Simplified acute physiology score II for measuring severity of illness in intermediate care units. Crit Care Med. 1998;26(8):1368–71.
7. Ferreira FL, Bota DP, Bross A, Mélot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA. 2001;286(14):1754–8.
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(4):1801585.
9. Yki-Järvinen H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome. Lancet Diabetes Endocrinol. 2014;2(11):901–10.
10. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya P, 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(2):389–97.e10.
11. Marella HK, Reddy YK, Jiang Y, Ganguli S, Podila PSB, Snell PD, et al. Accuracy of Noninvasive Fibrosis Scoring Systems in African American and White Patients With Nonalcoholic Fatty Liver Disease. Clin Transl Gastroenterol. 2020;11(4):e00165.
12. Sookoian S, Pirola CJ. Genetics of Nonalcoholic Fatty Liver Disease: From Pathogenesis to Therapeutics. Semin Liver Dis. 2019;39(2):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(3):1016–20.

15. Tracy BM, Wilson JM, Staley C, Frias B, Schenker ML, Gelbard RB. Metabolic Syndrome: Major Risk Factor for Morbidity and Mortality in Severely Injured Trauma Patients. J Am Coll Surg. 2020;230(1):145–150.
16. Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, 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.
17. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology. 2006;43(6):1317–25.
18. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;45(4):846–54.
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(4):1357–65.
20. Barré T, Protopopescu C, Bani-Sadr F, Piroth L, Rojas Rojas T, Salmon-Ceron D, 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(4):1182–1197.
21. Chen Q, Li Q, Li D, Chen X, Liu Z, Hu G, 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, Iadecola C, Merkler AE, Jesudian A, et al. Liver Fibrosis Indices and Outcomes After Primary Intracerebral Hemorrhage. Stroke. 2020;51(3):830–837.
23. Park JH, Choi IS, Han KD, Park H, Kim KH, Kim JS. Association Between Fatty Liver Index and Risk of Breast Cancer: A Nationwide Population-Based Study. Clin Breast Cancer. 2020;S1526–8209(20)30039–2.
24. Ze EY, Kim BJ, Jun DH, Kim JG, Kang H, Lee DY. The Fatty Liver Index: A Simple and Accurate Predictor of Colorectal Adenoma in an Average-Risk Population. Dis Colon Rectum. 2018;61(1):36–42.
25. Johnson AE, Pollard TJ, Shen L, Lehman LW, Feng M, Ghassemi M, 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(6):1070–7.
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(5):1167–74.
28. Delano MJ, Ward PA. The immune system's role in sepsis progression, resolution, and long-term outcome. Immunol Rev. 2016;274(1):330–353.
29. Johnson AEW, Aboab J, Raffa JD, Pollard TJ, Deliberato RO, Celi LA, et al. A Comparative Analysis of Sepsis Identification Methods in an Electronic Database. Crit Care Med. 2018;46(4):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(9963):117–71.
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(8):1778–85.
32. Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology. 2010;139(4):1246–56, 1256.e1–5.
33. Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol. 2014;60(6):1310–24.
34. McLaughlin D, Shellenback L. Sepsis in Patients With Cirrhosis. AACN Adv Crit Care. 2016;27(4):408–419.
35. Anastasiadis SN, Giouleme OI, Germanidis GS, Vasiliadis TG. Relative adrenal insufficiency in cirrhotic patients. Clin Med Insights Gastroenterol. 2015;8:13–7.
36. Byl B, Roucloux I, Crusiaux A, Dupont E, Devière J. Tumor necrosis factor alpha and interleukin 6 plasma levels in infected cirrhotic patients. Gastroenterology. 1993;104(5):1492–7.
37. Albillos A, Hera Ad Ade L, Reyes E, Monserrat J, Muñoz L, Nieto M, 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(4):624–31.
38. Caballería L, Pera G, Arteaga I, Rodríguez L, Alumà A, Morillas RM, et al. High Prevalence of Liver Fibrosis Among European Adults With Unknown Liver Disease: A Population-Based Study. Clin Gastroenterol Hepatol. 2018;16(7):1138–1145.e5.
39. Ben Ayed H, Koubaa M, Yaich S, Rekik K, Ben Jemaa T, Maaloul I, 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(8):607–615.
40. Garcia-Tsao G, Parikh CR, Viola A. Acute kidney injury in cirrhosis. Hepatology. 2008;48(6):2064–77.
41. Angeli P, Tonon M, Pilutti C, Morando F, Piano S. Sepsis-induced acute kidney injury in patients with cirrhosis. Hepatol Int. 2016;10(1):115–23.

Tables

Table 1 Baseline characteristic distributions of APRI-sepsis, FIB-4-sepsis and NFS-sepsis cohorts

Characteristics	APRI	FIB-4	NFS
	N = 1562	N = 1560	N = 105
Gender (men/women)	769/793	768/792	69/36
Age (years)	67.56 (52.88–81.25)	67.54 (52.84–81.25)	64.65 (53.88–75.34)
≤ 40, n (%)	181 (11.6)	181 (11.6)	9 (8.6)
> 40, ≤ 60, n (%)	385 (24.6)	385 (24.7)	36 (34.3)
> 60, ≤ 80, n (%)	561 (35.9)	560 (35.9)	43 (41.0)
> 80, n (%)	435 (27.8)	434 (27.8)	17 (16.2)
Race			
White, n (%)	1128 (72.2)	1127 (72.2)	72 (68.6)
Black, n (%)	131 (8.4)	131 (8.4)	10 (9.5)
Hispanic, n (%)	52 (3.3)	52 (3.3)	1 (1.0)
Other, n (%)	251 (16.1)	250 (16.0)	22 (21.0)
Comorbidities			
Congestive heart failure, n (%)	360 (23.0)	359 (23.0)	39 (37.1)
Cardiac arrhythmias, n (%)	492 (31.5)	492 (31.5)	40 (38.1)
Hypertension, n (%)	873 (55.9)	873 (56.0)	72 (68.6)
Chronic pulmonary, n (%)	351 (22.5)	350 (22.4)	22 (21.0)
Diabetes, n (%)	432 (27.7)	430 (27.6)	44 (41.9)
ICU interventions			
Vasopressor (first 24 hours), n (%)	449 (28.7)	448 (28.7)	43 (41.0)
Mechanical ventilation (first 24 hours), n (%)	696 (44.6)	695 (44.6)	57 (54.3)
Renal replacement therapy, n (%)	33 (2.1)	33 (2.1)	3 (2.9)
Severity of illness scores (first 24 hours)			
SOFA score	4.00 (3.00–6.00)	4.00 (3.00–6.00)	4.00 (3.00–6.00)
SAPS Ⅱ score	36.00 (29.00–44.00)	36.00 (29.00–44.00)	35.34 ± 11.00
Length of stay			
ICU LOS (days)	2.67 (1.61–5.13)	2.67 (1.61–5.13)	3.05 (1.97–5.12)
Hospital LOS (days)	6.94 (4.28–12.02)	6.94 (4.28–12.03)	6.81 (5.04–11.83)
Outcomes			
28-day mortality, n (%)	229 (14.7)	229 (14.7)	9 (8.6)
90-day mortality, n (%)	296 (19.0)	296 (19.0)	12 (11.4)
In-hospital mortality, n (%)	189 (12.1)	189 (12.1)	9 (8.6)
Scoring items			
Platelet (10^9/L)	215.00 (159.00–285.00)	215.00 (159.00–284.92)	221.51 ± 82.84
AST (IU/L)	36.50 (23.00–73.75)	36.50 (23.00–73.92)	39.00 (22.50–73.25)
ALT (IU/L)		28.00 (17.50–61.75)	27.00 (19.50–50.50)

BMI (kg/m^2)	27.98 (25.13–33.54)
Albumin (g/dL)	3.54 ± 0.52
Prediabetes/diabetes, n (%)	85 (81.0)

Data were expressed as mean ± standard deviation, median (interquartile range) or frequency (percentage). ALT, alanine aminotransferase; APRI, aspartate aminotransferase-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4; ICU, intensive care unit; LOS, length of stay; NFS, non-alcoholic fatty liver disease fibrosis score; SAPS Ⅱ, Simplified Acute Physiology Score Ⅱ; SOFA, Sequential Organ Failure Assessment.

Table 2 Association of APRI, FIB-4 and NFS with primary and secondary outcomes

Liver Fibrosis Indexes	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	0.686	0.722–1.639	1.129	0.521	0.780–1.633	1.145	0.566	0.722–1.815	1.671	0.484	0.397–7.041
Quartile 3	1.305	0.190	0.876–1.943	1.373	0.084	0.958–1.966	1.521	0.062	0.980–2.361	1.675	0.482	0.398–7.059
Quartile 4	1.181	0.419	0.789–1.770	1.187	0.360	0.823–1.712	1.453	0.098	0.933–2.261	6.954	**0.002**	2.049–23.598
FIB-4												
Quartile 1	Reference			Reference			Reference			Reference		
Quartile 2	1.570	0.061	0.980–2.515	1.536	**0.046**	1.008–2.340	1.743	**0.039**	1.029–2.952	2.016	0.324	0.501–8.117
Quartile 3	2.363	**<0.001**	1.512–3.692	2.486	**<0.001**	1.670–3.699	2.664	**<0.001**	1.619–4.385	2.702	0.144	0.711–10.260
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	1.000	1.000	0.222–4.512	1.000	1.000	0.222–4.512	1.394	0.685	0.279–6.953	–	0.998	–
Quartile 3	<0.001	0.998	–	0.212	0.179	0.022–2.035	<0.001	0.998	–	1.000	1.000	–
Quartile 4	0.220	0.190	0.023–2.119	0.717	0.685	0.144–3.578	0.639	0.640	0.098–4.180	–	0.998	–

The significant P-value was indicated in bold. APRI, aspartate aminotransferase-platelet ratio index; CI, confidence interval; FIB-4, fibrosis-4; NFS, non-alcoholic fatty liver disease fibrosis score; OR, odds ratio; RRT, renal replacement therapy.

Figures

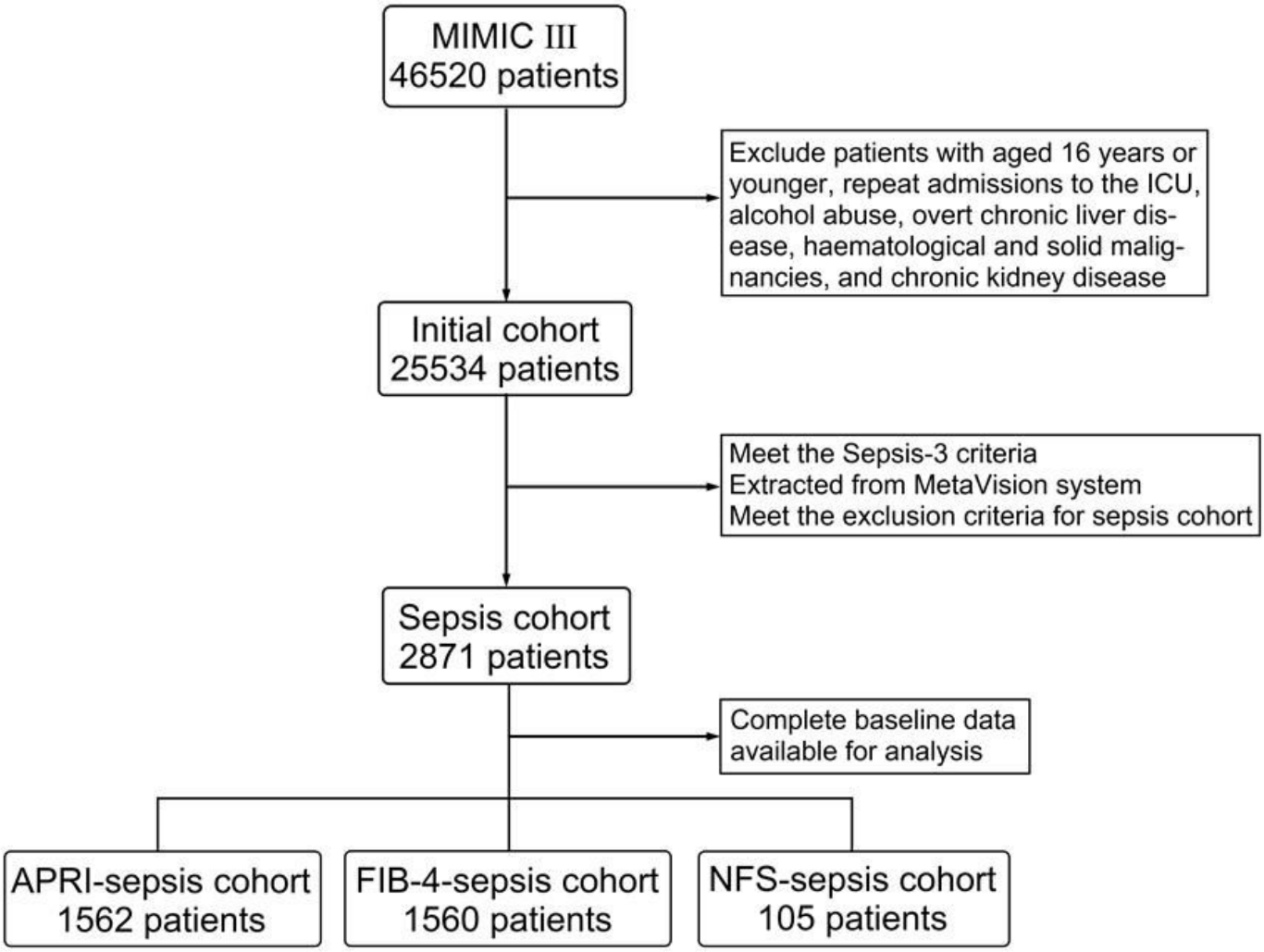

Figure 1

The flowchart of the inclusion and exclusion procedure for the MIMIC III database. APRI, aspartate aminotransferase-platelet ratio index; FIB-4, fibrosis-4; ICU, intensive care unit; MIMIC Ⅲ, Medical Information Mart for Intensive Care Ⅲ; NFS, non-alcoholic fatty liver disease fibrosis score.

$$\mathrm{APRI} = \frac{\frac{\mathrm{AST\,(IU/L)}}{\mathrm{ULN}^{\#}}}{\mathrm{PLT}\,(10^{9}/\mathrm{L})} * 100$$

$$\mathrm{FIB\text{-}4} = \frac{\mathrm{age\,(years)} * \mathrm{AST\,(IU/L)}}{\mathrm{PLT}\,(10^{9}/\mathrm{L}) * \sqrt{\mathrm{ALT\,(IU/L)}}}$$

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

$$(\mathrm{Yes} = 1,\ \mathrm{No} = 0) + 0.99 * \frac{\mathrm{AST\,(IU/L)}}{\mathrm{ALT\,(IU/L)}} - 0.013 * \mathrm{PLT}\,(10^{9}/\mathrm{L}) - 0.66 * \mathrm{albumin\,(g/dL)}$$

Figure 2

Formulas for three liver fibrosis indexes (APRI, FIB-4 and NFS). #, 37 IU/L for male and 31 IU/L for female. ALT, alanine aminotransferase; APRI, aspartate aminotransferase-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4; NFS, non-alcoholic fatty liver disease fibrosis score; PLT, platelet; ULN, upper limit of normal.

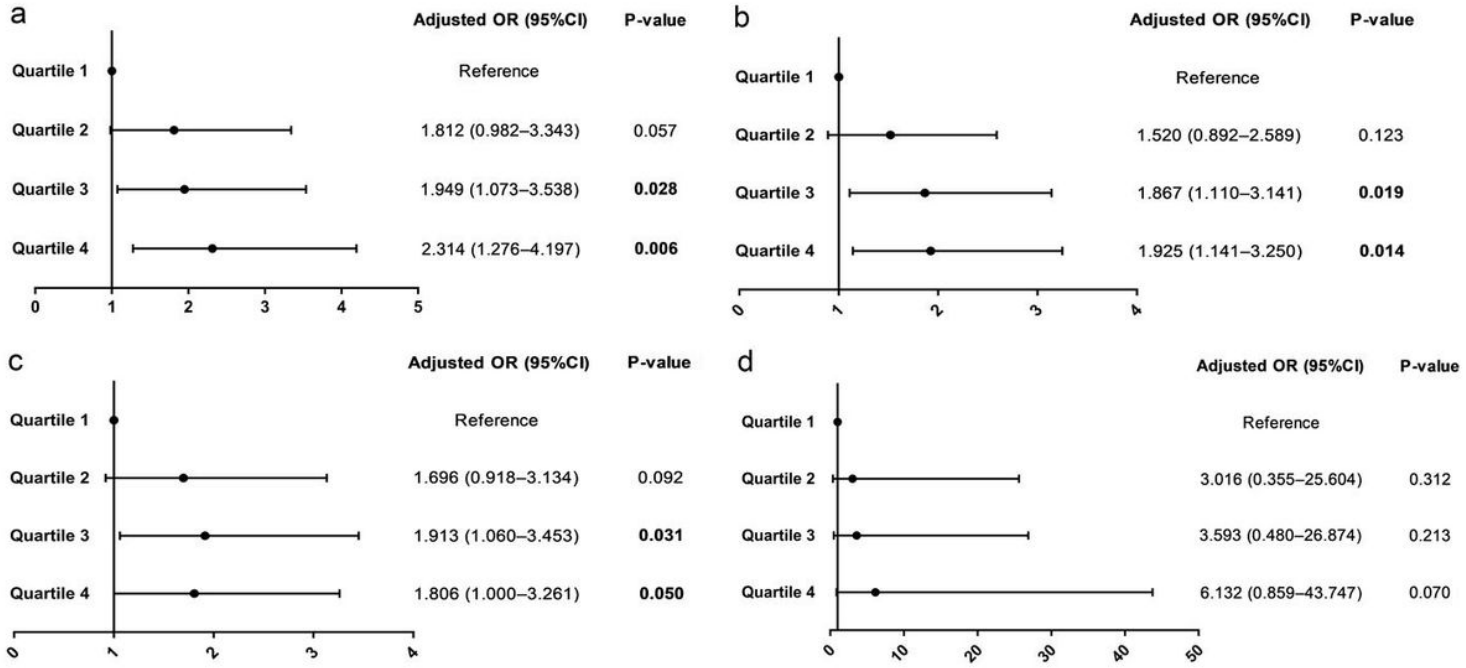

Figure 3

Formulas for three liver fibrosis indexes (APRI, FIB-4 and NFS). #, 37 IU/L for male and 31 IU/L for female. ALT, alanine aminotransferase; APRI, aspartate aminotransferase-platelet ratio index; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, fibrosis-4; NFS, non-alcoholic fatty liver disease fibrosis score; PLT, platelet; ULN, upper limit of normal.

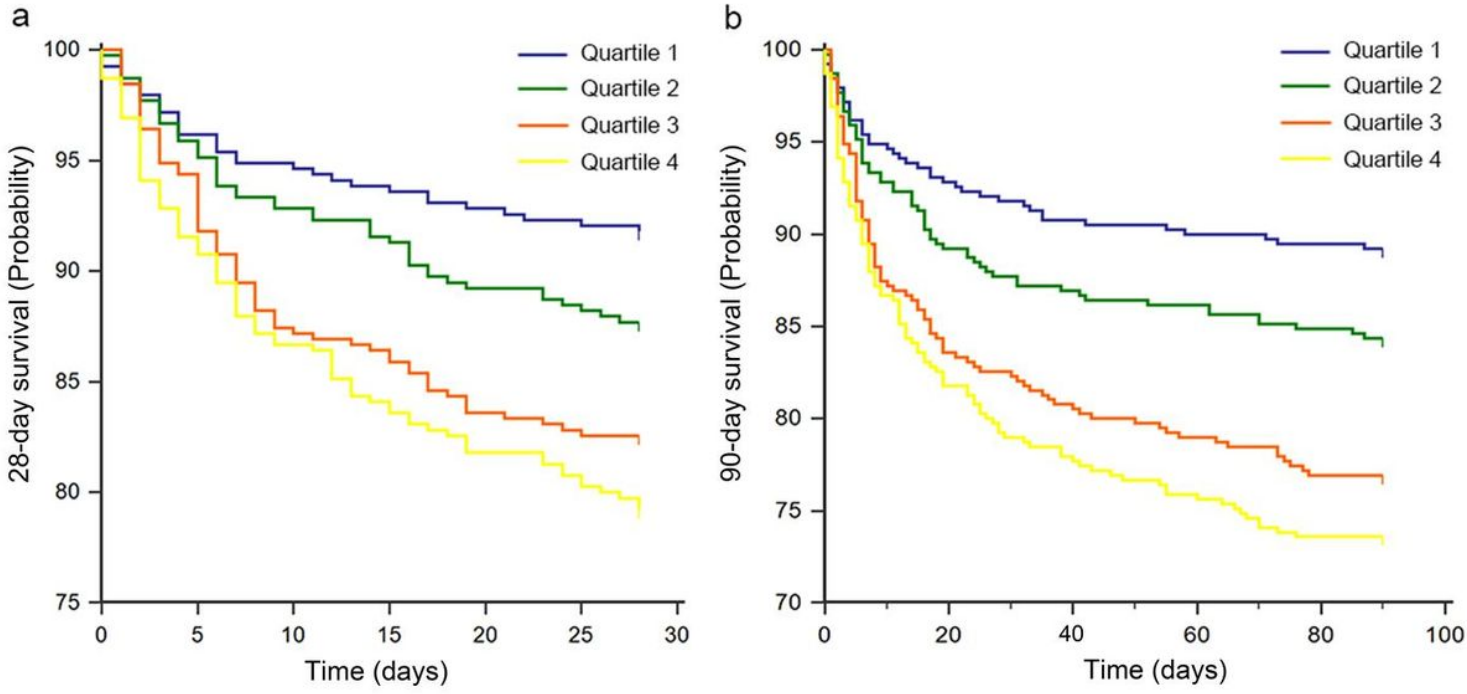

Figure 4

Kaplan-Meier survival analysis in the FIB-4-sepsis cohort. (a) 28-day survival curve and (b) 90-day survival curve.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS4.doc
- TableS4.doc
- TableS3.doc
- TableS3.doc
- FigureS2.tif
- FigureS2.tif
- TableS2.doc
- TableS2.doc
- TableS1.doc
- TableS1.doc
- FigureS1.tif
- FigureS1.tif