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Outcome of sepsis and prediction of mortality risk

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Outcome of sepsis and prediction of mortality risk

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Editorial: Outcome of sepsis and prediction of mortality risk

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Editorial on the Research Topic
Outcome of sepsis and prediction of mortality risk

Sepsis mortality is a serious concern in healthcare, as it remains one of the leading causes of death worldwide (1). Early identification and prediction of sepsis risk are crucial to improve patient outcomes (2). Advances in machine learning and data analytics have enabled healthcare professionals to develop more accurate predictive models, leveraging patient data to identify those at higher risk (3, 4). Timely intervention and appropriate care can make a significant difference in reducing sepsis mortality rates, highlighting the importance of predictive tools in the battle against this life-threatening condition.

The aim of the Research Topic of the articles in this issue, dedicated to patients with sepsis and septic shock, was to outline some interesting issues on mortality and its risk assessment. Thirteen articles were submitted to this thematic collection, all the articles were original research studies.

It is widely accepted that serum lactate is a parameter of tissue perfusion and represents a marker of sepsis diagnosis. López et al. focused on the lactate trend and made a comparison between septic oncological and non-oncological patients in a retrospective analysis of a prospective database. They showed that hyperlactatemia was associated with higher mortality, and this condition was more frequent in cancer patients than in non-oncological ones (65 vs. 49.1%, $p = 0.013$). In conclusion, immunosuppression due to the malignant disease or its treatment increased the risk for severe infections; lactate levels and poor performance status represented tools for the stratification risk of septic oncological patients. In addition, cancer patients are more exposed to acute kidney injury (AKI) during sepsis, as Yang et al. demonstrated in their retrospective study. Elevated serum lactate levels, high SOFA score and septic shock were strictly related to septic AKI in cancer patients. The 28-day–outcome after ICU admission was worse in oncologic patients with septic AKI than in those without it. Continuous renal replacement therapy, which is an effective treatment for AKI, did not influence the short-term prognosis of cancer patients with septic AKI in the ICU. These considerations could be useful to guide the definition of prognosis and treatment for these critically ill patients. Again, Chen et al. considered hyperlactatemia combined with hypoalbuminemia and patients' age in terms of Lactate/Albumin Ratio and Lactate/Albumin Ratio × Age Score in the assessment of prognosis in patients with sepsis. The statistical analysis showed that the Lac/Alb ratio was an independent risk death factor in septic patients. However, the Lac/Alb × age score was more accurate in the assessment of prognosis, so it could represent a useful tool for clinicians.

In the context of sepsis biomarkers, Peng et al. focused on hyperbilirubinemia and hepatic dysfunction. The propensity score matching showed that septic patients without previous hepatic disease and with total bilirubin (TBIL) levels during ICU admission equal to or more than 5 mg/dl had a higher risk of 1-year mortality than those with TBIL < 5 mg/dl. Moreover, recent studies showed that heparin-binding protein (HBP), a protein in the polymorphonuclear leukocyte, could assess the risk of progression to sepsis with good accuracy. Han et al. showed that serum HBP levels predicted sepsis-related acute organ dysfunction and might improve the accuracy of the qSOFA score. They also have created an online mortality risk calculator that incorporated HBP with qSOFA representing a useful and simple tool to calculate the predicted 30-day mortality.

Concerning inflammatory biomarkers, Li et al. studied the neutrophil/lymphocyte ratio (NLR), a representative parameter of the number of immune cells, associated with in-hospital mortality, and Monocyte/high-density lipoprotein cholesterol ratio (MHR), an indicator of systemic inflammation and oxidative stress. The retrospective analysis of 274 patients showed that high levels of procalcitonin, NLR, and MHR potentially aggravated the 28-day mortality risk of septic patients ($p < 0.001$). In the predictive model of MHR combined with NLR, the AUC maximum value was 0.934 with a better sensitivity and specificity than the single variable. This suggested that these parameters together represented independent risk factors for increased mortality and had predictive efficacies for 28-day mortality risk in septic patients. Again, in this context, many studies showed that decreased lymphocyte count and elevated glucose levels are strongly related to immune dysfunction and the severity of sepsis. These two variables were combined and analyzed in the glucose-to-lymphocyte ratio (GLR) of Cai et al. study on 10,118 patients with sepsis from the MIMIC IV database. Results showed that an elevated GLR was positively related to higher in-hospital mortality in ICU patients with sepsis in the United States, anyway this relationship was not linear. For this reason, further studies are necessary to establish if GLR could have a predictive role in sepsis mortality.

Pieroni et al. studied in-hospital mortality related to the origin of infection. Data were extracted from the eICU collaborative research database covering multi-center ICUs with over 200,000 admissions. The authors considered the three most frequent sources of sepsis: pulmonary, urinary, and abdominal, intending to develop prognostic models for hospital mortality. They made comparisons with the used prediction outcome scores such as APACHE IV and SOFA. They demonstrated that mortality varied significantly between the three sepsis groups with high heterogeneity of the factors that influenced in-hospital mortality. For this reason, the planning of sepsis treatment trials might consider a risk stratification based on the source of infection.

Another reported topic in this research collection was traumatic brain injury (TBI) and septic complications. Caceres et al. focused on lower respiratory tract infections (LRTIs) including hospital-acquired pneumonia, ventilator-associated pneumonia, and ventilator-associated tracheobronchitis. Multivariable analysis showed that age, severe TBI, thorax injuries, and mechanical ventilation on admission to ICU were correlated to the development of LRTIs. Moreover, patients with TBI and a diagnosis of LRTIs had a longer ICU stay and hospital stay and spent more days on mechanical ventilation with no influence on hospital mortality.

Another category of patients reported were severe burn patients, for whom sepsis is one of the main causes of death. Cao et al. made a bibliometric analysis, using the VOSviewer software, that collected the research about burn sepsis using the Web of Science platform, with the aim to establish the global research trends and hotspots in this field. They demonstrated that the treatments of burn sepsis were very different between hospitals worldwide and not standardized. In recent studies, the focus was on biomarkers for early diagnosis of burn sepsis. The hotspots for future research should be the identification of predictive tools for early diagnosis, prognosis, and treatment of burn sepsis using reliable indicators (burn area, biomarkers, etc.).

The early fresh frozen plasma (FFP) transfusion in patients with sepsis or septic shock admitted to ICU were reported by Qin et al.. Medical Information Mart for Intensive Care III database was used for a sensitivity analysis conducted to validate the effects of early FFP transfusion in the patients with sepsis with hypocoagulable and non-hypocoagulable state. They showed that septic patients with hypocoagulable state did not improve their outcomes after early FFP transfusion. Moreover, patients with no hypocoagulable state that received early FFP transfusion increased their mortality risk at 28 and 90 days. For these reasons, it was important to reduce the inappropriate use of FFP to avoid complications and adverse transfusion reactions.

Wedekind et al. developed risk-adjusted quality indicators for the long-term outcome of acute sepsis care in German hospitals based on health claims data on 32,552 patients. A total of 90-day mortality after hospital discharge was chosen as a short-term outcome. As a long-term outcome, they chose a binary outcome of 1-year mortality and an increase in dependency on chronic care during the year after hospital discharge. This health claims-based risk-adjustment methodology could provide a valuable tool in assessing and monitoring outcome quality achieved by German hospitals caring for patients with sepsis, using indicators of long-term mortality and morbidity.

As the final research edited in this collection, Kreitmann et al. analyzed an immune profiling panel prototype, a multiplexed transcriptomic assay that used the array technology to quantify mRNA expression in whole blood and delivered results in less than an hour. In the future, this prototype test could be able to provide clinicians with timely information about the immune system of septic patients and potentially aid in providing care.

Despite the good contribution provided by the 13 articles included in this collection relating to the sepsis outcome, the accurate prediction and assessment of mortality risk associated with sepsis is an area requiring further extensive research due to the absence of standardized tools currently available. The development of reliable methods for predicting and assessing the risk of mortality in sepsis patients remains a crucial and underexplored area in healthcare. As of now, there is a notable absence of universally accepted or standardized tools that effectively gauge the likelihood of mortality in individuals affected by sepsis. Therefore, the urgent need for comprehensive studies arises to

establish robust frameworks or methodologies capable of accurately predicting and evaluating the risk of mortality in patients suffering from sepsis.

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ORIGINAL RESEARCH
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Outcomes of Sepsis and Septic Shock in Cancer Patients: Focus on Lactate

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The number of oncological patients (OP) admitted to intensive care units (ICU) for sepsis/septic shock has dramatically increased in recent years. The definition of septic shock has been modified, adding hyperlactatemia as a severity biomarker for mortality. However, it remains poorly reported in septic OP. We performed a retrospective analysis from a prospective database of sepsis/septic shock patients admitted to our ICU between September 2017 and September 2019 and followed until day 90. We identified 251 patients and 31.9% had active oncological comorbidity, mainly solid tumor (81.3%). Septic shock criteria were met for 112 (44.6%). Hyperlactatemia was observed in 136 (54.2%) patients and this was associated with a lower survival rate. Overall 90-day mortality was 15.1%. In OP vs. non-OP, hyperlactatemia was more frequent (65% vs. 49.1%, $p = 0.013$) and associated with lower survival (65.4% vs. 85.7%, $p = 0.046$). In OP, poor performance status was also associated with lower survival (HR 7.029 [1.998–24.731], $p = 0.002$) In an adjusted analysis, cancer was associated with lower 90-day survival (HR 2.690 [1.402–5.160], $p = 0.003$). In conclusion, septic OP remains a high mortality risk group in whom lactate levels and performance status could help with better risk stratification.

Keywords: cancer, intensive care unit, septic shock, oncological patient, cancer prevention and control

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INTRODUCTION

Relevant advances in diagnosis and treatment of oncological patients (OP) have been reported in the past few years, with a significant improvement in their survival rates (1). Additional to cancer therapy advances, improvements in intensive care unit (ICU) support and admission policies have also have contributed to improving survival outcomes (2). The need for objectivity (3) has led to research about specific care for critically ill cancer patients (4–9) achieving better outcomes. Oncological patients account for up to 20% of ICU admission and sepsis denotes a leading reason for ICU admission in this group of patients (10). A higher prevalence of sepsis has been reported in OP vs. non-oncological patients (non-OP) (11). Immunosuppression due to underlying malignancy or its treatment can increase the risk for severe infections (12). Therefore,

cancer patients are recognized as a high-risk group for sepsis with high mortality (13). However, in recent decades, better short-term outcomes have been reported in OP admitted to ICU, even in the subgroup of patients with a need for vasopressor support (1). On the other hand, sepsis is one of the leading causes of death and critical illness in the world (14). Sepsis is a life-threatening organ dysfunction as a result of infection and dysregulated host response (15). When it is associated with cellular dysfunction (evidenced as hyperlactatemia) and the need for vasopressor despite appropriate fluid reanimation, septic shock is established and its mortality is close to 40% (16).

The most recent consensus on the definition of septic shock emphasizes higher mortality rates when vasopressor is needed and hyperlactatemia is present (16). However, prognostic markers are usually inferred from non-OP and might not as accurate in OP admitted to ICU. As an example, central venous saturation has been classically associated with worst outcomes; however, in a recent trial, it was not associated with an early complication in cancer patients presenting in the emergency department (17).

Data related to lactate in septic cancer patients is lacking. Moreover, studies regarding lactate levels or hyperlactatemia in septic cancer patients are underreported (1, 18). Therefore, this study aimed to describe survival rates in OP and non-OP patients according to hyperlactatemia status.

MATERIALS AND METHODS

Study Design and Patients

We performed a retrospective analysis from a prospective database as part of project "Registro prospectivo de pacientes ingresados a unidad de cuidados intensivos (RUCI)" in Clínica Alemana de Santiago, a university teaching hospital. All patients admitted between September 24, 2017, and September 21, 2019, were considered. They were followed until day 90 from ICU admission and mortality outcome was recorded. For patients with more than one ICU admission in this period, only the first was taken into account. This project was approved under protocol number 53-2012 by local ethical board "comité científico—ético of Clínica Alemana de Santiago" (IRB00011516), addressed in Av. Vitacura 5951, Santiago of Chile. Informed consent was obtained from each patient or relatives.

Variables of Interest and Definitions

- *Oncological patients:* Those who have a histological diagnosis of neoplasm and lower than 5 years of remission. (19).
- *Performance status:* We used the Eastern Cooperative Oncology Group (ECOG) score (20).
- *Severity at ICU admission:* We used the Acute Physiology and Chronic Health Evaluation II (APACHE II) score.
- *Sepsis related organ dysfunction:* We used Sequential Organ Failure Assessment (SOFA) score.
- *Sepsis:* Defined as proven or suspected infection with organ dysfunction associated, in agreement with Sepsis-3 consensus definition (15).
- *Sepsis related hyperlactatemia:* Arterial lactate level equal or > 2 mmol/L in a septic patient at ICU admission.
- *Sepsis-3 definition of septic shock:* In agreement with the last consensus definition, patients with proved or suspected infection and need for vasopressor support to achieve a mean arterial pressure of 65 mmHg and hyperlactatemia higher or equal to 2 mmol/L were categorized as septic shock (15).
- *Sepsis-2 definition of septic shock:* Patients with proved or suspected infection and need for vasopressor support to achieve a mean arterial pressure of 65 mmHg despite appropriate fluid therapy (21).
- *Vasopressor treatment:* Patients treated with noradrenaline to achieve a mean arterial pressure at least of 65 mmHg after appropriate fluid therapy.
- *Outcome:* Survival at day 90.

Statistical Analysis

First, we did a descriptive analysis of the whole group and then a characterization according to oncological status. Oncological patients was also described according to neoplasm type and performance status. Quantitative variables were described as mean (SD) and were compared between groups using an unpaired *t*-test. Distributions were explored by the *Kolmogorov-Smirnov* test. In agreement with the central limit theorem, the sample size allowed for the appropriate use of a parametric test with better rigor than a non-parametric test independently of sample distribution (22, 23). In the same way, in accordance with *Skovlund* and *Fenstad* (22), our sample meets the conditions for parametric test use. Qualitative variables were described as frequency (percentages) and were compared between groups by Fisher's exact test. The outcome was assessed using survival analysis and an adjusted comparison between OP and non-OP patients' survival was performed by Cox regression. To compare survival curves between patients with or without hyperlactatemia, we used the Log-Rank test. Significance was defined as $p < 0.05$. Statistical analysis was performed using the SPSS software, version 20.0 (SPSS, Chicago, IL, USA).

RESULTS

We identified 251 patients who meet sepsis-3 criteria for sepsis or septic shock. Patients were mainly male (57%) and they were 64.7 (18.4) years old. A moderate severity with an APACHE II score of 15.6 (7.9) points was observed. The source of infection was mainly pulmonary or digestive. 32.3% were admitted in the postoperative setting. A 44.6% meet septic shock criteria in agreement with the Sepsis-3 task force while 69.7% needed vasopressor. Hyperlactatemia > 2 mmol/L was seen in 54.2%. Hundred and forty-five patients were supported with invasive mechanical ventilation (IMV), however, only 46 of them meet Berlin's criteria for acute respiratory distress syndrome.

Abbreviations: OP, oncological patients; ICU, intensive care unit; non-OP, non-oncological patients; ECOG, Eastern cooperative oncology group; APACHE II, acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; IMV, invasive mechanical ventilation; ARDS, acute respiratory distress syndrome; ICU LOS, intensive care unit length of stay.

TABLE 1 | Patients' characterization according to oncological or non-oncological status.

Variable	All *N* = 251	OP *N* = 80	non-OP *N* = 171	*P*-value
DEMOGRAPHICS				
Age, years	64.7 (18.4)	67.7 (11.9)	63.4 (20.7)	0.039
Male, *N* (%)	143 (57.0)	51 (63.8)	92 (53.8)	0.089
APACHE II, points	15.6 (7.9)	17.8 (6.8)	14.7 (8.2)	0.004
SOFA, points	6.8 (3.5)	7.1 (3.5)	6.7 (3.4)	0.377
AKI at admission, *N* (%)	106 (42.2)	36 (45.0)	70 (40.9)	0.318
ARDS at admission, *N* (%)	46 (18.3)	15 (18.8)	31 (18.1)	0.517
IMV, *N* (%)	145 (57.8)	50 (62.5)	95 (55.6)	0.184
Surgical, *N* (%)	81 (32.3)	29 (36.3)	52 (30.4)	0.218
Lactate, mmol/L	2.9 (2.9)	2.9 (2.0)	2.9 (3.3)	0.938
Hyperlactatemia, *N* (%)	136 (54.2)	52 (65.0)	84 (49.1)	0.013
Septic shock, *N* (%)	112 (44.6)	42 (52.5)	70 (40.9)	0.057
SOURCE				0.082
Bacteremia, *N* (%)	7 (2.9)	1 (1.3)	6 (3.5)	
Pulmonary, *N* (%)	80 (31.9)	21 (26.3)	59 (34.5)	
Digestive, (%)	94 (37.5)	40 (50.0)	54 (31.6)	
Urinary, *N* (%)	32 (12.7)	6 (7.5)	26 (15.2)	
Skin and soft tissue, *N* (%)	11 (4.4)	3 (3.8)	8 (4.7)	
Other, *N* (%)	27 (10.8)	9 (11.3)	18 (10.5)	
OUTCOMES				
ICU LOS, days	8 (9)	9 (10)	7 (9)	0.353
90-day mortality, *N* (%)	38 (15.1)	22 (27.5)	16 (9.4)	<0.001

OP, oncological patient; non-OP, non-oncological patient; APACHE II, acute physiology and chronic health evaluation II score; SOFA, sequential organ failure assessment score; AKI, acute kidney injury at admission; ARDS, acute respiratory distress syndrome; IMV, invasive mechanical ventilation; ICU LOS, intensive care unit length of stay.

Overall, the 90-day mortality rate was 15.1%. A detailed patients description is shown in **Table 1**.

We identified 80 (31.8%) as OP; being 81.3% solid tumor and 65.7% were stage IV. Interestingly, 70.1% were ECOG 1 (**Table 2**). In comparison with non-OP, cancer patients were elderly and had more severe illnesses. Hyperlactatemia higher than 2 mmol/L was more frequent in OP (65% vs. 49.1%, respectively; $p = 0.013$).

In OP, a significant association with lower survival was observed when the results were categorized according to hyperlactatemia (yes 65.4% vs. no 85.7%, $p = 0.046$), but not when they were categorized according to vasopressor need (yes 69.5% vs. no 81%, $p = 0.336$).

The overall 90-day mortality rate was higher in OP vs. non-OP (27.5% vs. 9.4%, respectively, $p < 0.001$). The distribution of outcomes according to hyperlactatemia and vasopressor need between OP and non-OP are shown in **Figures 1**, **2**.

In a survival analysis adjusted by APACHE II score, SOFA score, hyperlactatemia, and surgical admission, we found a lower survival in OP with a hazard ratio (HR) of 2.690 [1.402–5.160], $p = 0.003$ (**Figure 3A**). When outcome performance was assessed according to ECOG status, patients with ECOG 1-2 had lower survival than non-OP but better survival rates than patients who were ECOG-3 (**Figure 3B**).

Finally, only the outcomes for OP were sensitive to septic shock definition (Sepsis task force 2 or 3, **Figure 4**).

DISCUSSION

The main finding of this study was a lower survival rate in OP vs. non-OP with sepsis/septic shock. The antecedent of neoplasm was an independent variable associated with worse outcomes. Remarkably, in our clinical institution, close to a third of patients admitted by sepsis/septic shock were OPs. Among OP, those with poor performance status were independently associated with worse survival. Interestingly, in our patients, hyperlactatemia was associated with lower survival mainly in OP. Likewise, mortality in OP was sensitive to septic shock definition, while in non-OP a relatively low mortality rate with both definitions was observed.

We also observed an overall unadjusted mortality in the lower limit to that reported in other literature and in agreement with a previous report (15). Patients with the sepsis-3 definition of septic shock were a high mortality risk group. Classically, OPs are considered as a group of high risk for infection and present higher mortality rates (13). However, significant improvements in outcomes in these patients have been recently reported (18). Mortality rates over 50% in OP were reported during the 1990s while more recently, cancer patients with sepsis/septic shock mortality rates lower than 35% have been reported (18). Therefore, our results are in agreement with the hypothesis that cancer patients with sepsis are a high-risk group in terms of worse outcomes, but these results also indicate improvement in outcomes in this group in the past few years

Lactate is a biomarker classically linked with worse outcomes in sepsis (18, 19, 22–24) but an elevated serum lactate level is not specific for cellular dysfunction in sepsis (24–27). Specifically, during the course of an infection, an increased lactate >2 mmol/L has been consistently associated with increased mortality (16, 23–25). Moreover, in the last septic shock consensus definition, hyperlactatemia is part of diagnosis criteria (15). Adding hyperlactatemia to continuous vasopressor therapy achieves a better selection of patients with worse outcomes (15, 16). However, in previous studies regarding outcomes in septic cancer patients, lactate levels or frequency of hyperlactatemia are underreported (1, 18).

TABLE 2 | Patients' characterization according to oncological or non-oncological status.

Oncological characteristics	Patients, *N* (%)
Hematological	15 (18.7)
Solid	65 (81.3)
Lung	6 (9.2)
Breast	5 (7.7)
Colon	9 (13.8)
Gastric	3 (4.6)
Other	41 (63.1)
Stage	
I	2 (2.9)
II	9 (12.9)
III	13 (18.6)
IV	46 (65.7)
ECOG	
1	54 (70.1)
2	18 (23.4)
3	5 (6.5)

ECOG, East cooperative oncology group performance status.

In our study, OP was recognized as a sensitive group to septic shock outcome according to the definition used. Similarly, Costa et al. found a higher mortality rate in cancer patients with septic shock according to sepsis-3 definitions in comparison with sepsis 2 definitions (27, 28). We found different survival curve behaviors according to whether hyperlactatemia was present or not in septic cancer patients at admission. This was an expected but not obvious finding. For example, venous central saturation, another classical parameter with prognostic value in cancer patients, had not been associated with worse outcomes (17). However, our findings demonstrate that lactate could be a valuable tool in septic cancer patient evaluation. Therefore, lactate levels should be assessed in all patients with suspected sepsis and especially in OP.

This approach is currently being taken into consideration in our clinical practice. In our center, all patients with proven or suspected infection are stratified using lactate levels and if this biomarker is equal or higher than 2 mmol/L, patients are admitted to critical care (intensive care unit or intermediate care unit according to organ dysfunction at admission). In the same way, a clinical researcher should be alert to lactate assessment at admission and include it in future reports regarding outcomes in cancer patients with sepsis.

Another remarkable result was the differentiation of survival according to performance status. This finding is in agreement with data published last year, where intensive care support

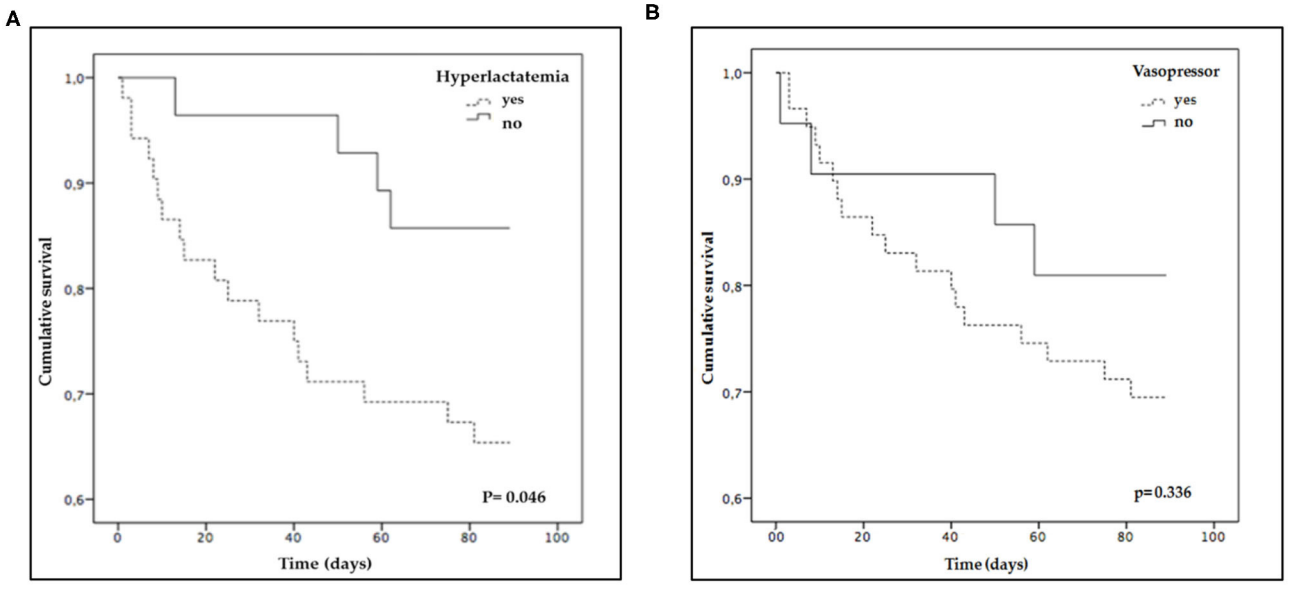

FIGURE 1 | Survival curves of oncological patients. The curves comparison was performed using Log-Rank test: **(A)** Categorized according to hyperlactatemia (>2 mmol/L); **(B)** Categorized according to vasopressor need.

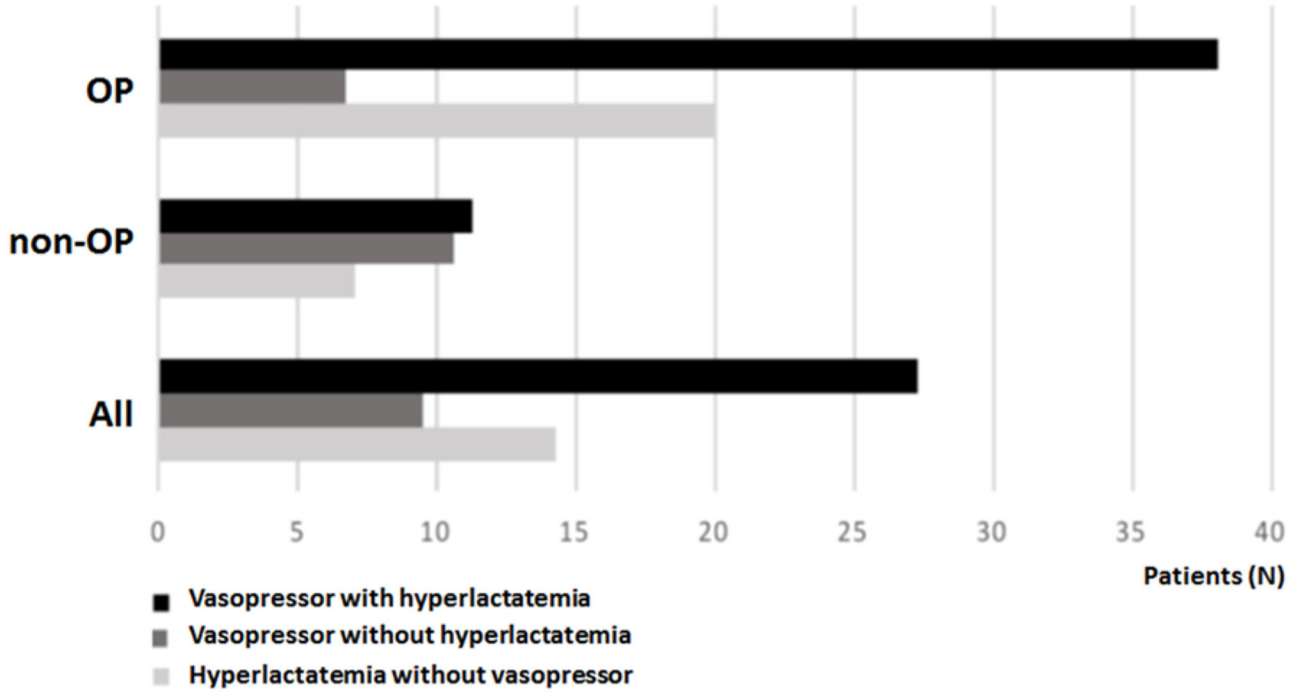

FIGURE 2 | Outcome distribution in oncological, non-oncological and all patients according to vasopressor need with hyperlactatemia (>2 mmol/L), vasopressor need without hyperlactatemia, and hyperlactatemia (>2 mmol/L) without vasopressor need.

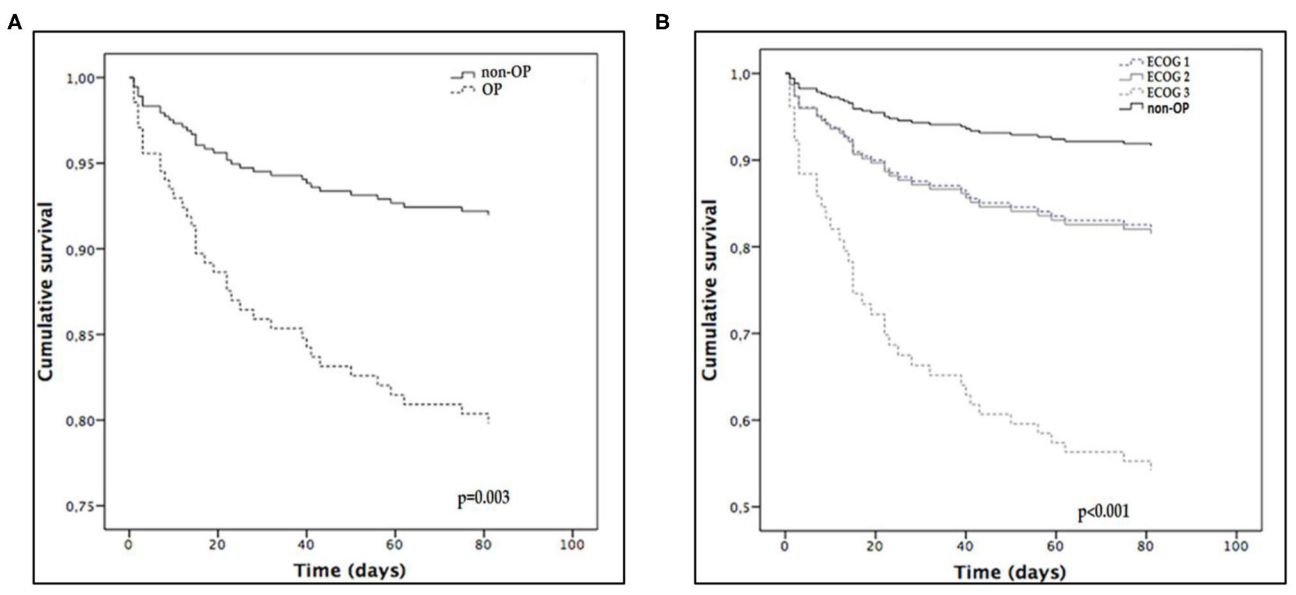

FIGURE 3 | Adjusted survival curves where OP is oncological patients. **(A)** non-OP vs. OP; **(B)** non-OP (as reference) and OP categorized according to ECOG performance status. ECOG, East cooperative oncology group.

was followed by better outcomes in cancer patients with good performance status (20, 21, 29). The improvement in outcomes in the last year of critically ill cancer patients and a better patients' risk stratification should lead to the actualization of ICU admission policies (30, 31).

Our study has some limitations and our findings should be taken carefully. First, this is a retrospective analysis; however, the database was prospectively collected. Second, this is a single center study with a relatively small sample, and external validity is limited. Likewise, due to sample size limitations,

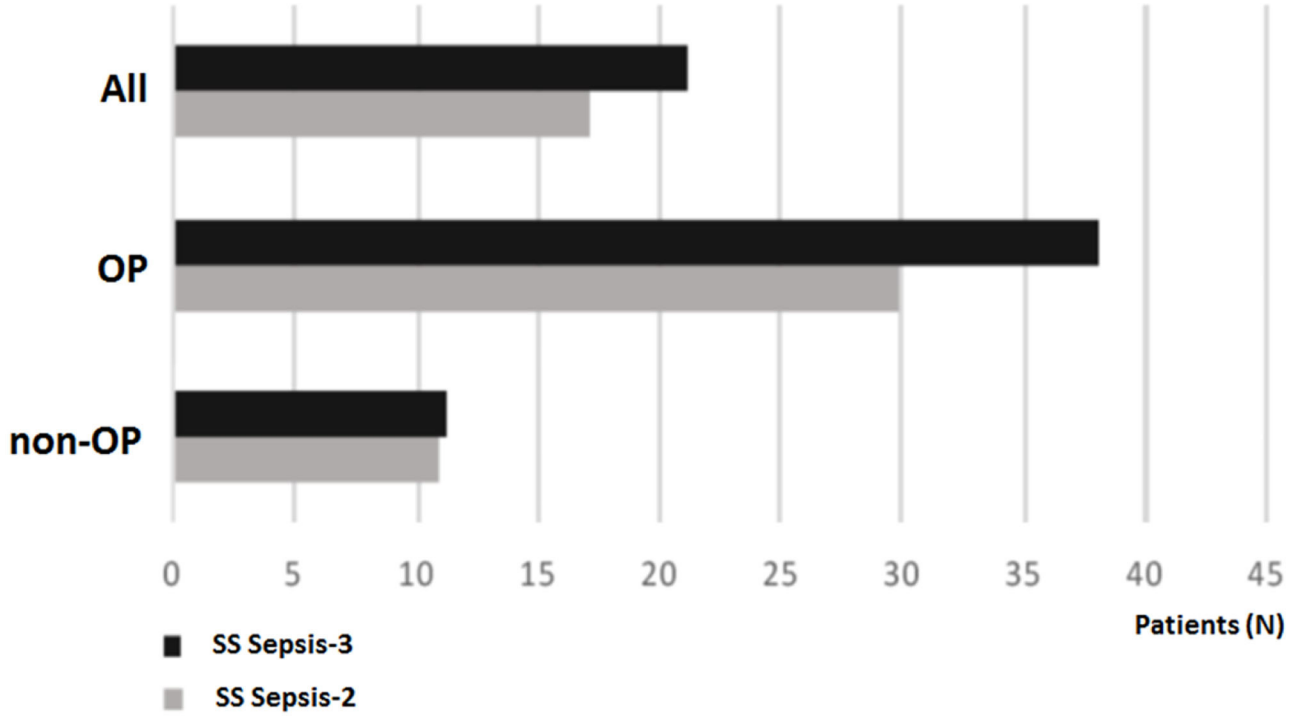

FIGURE 4 | Outcome in all patients, oncological patients (OP) and non-OP, according to septic shock task force definition. SS Sepsis-3, Septic shock according to Sepsis-3 task force; SS Sepsis-2, Septic shock according to Sepsis-2 task force.

specific cancer patients' subgroups such as neutropenic or hematological information were not independently analyzed. However, this study achieved the important finding in terms of its reappraisal of lactate in cancer patients with sepsis and invites others to take into account this biomarker in clinical and research settings. The strengths of the study include that this data indicates different survival rates according to oncological status, septic shock definition, and hyperlactatemia status. Moreover, our patients were followed up for 90 days while most studies on sepsis outcomes in cancer patients take into account a follow-up of 30 days or are limited to hospital stay. We also provide a comparison with non-OP patients.

CONCLUSIONS

The outcome in ICU OP with sepsis has improved in recent years, however, these patients remain a high mortality risk group, especially those with poor performance status. Lactate should be used as a biomarker for risk stratification in cancer patients with suspected sepsis. Outcome improvement and better patient stratification could lead to the actualization of ICU admission policies.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comite de Etica Clinica Alemana. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RL and SS contributed to conceptualization, methodology, and study design. RP-A, RL, and SS are responsible for data management. RL, RP-A, JM, JG, and SS. undertook formal analysis, writing, and original draft preparation. All authors contributed to the article and approved the submitted version.

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The Hyperbilirubinemia and Potential Predictors Influence on Long-Term Outcomes in Sepsis: A Population-Based Propensity Score-Matched Study

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Objective: Although hyperbilirubinemia has been associated with mortality in patients who are critically ill, yet no clinical studies dissect the effect of dynamic change of hyperbilirubinemia on long-term septic prognosis. The study aims to investigate the specific stages of hyperbilirubinemia and potential risk factors on long-term outcomes in patients with sepsis.

Methods: In this retrospective observational cohort study, patients with sepsis, without previous chronic liver diseases, were identified from the Medical Information Mart for the Intensive Care III MIMIC-III database. We used propensity scores (PS) to adjust the baseline differences in septic patients with hyperbilirubinemia or not. The multivariate Cox was employed to investigate the predictors that influence a clinical outcome in sepsis.

Results: Of 2,784 patients with sepsis, hyperbilirubinemia occurred in 544 patients (19.5%). After PS matching, a survival curve demonstrated that patients with sepsis with the new onset of total bilirubin (TBIL) levels more than or equal to 5 mg/dl survived at significantly lower rates than those with TBIL levels <5 mg/dl. Multivariate Cox hazard analysis showed that patients with TBIL at more than or equal to 5 mg/dl during sepsis exhibit 1.608 times (95% CI: 1.228–2.106) higher risk of 1-year mortality than those with TBIL levels <5 mg/dl. Also, age above 65 years old, preexisting malignancy, a respiratory rate above 30 beats/min at admission, serum parameters levels within 24-h admission, containing international normalized ratio (INR) above 1.5, platelet <50*10^9/L, lactate above 4 mmol/L, and bicarbonate <22 or above 29 mmol/L are the independent risk factors for long-term mortality of patients with sepsis.

Conclusions: After PS matching, serum TBIL levels at more than or equal to 5 mg/dl during hospitality are associated with increased long-term mortality for patients with sepsis. This study may provide clinicians with some cutoff values for early intervention, which may improve the prognosis of patients with sepsis.

Keywords: sepsis, liver, risk factors, mortality, hyperbilirubinemia

INTRODUCTION

Sepsis is defined as a life-threatening acute organ dysfunction secondary to infection. A high incidence rate and high mortality of sepsis make it one of the leading causes of death as a global health priority (1, 2). Notably, sepsis-induced organ dysfunction is an important predictor for poor prognosis (3–5). The liver plays a central role in homeostasis, immune surveillance, inflammation, and bacterial clearance (6, 7). A large body of evidence has suggested that the liver is the main target of sepsis and decompensation of liver function can trigger overwhelming inflammation, immune response, and organ damage in sepsis (8, 9). However, despite extensively studied lung, kidney, and heart injury in the course of sepsis, the question of whether dysfunction of the liver is associated with mortality or a poor outcome in sepsis remains unresolved. Hepatic dysfunction and hyperbilirubinemia commonly occur in patients who are critically ill with an incidence rate of 40% and up to 20% in patients with bacterial infection (10).

Hyperbilirubinemia may result from bacterial products or as a consequence of the response of the host to infection. The etiology of hyperbilirubinemia in patients who are critically ill is multifactorial, probably cholestasis or sclerosing cholangitis caused by circulating endotoxins, inflammation, hypoxia hepatitis, lower liver perfusion and ischemia, genetic and metabolic variations, and so on (11–16). Hyperbilirubinemia has been shown to represent an important marker of mortality and poor outcomes for patients who are critically ill (17, 18). Patients with a preexisting liver deficit, like cirrhosis, have a worse outcome of sepsis than ones without liver dysfunction due to impaired immunity (19). The underlying mechanism may relate to the reversal of bilirubin transport from intrahepatic toward the circulation, which is beneficial for relieving the high-energy burden for hepatocytes and serves as a metabolic and inflammatory stress response as well (20). Hence, elevated serum bilirubin might indicate the impairment of energy consumption due to liver injury, and total serum bilirubin level has been widely recognized as a powerful maker for assessing hepatic function compared with other serum activities on laboratory tests.

Thus far, several studies have demonstrated the potential effect of liver dysfunction on short-term mortality of patients with sepsis by using different definitions of hepatic dysfunction (21–23). Whereas, it is still unclear of the long-term impact of dynamic change of hyperbilirubinemia in patients with sepsis. The appendant result derived from PROWESS-SHOCK (Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis and Septic Shock) trial showed that liver dysfunction is associated with 180-day mortality in patients with septic shock by using criteria of serum bilirubin ≥20 mmol/L (24). However, as hyperbilirubinemia is multifactorial, there is no large study dissecting the effect of liver dysfunction on long-term mortality of more than 180 days in patients with general sepsis. Therefore, we performed a large cohort study to analyze the dynamic change of hyperbilirubinemia and its influence on outcomes in patients with sepsis by using an openly available US-based critical care database named Medical Information Mart for Intensive Care (MIMIC)-III v 1.4, which includes 52,963 ICU admissions. Our results revealed a significant association between total bilirubin (TBIL) levels with long-term mortality in patients with sepsis.

Abbreviations: MIMIC, medical information mart for intensive care; STROBE, STrengthening the Reporting of OBservational studies in Epidemiology; ICD-9, International Classification of Diseases, 9th revision; IRB, institutional review board; SOFA, sequential organ failure assessment; TBIL, total bilirubin; CHF, congestive heart failure; AFIB, atrial fibrillation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ALT, alanine aminotransaminase; AST, aspartate aminotransferase; CI, confidence interval; HR, hazard ratio; OR, odds ratio; pCO_2, partial pressure of CO_2; INR, international normalized ratio; BAIBF, bile acid-independent bile flow; USA, United States.

METHODS

Study Population

We conducted the cohort study according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement by using the MIMIC-III database, a large, integrated, de-identified, open-free, comprehensive clinical dataset, comprised of all the patients admitted to the ICUs Beth Israel Deaconess Medical Center in Boston, MA, from June 2001 to October 2012. For all of the data that are deidentified, patient consent or ethics approval will not be needed. Demographics records, laboratory results, radiology examinations, diagnosis, clinical treatment parameters, and dates of death were also concluded. The diagnosed diseases by the physician were according to the International Classification of Diseases, 9th revision (ICD-9) on patient discharge. Since the study was an analysis of a third-party anonymized publicly available database with preexisting institutional review board (IRB) approval, approval from our institution was exempted.

Sepsis was defined according to Sepsis-3 criteria: the suspected infection and Sequential Organ Failure Assessment (SOFA) score was of 2 points or more (25, 26). Hyperbilirubinemia was diagnosed in patients with the new onset of serum TBIL at more than or equal to 2 mg/dl during the hospitalization. The included criteria were as follows: age ≥18 years old; patients without previous chronic liver diseases according to the recorded ICD-9 codes, including liver cirrhosis; at ICU admission more than 24 h; missing data <50%. The excluded criteria were preexisting bilirubin at more than or equal to 2 mg/dl before admission, and previous chronic liver diseases like chronic hepatitis, acute-on-chronic liver failure, cirrhosis, liver cancer, hepatobiliary duct-related tumors, or acute liver conditions like drug or toxin-induced hepatitis. After being included, all the patients with sepsis were divided into a hyperbilirubinemia group (serum TBIL during hospitalization at more than or equal to 2 mg/dl) and a non-hyperbilirubinemia group (serum TBIL <2 mg/dl).

Measures and Variable Definition

For the patients in the study, we retrieved demographic and admission information from the database during the first 24 h of ICU admission, including age, gender, ethnicity (White, Hispanic, Black, or other), weight, time of admission or discharge, the severity of illness parameters: the SOFA score (clarified into four different strata: 2–4, 5–9, more than or

equal to 10 scores) and the Elixhauser comorbidity score, and vital signs: heart rate (clarified into two different strata: <100 beats/min, more than or equal to 100 beats/min), and respiratory rate (clarified into two different strata: <30 beats/min, more than or equal to 30 beats/min). In addition, we routinely collected laboratory parameters within the first 24 h of ICU admission, including maximum levels of white blood cell count (WBC); levels of hemoglobin (g/dl); hematocrit; platelet levels (stratified into five different scales: more than or equal to 250*10^9/L, at 150–249*10^9/L, at 100–149*10^9/L, at 50–99*10^9/L, and <50*10^9/L); serum potassium/sodium/chloride levels; serum bicarbonate levels (stratified into three different scales: <22 mmol/L, at 22–29 mmol/L, and more than 29 mmol/L); serum blood urea nitrogen (BUN)/creatinine; serum lactate levels (stratified into four different scales: at 0–2 mmol/L, at 2.1–4 mmol/L, at 4.1–10 mmol/L, and more than 10 mmol/L); international normalized ratio (INR, stratified into two different scales: ≤1.5, more than 1.5); arterial blood gas with PH, partial pressure of oxygen (pO2), partial pressure of carbon dioxide (pCO2); alanine transaminase (ALT)/aspartate transaminase (AST). We also collected parameters in the course of sepsis: use of mechanical ventilation, use of vasopressor agents, and use of sedative drugs. By collecting in 24, 48, and 72 h, 7 days, and the day of discharge after ICU admission, serum levels of TBIL were classified into four different scales: at 0–1.9, 2–4.9, 5–10 mg/dl, and more than 10 mg/dl.

We also included preexisting medical comorbidities according to the recorded ICD-9 codes, including congestive heart failure (CHF), renal disease, atrial fibrillation (AFIB), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), stroke, and malignant tumor. The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines were used to define acute kidney injury (AKI). We conducted the follow-up at day 30 (30 days), 90 days, 180 days, and 1 year from the database.

Statistical Analysis

Statistical analysis was performed using SPSS 23 (SPSS, Inc., Chicago, IL). The parameters with missing data of more than 50% were excluded from our study. The mean-value imputation algorithm was selected to substitute missing values. Baseline characteristics and clinical parameters after ICU admission between the hyperbilirubinemia group and the control group were compared. All continuous variables were expressed as means (SD) or medians (interquartile range, IQR) by using either Student *t*-test or Mann–Whitney U test as appropriate. Categorical variables were compared by the chi-square test or Fisher's exact test. The survival curves for patients with sepsis were plotted using the Kaplan-Meier method, and differences between the curves were assessed using the log-rank test. To identify the association between the dynamic change and the levels of hyperbilirubinemia and a long-term outcome in sepsis, Cox regression analysis was used. Univariate Cox proportional hazards regression of clinical parameters was performed to identify potential predictors. Hazard ratios (HRs) were calculated with 95% CIs as an estimate of the risk associated with a particular variable. To determine independent predictors of the composite end points, variables in univariate Cox analysis with $p < 0.1$ were entered into multivariate Cox proportional hazards regression, and the predictors were performed with a likelihood ratio-forward selection.

To account for selection bias and potential confounding factors between groups in comparison of an outcome, we used the propensity score (PS) matching (1:1) to balances covariates for those who had hyperbilirubinemia and those who had not (532 pairs). A multivariable logistic regression model with confounding baseline characteristics was used to calculate the PS for each patient as the predicted probability of the hyperbilirubinemia group. The following variables were adjusted (**Table 1**): age; sex; race/ethnicity; preexisting medical conditions: CHF, AFIB, CAD, COPD, stroke, malignant tumor, and chronic renal disease; Elixhauser comorbidity score; respiratory rate; and biochemical parameters. One-to-one nearest-neighbor matching without replacement with a caliper width of.1 was conducted. We evaluated the balance test after matching, with no significant difference with chi-square ($X^2 = 16.468$, $P = 0.870$), which demonstrated a good balance following PS matching between the hyperbilirubinemia and non-hyperbilirubinemia groups.

After matching, survival curves were computed and plotted using the Kaplan-Meier method. Univariate and multivariate Cox proportional hazards regression models were constructed to explore the independent risk factors of influence on long-term outcomes in sepsis. A $P < 0.05$ (two-sided) was considered significant.

RESULTS

Of the 52,963 ICU admissions from the MIMIC-III database, 5,784 patients meet the definition of sepsis. About 3,310 participants were identified in our analysis according to the inclusion criteria; afterward, patients with preexisting liver disease ($n = 526$) were excluded from our study. Finally, 544 (19.5%) patients developed hyperbilirubinemia, while the remaining 2,240 (80.5%) patients did not (**Figure 1**).

Patient Characteristics Before Matching

Table 1 shows the notable differences in baseline characteristics between the hyperbilirubinemia and non-hyperbilirubinemia groups of sepsis before PS matching. The results showed that men were prone to develop hyperbilirubinemia in the course of sepsis (58.3 vs. 53.6%; $P = 0.049$). The hyperbilirubinemia group had higher prevalence of preexisting medical comorbidities, including AFIB (32.2 vs. 26.4%; $P = 0.009$), and malignancy (27.9 vs. 21.3%; $P = 0.001$); lower prevalence of COPD (9.7 vs. 14.9%; $P = 0.001$), stroke (3.5 vs. 8.7%; $p < 0.001$), and renal disease (15.4 vs. 21.8%; $P = 0.001$) than the non-hyperbilirubinemia group (**Table 1**).

There was also a significantly higher severity of illness in the hyperbilirubinemia group than the non-hyperbilirubinemia group, with higher rates of the SOFA score at more than 4 (83.9 vs. 56.1%; $p < 0.001$), higher levels of Elixhauser comorbidity index [5. (10) vs. 4. (9)], and higher frequency of the respiratory rate at more than or equal to 30 beats/min (45.6 vs. 38.4%; $P = 0.002$; **Table 1**). At 24 h after admission to ICU, the

TABLE 1 | Demographic characteristics between hyperbilirubinemia and non-hyperbilirubinemia groups before propensity score matching.

Parameters	Full cohort		*P*
	Hyperbilirubinemia group (*n* = 544)	No-hyperbilirubinemia group (*n* = 2240)	
Age, mean (SD), y	67.19 (27)	67.27 (26)	0.777
Male, *n* (%)	317 (58.3)	1200 (53.6)	0.049
Race, *n* (%)			
White	381 (70.0)	1569 (70.0)	0.518
Hispanic	15 (2.8)	67 (3.0)	0.888
Black	42 (7.7)	236 (10.5)	0.055
Other	106 (19.5)	368 (16.4)	0.098
Weight, mean (SD)	81.0 (25)	80.0 (25)	0.292
Preexisting medical conditions, *n* (%)			
CHF	134 (24.6)	579 (25.8)	0.584
AFIB	175 (32.2)	592 (26.4)	0.009
COPD	53 (9.7)	334 (14.9)	0.001
CAD	117 (21.5)	480 (21.4)	0.954
Stroke	19 (3.5)	194 (8.7)	<0.001
Malignancy	152 (27.9)	476 (21.3)	0.001
Renal disease	84 (15.4)	489 (21.8)	0.001
SOFA score at admission, *n* (%)			<0.001
Score at 2∼4	88 (16.2)	982 (43.8)*	
Score at 5∼9	274 (50.4)	1004 (44.8)*	
Score at ≥10	182 (33.5)	254 (11.3)*	
Elixhauser comorbidity index, mean (SD)	5.00 (10)	4.00 (9)	<0.001
Heart rate ≥ 100 (beats/min), *n* (%)	362 (66.5)	1414 (63.1)	0.149
Respiratory rate ≥ 30 (beats/min), *n* (%)	248 (45.6)	860 (38.4)	0.002
Laboratory parameters within the first 24 h of ICU admission			
Maximum WBC, mean (SD)	14.40 (9.68)	13.90 (9.60)	0.202
Maximum hemoglobin, mean (SD)	12.00 (2.88)	11.80 (3.10)	0.189
Maximum platelet levels (10^9/L), *n* (%)			<0.001
Platelet≥ 250	170 (31.3)	1035 (46.2)*	
Platelet at 150∼249	210 (38.6)	845 (37.7)	
Platelet at 100∼149	98 (18.0)	232 (10.4)*	
Platelet at 50∼99	47 (8.6)	93 (4.2)*	
Platelet at <50	19 (3.5)	35 (1.6)*	
Maximum potassium, mean (SD)	4.50 (1.2)	4.50 (1.0)	0.734
Maximum sodium, mean (SD)	140.00 (6.0)	141.00 (5.0)	0.051
Maximum bicarbonate levels, *n* (%)			<0.001
At <22	192 (35.3)	558 (24.9)*	
At 22–29	314 (57.7)	1398 (62.4)*	
At >29	38 (7.0)	284 (12.7)*	
Maximum chloride, mean (SD)	108.00 (8.0)	108.00 (8.0)	0.926
Maximum Bun, mean (SD)	29.00 (29.75)	26.00 (26.00)	0.060
Maximum lactate levels(mmol/L), *n* (%)			<0.001
Lactate at 0–2	190 (34.9)	1029 (45.9)*	
Lactate at 2.1–4	171 (31.4)	767 (34.2)	
Lactate at 4.1–10	149 (27.4)	392 (17.5)*	
Lactate at >10	34 (6.3)	52 (2.3)*	
Maximum creatinine, mean (SD)	1.40 (1.30)	1.30 (1.20)	0.010
Maximum hematocrit, mean (SD)	35.3 (7.85)	35.5 (8.60)	0.838
Maximum INR levels, *n* (%)			
At >1.5	288 (52.9)	651 (29.1)	<0.001

(Continued)

TABLE 1 | Continued

Parameters	Full cohort		*P*
	Hyperbilirubinemia group (*n* = 544)	No-hyperbilirubinemia group (*n* = 2240)	
Maximum PH, mean (SD)	7.40 (0.07)	7.40 (0.07)	0.377
Maximum pO2, mean (SD)	214.0 (113)	214.0 (142)	0.921
Maximum pCO2, mean (SD)	47.0 (11)	47.0 (9)	0.030
Maximum ALT, mean (SD)	117.00 (292.50)	30.00 (52.00)	<0.001
Maximum AST, mean (SD)	155.00 (366.75)	41.00 (77.00)	<0.001
Maximum total bilirubin at 24 h, mean (SD)	3.30 (3.10)	0.50 (0.50)	<0.001
Maximum total bilirubin at 48 h, mean (SD)	3.50 (3.50)	0.60 (0.50)	<0.001

Continuous variables are reported as mean (Standard deviation, SD), and Categorical variables are reported as count (% of column total).
CHF congestive heart failure, AFIB atrial fibrillation, CAD coronary artery disease, COPD chronic obstructive pulmonary disease, SOFA Sequential Organ Failure Assessment, WBC white blood cell, INR International Normalized Ratio, BUN blood urea nitrogen, AST aspartate transaminase, ALT alanine transaminase, pCO_2 partial pressure of carbon dioxide, pO_2 partial pressure of oxygen.
**Represent significant difference with P < 0.05.*

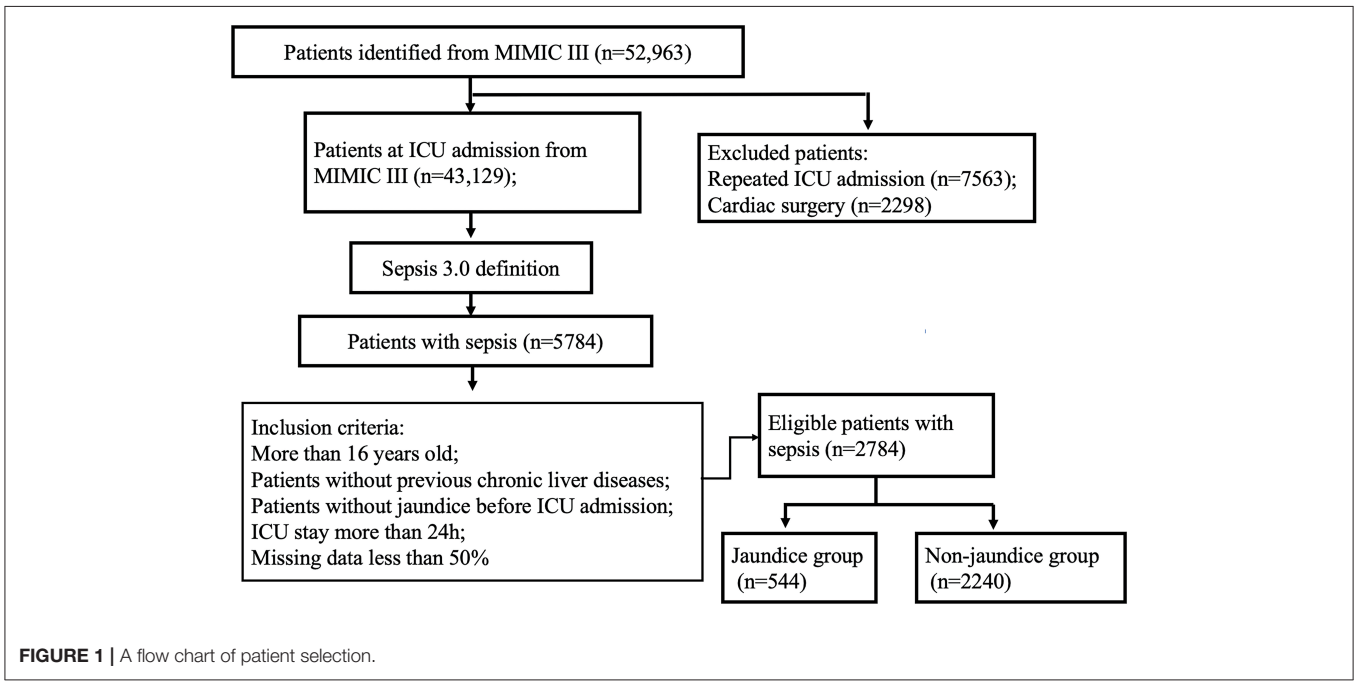

FIGURE 1 | A flow chart of patient selection.

hyperbilirubinemia group had significant higher rates of serum platelet levels at <150*10^9/L (30.1 vs. 17.2%; $p < 0.001$), serum bicarbonate levels at <22 mmol/L (35.3 vs. 24.9%; $p < 0.001$), serum lactate levels at more than 4 mmol/L (33.7 vs. 29.8%; $p < 0.001$), and INR levels at more than 1.5 (52.9 vs. 29.1%; $p < 0.001$) when compared with the non-hyperbilirubinemia group (**Table 1**).

The patients from the non-hyperbilirubinemia group all had TBIL levels below 1.9 mg/dl. By contrast, 62.1% of patients from the hyperbilirubinemia group had serum TBIL levels at 2–4.9 mg/dl, 25.9% had TBIL levels at 5–10 mg/dl, and 11.9% had TBIL levels at more than 10 mg/dl (**Table 2**). In addition, the hyperbilirubinemia group had higher rates of vasopressor usage when compared with the non-hyperbilirubinemia group. The overall in-hospital mortality of patients with sepsis was 23.5%. The patients in the hyperbilirubinemia group had significantly higher rates of in-hospital mortality (16.2 vs. 10.7%, $P = 0.002$), 30-day mortality (21.7 vs. 16.3%, $P = 0.011$), 90-day mortality (25.4 vs. 19.5%, $P = 0.010$), 180-day mortality (27.2 vs. 22.1%, $P = 0.039$), and 1-year mortality after discharge (29.8 vs. 24.5%, $P = 0.037$) than in the non-hyperbilirubinemia group, respectively (**Table 2**). Kaplan-Meier's analysis also showed that the 1-year survival rate was significantly lower in the hyperbilirubinemia group than in the non-hyperbilirubinemia group ($P = 0.006$) before matching (**Figure 2A**). Moreover, it is of note that TBIL levels more than or equal to 5 mg/dl at

TABLE 2 | Clinical outcomes between hyperbilirubinemia and non-hyperbilirubinemia groups before propensity score matching.

Parameters	Full cohort		*P*
	Hyperbilirubinemia group (*n* = 544)	No-hyperbilirubinemia group (*n* = 2,240)	
Serum total bilirubin levels during the course of disease (mg/dL), *n* (%)			<0.001
Serum total bilirubin at 0–1.9 mg/dL	0 (0)	2240 (100.0)	
Serum total bilirubin at 2–4.9 mg/dL	338 (62.1)	0	
Serum total bilirubin at 5–10 mg/dL	141 (25.9)	0	
Serum total bilirubin at >10 mg/dL	65 (11.9)	0	
The life support			
Vasopressor usage, *n* (%)	251 (46.1)	878 (39.2)	0.003
Mechanical ventilation, *n* (%)	273 (50.2)	1208 (53.9)	0.125
Sedative drug usage	271 (49.8)	1143 (51.0)	0.633
AKI KDIGO stage, *n* (%)			0.097
AKI at 1 stage	118 (21.7)	532 (23.8)	
AKI at 2 stage	171 (31.4)	617 (27.5)	
AKI at 3 stage	101 (18.6)	370 (16.6)	
Clinical outcomes			
In-hospital mortality, *n* (%)	88 (16.2)	240 (10.7)	0.002
30 d mortality, *n* (%)	118 (21.7)	364 (16.3)	0.011
90 d mortality, *n* (%)	138 (25.4)	437 (19.5)	0.010
180 d mortality, *n* (%)	148 (27.2)	495 (22.1)	0.039
One-year mortality, *n* (%)	162 (29.8)	548 (24.5)	0.037

Categorical variables are reported as count (% of column total).
Abbreviations: AKI acute kidney injury, KDIGO the Kidney Disease: Improving Global Outcomes.

the hospital significantly increases the risk of mortality in sepsis ($p < 0.001$, **Figure 2B**).

Univariate and Multivariate Cox Hazard Analysis of Risk Factors for Mortality in Sepsis Before Matching

Having identified that several laboratory serum activities, such as serum platelet levels, bicarbonate levels, lactate levels, and INR levels that are significantly associated with hyperbilirubinemia in ICU, we tested whether these serum activities, as well as other clinical outcomes, could be predictors of sepsis prognosis. We first deployed the univariate Cox proportional hazard model to analyze the predictors of mortality in sepsis. We employed a variety of categorical variables with a reference variable: serum platelet levels with platelet levels above or equal to 250*10^9/L being a reference variable; serum lactate levels with lactate levels ≤2 mmol/L being a reference variable; serum bicarbonate levels with bicarbonate levels at 22–29 mmol/L being a reference variable; serum TBIL levels with TBIL levels <2 mg/dl being a reference variable; the AKI KDIGO stage without AKI as a reference variable.

Univariate analysis indicated that age at more than 65 years, weight, race in Black, Hispanic, or other, preexisting medical conditions (Malignancy, Stroke, AFIB, and renal disease), Elixhauser comorbidity index, respiratory rate at more than 30 m beats/min, serum INR levels at more than 1.5, serum platelet levels at <50*10^9/L, serum lactate levels at more than 2 mmol/L, serum bicarbonate levels at more than 29 mmol/L, or <22 mmol/L, AKI at two or three stages, mechanical ventilation usage, vasoactive drug usage, and serum TBIL at more than or equal to 5 mg/dl were the significant risk factors in mortality in sepsis.

To test the prognostic predictors of mortality in sepsis, we performed multivariate analysis using the Cox proportional hazard model for all variables identified as significant by univariate analysis. Following control of confounders and Likelihood ratio (LR) forward elimination, results indicated (**Table 3**) that TBIL levels at 5–10 mg/dl during sepsis have a correlation with 1-year mortality risks [HR 1.396; 95% CI (1.040–1.875); $P = 0.027$]. The finding showed that age above 65 years old [Hazard ratio, HR 2.169; 95% CI (1.829–2.572); $p < 0.001$], other race [HR 1.391; 95% CI (1.158–1.671); $p < 0.001$], preexisting malignancy [HR 1.821; 95% CI (1.544–2.146); $p < 0.001$], preexisting stroke [HR 1.604; 95% CI (1.258–2.044); $p < 0.001$], Elixhauser comorbidity index at admission [HR 1.019; 95% CI (1.008–1.031); $P = 0.001$], respiratory rate above 30 beats/min at admission [HR 1.442; 95% CI (1.242–1.675); $p < 0.001$], serum INR above 1.5 at 24 h of admission [HR 1.217; 95% CI (1.038–1.426); $P = 0.016$], serum platelet <50*10^9/L at 24 h of admission [HR 1.442; 95% CI (1.242–1.675); $p < 0.001$], serum lactate more than 10 mmol/L at 24 h of admission [HR 2.605; 95% CI (1.880–3.609); $p < 0.001$], serum bicarbonate <22 mmol/L [HR 1.375; 95% CI (1.162–1.626); $p < 0.001$], or above 29 mmol/L [HR 1.434; 95% CI (1.140–1.804); $P = 0.002$], and mechanical

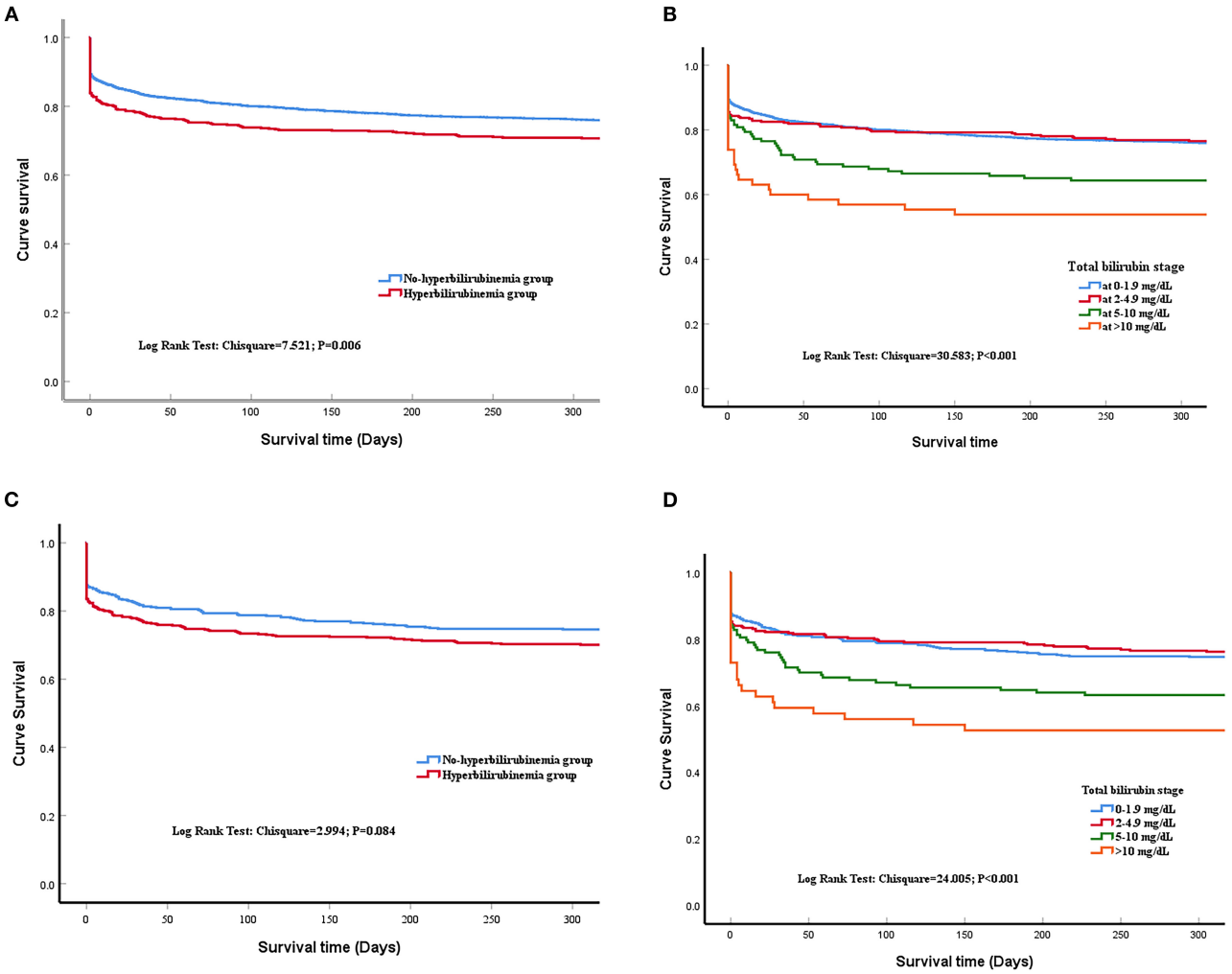

FIGURE 2 | Time to death analysis. **(A)** shows the survival curves for all included patients at 1 year after admission of the last patients before matching, with a significant difference between liver injury and non-liver injury groups (Log-rank $P = 0.006$). **(B)** shows the survival curves for different stages of serum total bilirubin (TBIL) levels before propensity matching. Kaplan-Meier analysis showed survival time did not differ between the hyperbilirubinemia group and the normal group. Log-rank $p < 0.001$. **(C)** shows the survival curves between liver injury and non-liver injury groups after matching (log-rank $P = 0.084$); **(D)** shows the survival curves for different stages of serum TBIL levels after propensity matching (Log-rank $p < 0.001$).

ventilation [HR 1.281; 95% CI (1.093–1.501); $P = 0.002$] were independent risk factors in 1-year mortality before matching by stepwise multivariate Cox hazard analysis.

PS Analysis

From the above results, we found that the baseline clinical information significantly influenced the hyperbilirubinemia group and long-term clinical outcomes. Thus, we applied propensity-score matching to minimize confounding biases. One-to-one propensity-score matching yielded a cohort of 532 patients in the hyperbilirubinemia group and 532 in the control group. Baseline characteristics for patients with and without hyperbilirubinemia were well-balanced after matching, as shown in **Table 4**. Standardized biases for all variables were.05 or less. The SOFA score at admission was excluded as a matching variable for one of its evaluated parameters, including TBIL. In the hyperbilirubinemia group after matching, the rates of the SOFA score at admission above 4 was significantly higher in the hyperbilirubinemia group when compared with the non-hyperbilirubinemia group (83.4 vs. 59.8%; $p < 0.001$).

The matched results also showed that the patients with sepsis with the new onset of hyperbilirubinemia were associated with significantly increased risks of mortality at the hospital (16. vs. 11.8%, $P = 0.036$), 30 days (21.4 vs. 16.7%, $P = 0.038$), 90 days (25 vs. 19.5%, $P = 0.027$), and 1 year (29.5 vs. 24.4%, $P = 0.047$), but not statistically increased in 90 days, 180 days, and 1-year mortality in the overall population (**Table 5**). The duration of mechanical ventilation, vasoactive drug or sedative drug usage, and AKI stage did not significantly differ between the two groups.

TABLE 3 | Univariate and stepwise multivariate Cox hazard analysis of risk factors for mortality in sepsis before matching.

Parameters	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
Age>65 years	2.281	1.934–2.692	<0.001	2.169	1.829–2.572	<0.001
Weight	0.993	0.989–0.996	<0.001			
Gender (male)	0.924	0.798–1.071	0.294			
Race						
Race white	0.929	0.793–1.089	0.364			
Race black	0.760	0.580–0.997	0.047			
Race Hispanic	0.440	0.236–0.822	0.010	0.536	0.286–1.004	0.051
Race other	1.440	1.205–1.722	<0.001	1.391	1.158–1.671	<0.001
Preexisting medical conditions						
Malignancy	2.141	1.837–2.495	<0.001	1.821	1.544–2.146	<0.001
Stroke	1.530	1.205–1.944	<0.001	1.604	1.258–2.044	<0.001
AFIB	1.520	1.303–1.773	<0.001	-		
CAD	1.047	0.901–1.281	0.427			
Renal disease	1.337	1.129–1.583	0.001			
Elixhauser comorbidity index				1.019	1.008–1.031	0.001
Respiratory rate (> 30 beats/min)	1.441	1.244–1.670	<0.001	1.442	1.242–1.675	<0.001
Heart rate (> 100 beats/min)	1.100	0.942–1.284	0.227	-		
Laboratory parameters within the first 24 h of ICU admission						
INR levels at >1.5	1.486	1.279–1.725	<0.001	1.217	1.038–1.426	0.016
Maximum platelet levels (10^9/L)						
Platelet ≥ 250						
Platelet at 150∼249	0.805	0.680–0.953	0.012	0.791	0.668–0.938	0.007
Platelet at 100∼149	1.041	0.826–1.312	0.735	0.877	0.691–1.112	0.278
Platelet at 50∼99	1.043	0.748–1.453	0.806	1.274	0.815–1.990	0.288
Platelet at <50	1.575	1.023–2.426	0.039	1.442	1.242–1.675	<0.001
Maximum lactate levels (mmol/L)						
Lactate at 0–2						
Lactate at 2.1–4	1.233	1.035–1.469	0.019	1.121	0.938–1.339	0.208
Lactate at 4.1–10	1.492	1.225–1.816	<0.001	1.219	0.991–1.500	0.061
Lactate at >10	3.616	2.663–4.910	<0.001	2.605	1.880–3.609	<0.001
Maximum Bicarbonate levels				-		
Bicarbonate levels at 22–29						
Bicarbonate levels at <22	1.610	1.369–1.892	0.001	1.375	1.162–1.626	<0.001
Bicarbonate levels at >29	1.365	1.008–1.714	0.007	1.434	1.140–1.804	0.002
AKI KDIGO stage						
AKI at 1 stage	1.113	0.892–1.388	0.342			
AKI at 2 stage	1.653	1.361–2.008	<0.001			
AKI at 3 stage	1.704	1.369–2.120	<0.001			
Mechanical ventilation	1.297	1.118–1.506	0.001	1.281	1.093–1.501	0.002
Sedative drug usage	1.099	0.948–1.273	0.210			
The use of vasoactive drug	1.475	1.273–1.709	<0.001			
Serum total bilirubin levels during the course of disease (mg/dL)						
Serum total bilirubin at 0–1.9 mg/dL						
Serum total bilirubin at 2–4.9 mg/dL	0.977	0.772–1.235	0.844	0.830	0.651–1.058	0.132
Serum total bilirubin at 5–10 mg/dL	1.616	1.216–2.147	0.001	1.396	1.040–1.875	0.027
Serum total bilirubin at >10 mg/dL	2.203	1.525–3.182	<0.001	1.287	0.877–1.888	0.197

AFIB atrial fibrillation, INR International Normalized Ratio, BUN blood urea nitrogen, KDIGO the Kidney Disease: Improving Global Outcomes.

After matching, Kaplan-Meier's analysis showed that the patients with new onset hyperbilirubinemia had a lower long-term survival rate compared with the non-hyperbilirubinemia group but did not reach statistical significance ($P = 0.084$; **Figure 2C**). However, TBIL levels more than or equal to 5 mg/dl at the hospital also

TABLE 4 | Demographic characteristics and clinical outcomes for hyperbilirubinemia and non-hyperbilirubinemia groups after propensity score matching.

Parameters	Full cohort		*P*
	Hyperbilirubinemia group (*n* = 532)	No-hyperbilirubinemia group (*n* = 532)	
Age, mean (SD), y	67.35 (26.96)	66.99 (26.09)	0.545
Male, *n* (%)	308 (57.9)	320 (60.2)	0.493
Race			
White	376 (72.4)	376 (70.7)	0.587
Hispanic	15 (2.8)	15 (2.8)	1.000
Black	39 (7.3)	49 (9.2)	0.316
Other	102 (19.2)	83 (15.6)	0.145
Weight, mean (SD)	81.00 (25.63)	79.75 (23.72)	0.355
Preexisting medical conditions, *n* (%)			
CHF	133 (25.0)	135 (25.4)	0.944
AFIB	171 (32.1)	154 (28.9)	0.287
COPD	53 (10.0)	54 (110.2)	1.000
CAD	116 (21.8)	121 (22.7)	0.768
Stroke	19 (3.6)	15 (2.8)	0.602
Malignancy	141 (26.5)	141 (26.5)	1.000
Renal disease	84 (15.8)	84 (15.8)	1.000
SOFA score at admission, *n* (%)			<0.001
Score at 2∼4	88 (16.5)	214 (40.2)*	
Score at 5∼9	271 (50.9)	244 (45.9)	
Score at ≥10	173 (32.5)	74 (13.9)*	
Elixhauser comorbidity index, mean (SD)	5.00 (10)	5.00 (9)	0.895
Heart rate ≥ 100 (beats/min), *n* (%)	351 (66.0)	368 (69.2)	0.295
Respiratory rate ≥ 30 (beats/min), *n* (%)	240 (45.1)	255 (47.9)	0.390
Laboratory parameters within the first 24 h of ICU admission			
Maximum WBC, mean (SD)	14.40 (9.58)	13.45 (10.60)	0.100
Maximum hemoglobin, mean (SD)	12.00 (2.80)	11.70 (3.20)	0.089
Maximum platelet levels (10^9/L), *n* (%)			0.356
Platelet≥ 250	170 (32.0)	182 (34.2)	
Platelet at 150∼249	209 (39.3)	198 (37.2)	
Platelet at 100∼149	94 (17.7)	77 (14.5)	
Platelet at 50∼99	43 (8.1)	53 (10.0)	
Platelet at <50	16 (3.0)	22 (4.1)	
Maximum potassium, mean (SD)	4.50 (1.2)	4.50 (1.2)	0.399
Maximum sodium, mean (SD)	140.00 (6.0)	140.00 (5.0)	0.326
Maximum bicarbonate levels, *n* (%)			0.174
At <22	184 34.6)	156 (29.3)	
At 22–29	310 (58.3)	332 (62.4)	
At >29	38 (7.1)	44 (8.3)	
Maximum chloride, mean (SD)	108.00 (8.0)	108.00 (7.0)	0.601
Maximum Bun, mean (SD)	28.50 (29.00)	26.50 (31.00)	0.967
Maximum lactate levels(mmol/L), *n* (%)			0.407
Lactate at 0–2	190 (35.7)	199 (37.4)	
Lactate at 2.1–4	170 (32.0)	186 (35.0)	
Lactate at 4.1–10	143 (26.9)	123 (23.1)	
Lactate at >10	29 (5.5)	24 (4.5)	
Maximum creatinine, mean (SD)	1.40 (1.28)	1.30 (1.30)	0.324
Maximum hematocrit, mean (SD)	35.5 (7.65)	34.9 (9.58)	0.157
Maximum INR levels, *n* (%)			

(Continued)

TABLE 4 | Continued

Parameters	Full cohort		*P*
	Hyperbilirubinemia group (*n* = 532)	No-hyperbilirubinemia group (*n* = 532)	
At >1.5	276 (51.9)	270 (50.8)	0.759
Maximum PH, mean (SD)	7.40 (0.07)	7.40 (0.07)	0.796
Maximum pO2, mean (SD)	214.0 (111)	214.0 (144)	0.501
Maximum pCO2, mean (SD)	47.0 (10)	47.0 (9)	0.262
Maximum ALT, mean (SD)	115.00 (288.00)	33.50 (70.75)	<0.001
Maximum AST, mean (SD)	152.50 (354.50)	43.00 (120.50)	<0.001
Maximum total bilirubin at 24 h, mean (SD)	3.30 (3.10)	0.60 (0.60)	<0.001
Maximum total bilirubin at 48 h, mean (SD)	2.10 (3.20)	0.00 (0.50)	<0.001

Continuous variables are reported as mean (Standard deviation, SD), and Categorical variables are reported as count (% of column total).
CHF congestive heart failure, AFIB atrial fibrillation, CAD coronary artery disease, COPD chronic obstructive pulmonary disease, SOFA Sequential Organ Failure Assessment, WBC white blood cell, INR International Normalized Ratio, BUN blood urea nitrogen, AST aspartate transaminase, ALT alanine transaminase, pCO2 partial pressure of carbon dioxide, pO2 partial pressure of oxygen.
**Represent significant difference with P < 0.05.*

TABLE 5 | Clinical outcomes between hyperbilirubinemia and non-hyperbilirubinemia groups after propensity score matching.

Parameters	Full cohort		*P*
	Hyperbilirubinemia group (*n* = 532)	No-hyperbilirubinemia group (*n* = 532)	
Serum total bilirubin levels during the course of disease (mg/dL), *n* (%)		<0.001	
Serum total bilirubin at 0–1.9 mg/dL	0 (0)	532 (100.0)	
Serum total bilirubin at 2–4.9 mg/dL	333 (62.6)	0	
Serum total bilirubin at 5–10 mg/dL	139 (26.1)	0	
Serum total bilirubin at >10 mg/dL	60 (11.3)	0	
The life support			
Vasopressor usage, *n* (%)	242 (45.5)	222 (41.7)	0.240
Mechanical ventilation, *n* (%)	267 (50.2)	263 (49.4)	0.854
Sedative drug usage	265 (49.8)	248 (46.6)	0.326
AKI KDIGO stage, *n* (%)			0.110
AKI at 1 stage	117 (22.0)	176 (23.1)	
AKI at 2 stage	167 (31.4)	132 (24.8)	
AKI at 3 stage	95 (17.9)	101 (19.0)	
Clinical outcomes			
In-hospital mortality, *n* (%)	85 (16.0)	63 (11.8)	0.036
30 d mortality, *n* (%)	114 (21.4)	89 (16.7)	0.038
90 d mortality, *n* (%)	133 (25.0)	104 (19.5)	0.027
180 d mortality, *n* (%)	143 (26.9)	120 (22.6)	0.066
One-year mortality, *n* (%)	157 (29.5)	130 (24.4)	0.047

Categorical variables are reported as count (% of column total).
AKI acute kidney injury, KDIGO the Kidney Disease: Improving Global Outcomes.

significantly increases the risk of mortality in sepsis ($p < 0.001$, **Figure 2D**).

To further verify the levels of TBIL at the hospital on clinical outcomes, we then classified the patients into TBIL levels at the <5 mg/dl group and TBIL levels at the ≥5 mg/dl group. The results demonstrated that patients with sepsis with serum TBIL levels at ≥5 mg/dl during the hospital stage could bring significant poor outcomes on 30-day (28.1 vs. 17%), 180-day (34.7 vs. 19.4%), and 1-year mortality (37.7 vs. 21.7%), but with noninfluence on hospital mortality (18.6 vs. 12.8%) when compared with those with TBIL levels at the <5 mg/dl group (**Supplementary Table 1**).

TABLE 6 | Univariate and multivariate regression analysis to explore independent predictors affecting long-term mortality in sepsis after propensity score matching.

Parameters	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
Age>65 years	2.041	1.583–2.633	<0.001	2.216	1.710–2.874	<0.001
Weight	0.998	0.993–1.003	0.369			
Gender (male)	0.890	0.705–1.124	0.329			
Race						
Race white	0.837	0.653–1.074	0.161			
Race black	0.706	0.432–1.152	0.164			
Race hispanic	0.330	0.106–1.029	0.056			
Race other	1.712	1.309–2.238	<0.001	1.647	1.256–2.160	<0.001
Preexisting medical conditions						
Malignancy	1.859	1.465–2.358	<0.001	1.688	1.314–2.167	<0.001
Stroke	1.282	0.702–2.342	0.419			
AFIB	1.550	1.223–1.965	<0.001	-		
CAD	1.178	0.904–1.537	0.226			
COPD	1.228	0.858–1.756	0.261			
Renal disease	1.354	1.013–1.809	0.041			
Elixhauser comorbidity index	1.047	1.030–1.064	<0.001			
Respiratory rate (>30 beats/min)	1.340	1.062–1.689	0.013	1.298	1.025–1.644	0.030
Heart rate (>100 beats/min)	1.184	0.919–1.527	0.192	-		
Laboratory parameters within the first 24 h of ICU admission						
INR levels at >1.5	1.690	1.331–2.147	<0.001	1.325	1.031–1.704	0.028
Maximum platelet levels (10^9/L)						
Platelet≥ 250						
Platelet at 150∼249	0.741	0.561–0.980	0.035	0.669	0.504–0.887	0.005
Platelet at 100∼149	0.943	0.670–1.327	0.736	0.777	0.550–1.097	0.777
Platelet at 50∼99	0.822	0.528–1.281	0.387	0.789	0.505–1.233	0.789
Platelet at <50	1.593	0.954–2.659	0.075	1.787	1.047–3.048	0.033
Maximum lactate levels(mmol/L)						
Lactate at 0–2						
Lactate at 2.1–4	1.227	0.905–1.663	0.189	1.107	0.813–1.507	0.518
Lactate at 4.1–10	1.715	1.264–2.328	0.001	1.435	1.042–1.977	0.027
Lactate at >10	4.990	3.354–7.423	<0.001	3.976	2.586–6.112	<0.001
Maximum Bicarbonate levels				-		
Bicarbonate levels at 22–29						
Bicarbonate levels at <22	1.982	1.555–2.526	<0.001	1.536	1.192–1.980	0.001
Bicarbonate levels at >29	1.487	0.970–2.279	0.068	1.767	1.147–2.725	0.010
AKI KDIGO stage						
AKI at 1 stage	0.921	0.638–1.328	0.659			
AKI at 2 stage	1.600	1.177–2.174	0.003			
AKI at 3 stage	1.868	1.346–2.593	<0.001			
Mechanical ventilation	1.459	1.155–1.845	0.002			
Sedative drug usage	1.293	1.025–1.631	0.030			
The use of vasoactive drug	1.447	1.148–1.824	0.002			
Serum total bilirubin levels during the course of disease (mg/dL)						
Serum total bilirubin < 5 mg/dL						
Serum total bilirubin at ≥ 5 mg/dL	1.776	1.370–2.301	<0.001	1.608	1.228–2.106	0.001

CHF congestive heart failure, AFIB atrial fibrillation, CAD coronary artery disease, COPD chronic obstructive pulmonary disease, SOFA Sequential Organ Failure Assessment. AKI acute kidney injury, KDIGO the Kidney Disease: Improving Global Outcomes.

Univariate and Multivariate Cox Hazard Proportional Analysis to Explore Independent Predictors Affecting Long-Term Mortality in Sepsis After Matching

We then explored the direct effects of different levels of hyperbilirubinemia during the cause of sepsis on a long-term clinical outcome after matching. Multivariate analysis using the Cox proportional hazard model for all variables was identified as significant by univariate analysis. Following control of confounders and LR forward elimination, it was still shown in **Table 6** that, when TBIL levels were <5 mg/dl as a reference variable, TBIL at ≥5 mg/dl during sepsis increased the risk of 1-year mortality with 1.608 times [95% CI (1.228–2.106); $P = 0.001$].

We also found that age above 65 years old [HR 2.216; 95% CI (1.710–2.874); $p < 0.001$], other race [HR 1.647; 95% CI (1.256–2.160); $p < 0.001$], preexisting malignancy [HR 1.688; 95% CI (1.314–2.167); $p < 0.001$], respiratory rate above 30 beats/min at admission [HR 1.298; 95% CI (1.025–1.644); $P = 0.030$], serum INR above 1.5 at 24 h of admission [HR 1.325; 95% CI (1.031–1.704); $P = 0.028$], serum platelet <50*10^9/L at 24 h of admission [HR 1.787; 95% CI (1.047–3.048); $P = 0.033$], serum lactate more than 4 mmol/L [HR 1.435; 95% CI (1.042–1.977); $P = 0.027$], or even more than 10 mmol/L at 24 h of admission [HR 3.976; 95% CI (2.586–6.112); $p < 0.001$], and serum bicarbonate <22 mmol/L [HR 1.536; 95% CI (1.192–1.980); $P = 0.001$], or above 29 mmol/L [HR 1.767; 95% CI (1.147–2.725); $P = 0.010$] were independent risk factors in 1-year mortality in sepsis after matchings. When using serum platelet ≥ 250*10^9/L as a reference variable, the result demonstrated that serum platelet at 150–249*10^9/L was the only protective factor in long-term mortality in sepsis [HR 0.669; 95% CI (0.504–0.887; $P = 0.005$)].

DISCUSSION

In this large cohort study, we find the incidence rate of the new onset of hyperbilirubinemia during sepsis is 19.5%, which is considerably lower than the rate of hyperbilirubinemia in other patients who are critically ill (14, 27). The difference is mainly due to the hyperbilirubinemia in our study that is defined as the new onset excluding past liver diseases, while previous studies included patients with preexisting chronic liver conditions (22, 28). Our data show that, after PS matching, the new onset of hyperbilirubinemia during sepsis cannot significantly increase the risk of long-term mortality, but the patients with TBIL levels are more than or equal to 5 mg/dl do. Further multivariate Cox hazard analysis shows that age above 65 years old, other race, preexisting malignancy, respiratory rate above 30 beats/min at admission, serum parameters levels within 24-h admission containing INR above 1.5, platelet <50*10^9/L, lactate above 4 mmol/L, bicarbonate <22 or above 29 mmol/L, serum TBIL during sepsis at more than or equal to 5 mg/dl are the independent risk factors in 1-year mortality of patients with sepsis.

Furthermore, the low level of platelet, the INR level more than 1.5, the respiratory rate more than or equal to 30 (beats/min), the higher creatinine level, the higher arterial pCO2, and the lower bicarbonate level in the hyperbilirubinemia group compared with the non-hyperbilirubinemia group indicate that there is a close correlation between hyperbilirubinemia and the deterioration of hematologic, coagulation, respiratory, urinary, and acid-base balance systems function in sepsis. In stepwise multivariate Cox hazard analysis, Elixhauser comorbidity index, the respiratory rate above 30 beats/min at admission, serum INR above 1.5, serum platelet <50*10^9/L, serum lactate more than 4 mmol/L, serum bicarbonate <22 mmol/L, or above 29 mmol/L at 24 h of admission, and mechanical ventilation as independent risk factors in 1-year mortality of patients with sepsis hint that hematologic, coagulation, respiratory, and acid-base systems that are imbalance at the early stage of sepsis predict poor prognosis of long-term mortality of sepsis. In addition, when serum TBIL at more than or equal to 5 mg/dl as a predictive factor in 1-year mortality of patients with sepsis consolidates our speculation: the new onset of hyperbilirubinemia reach at some extent aggravates sepsis prognosis.

Intriguingly, we observe that the hyperbilirubinemia group has a significantly higher rate of preexisting AFIB and malignancy but a lower rate of past COPD, stroke, and renal disease than the non-hyperbilirubinemia group. The mechanism of the potential relationship between the new onset of hyperbilirubinemia and past medical history in sepsis is not clear and needs further study. Multivariate Cox analysis results suggest that preexisting diseases, such as malignancy, affect the long-term survival of patients with sepsis, which is consistent with recent findings (29). Given that great bias was frequently generated when analyzing the sole effect of hyperbilirubinemia on sepsis, we used PS matching analysis to balance baseline characteristics to minimize confounding bias. After matching, baseline variants are well adjusted to parallel, thus reducing confounding bias to the maximum extent. Importantly, the new onset of hyperbilirubinemia when TBIL levels achieve at more than or equal to 5 mg/dl is associated with significantly increased long-term mortality of patients with sepsis after matching. Compared with the previous study, which did not use PS matching to strictly control possible confounders (24), our study provides solid evidence and comprehensive dissection of the relationship between the dynamic change of hyperbilirubinemia and sepsis prognosis, and, at the same time, we seek a cutoff value of TBIL levels associated with a poor outcome in sepsis, which may guide for early intervention for ICU physicians. Our results are consistent with previous basic research, which shows that the liver plays an important role in endotoxin-induced acute lung injury (30). Moreover, Zhang et al. (31) have proposed a Cox regression model with time-varying covariates, which is useful for evaluating the dynamic change of hyperbilirubinemia on clinical outcomes and can be used in further analysis. The liver is the key detoxification organ and the critical site to clear invasive pathogens and alleviate inflammation reaction by exerting innate immune system function (6, 7). Meanwhile, liver dysfunction

and associated hyperbilirubinemia lead to inflammation and immune response out of control and cascading organ damage in sepsis (8, 9).

Furthermore, we explore the independent risk factors affecting 1-year mortality of patients with sepsis after PS matching, and we find that old age, preexisting malignancy, respiratory rate above 30 beats/min at admission, serum parameters within 24-h admission with INR above 1.5, serum platelet <50*10^9/L, serum lactate more than 4 mmol/L, and bicarbonate <22 or above 29 mmol/L are the independent risk factors in 1-year mortality of patients with sepsis. These parameters may provide early warning of the prognosis of patients with sepsis. Previous basic pieces of research show that sepsis-induced acute kidney and myocardial injury are age-dependent (32, 33), and a recent clinical study has shown that the odds for mortality of patients with sepsis in ICU increase with age (34), which are consistent with our results. In qSOFA definition, expert consensus shows the respiratory rate of 22/min or greater, which is the predictor for a poor outcome of patients with sepsis (25); our results further demonstrate the respiratory rate of 30/min or greater at admission is the independent risk factor in long-term mortality. Abundant studies have focused on the correlation between the serum lactate level and short-term mortality of patients with sepsis; the lactate level ≥2 mmol/L around is demonstrated having the predictive value (35, 36). However, the cutoff of the lactate level for predicting long-term mortality of sepsis remains unclear. Our results show lactate above 4 mmol/L within 24-h admission is the independent predictor for 1-year mortality of sepsis, and patients with lactate above 10 mmol/L will bring a poor prognosis in sepsis. Of note, recent studies have shown that platelets play a vital role in immunological surveillance against pathogens invaders and contribute to innate immune system function (37, 38). Wong et al. demonstrated that platelets collaborate with macrophages to fight against certain blood-borne infections. In addition, the absence of the platelet resulted in the platelet being unable to localize to the sites of infection, leading to rapid death of the Kupffer cells and endothelium, followed by more leakage of plasma out of blood vessels, and even host mortality (39). This may explain why patients with sepsis with lower-level platelets have poor outcomes in our study. Besides, we find that bipolar serum bicarbonate levels are another risk factor in the long-term mortality of patients with sepsis. Previous experimental studies indicate that endotoxemia significantly decreases bile acid-independent bile flow (BAIBF) and associated biliary HCO_3^- output (40), thus reducing the serum bicarbonate level. As there are no studies that have reported the correlation between the bicarbonate level and sepsis mortality, our study first shows that bicarbonate <22 or above 29 mmol/L is an independent predictor for 1-year mortality of sepsis.

To our knowledge, this is the first and largest study so far to dissect the correlation between the dynamic change of hyperbilirubinemia and outcomes of sepsis. However, there are several limitations to our study. First, we used the database from a single academic medical center in the USA; therefore, some of the cases from almost 10 years ago, as diagnosis or treatment strategies at that time, would be inconsistent with current guidelines, which brings great bias. There is residual confounding by variables not collected into the MIMIC-III database. However, we include all the patients with sepsis according to the uniform standard of Sepsis 3.0 and apply PSs analysis and match the baseline characteristics of the patients to eliminate confounding factors and decrease bias to the maximum. Second, there are a few missing data that bring bias, yet we delete the data whose missing percentage is larger than 50% to decrease bias. The mean-value imputation algorithm is selected to substitute missing values. Third, the single-centered design restricts generalizability to apply our conclusion to other regions, while we use a large sample size and PS matching analysis to guarantee the quality of our study.

CONCLUSION

In conclusion, patients with serum TBIL at more than or equal to 5mg/dl during sepsis decrease survival rates after PS matching. In addition, we conclude that age above 65 years old, preexisting malignancy, respiratory rate above 30 beats/min at admission, serum parameter levels within 24-h admission, containing INR above 1.5, platelet <50*10^9/L, lactate above 4 mmol/L, and bicarbonate <22 or above 29 mmol/L are independent risk predictors for long-term mortality of sepsis. Our study provides solid evidence and will rekindle the awareness of the risk factors leading to poor prognosis in sepsis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Files**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The Ethics approval statement was approved by the Institutional Review Boards of Beth Israel Deaconess Medical Center (Boston, MA), and all the data were under a deidentification process to protect individual privacy and waived the need for a patient consent statement. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MP, DQ, LZ, and ZH contributed to the conception and design of the research. MP and FD contributed to the acquisition and analysis of the data. MP, ZH, and LZ contributed to the interpretation of the results. MP and DQ drafted the manuscript. DQ, ZH, and LZ revised the manuscript. All authors have agreed to be fully accountable for ensuring the accuracy of the work, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.713917/full#supplementary-material

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Efficiency of Monocyte/High-Density Lipoprotein Cholesterol Ratio Combined With Neutrophil/Lymphocyte Ratio in Predicting 28-Day Mortality in Patients With Sepsis

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Background: Sepsis can cause unpredictable harm, and early identification of risk for mortality may be conducive to clinical diagnosis. The present study proposes to assess the efficacy of the monocyte/high-density lipoprotein cholesterol ratio (MHR) combined with the neutrophil/lymphocyte ratio (NLR) on the day of admission in predictive efficacy in the 28-day mortality risk in critical patients with sepsis.

Material and Methods: We administered observational and retrospective cohort research from a single center. The correlation of the clinical variables, together with the system severity scores of APACHE II and SOFA, are displayed by correlation analysis, and a Cox regression model could be performed to screen the independent risk factors and estimate the capacity of multiple markers in predicting 28-day mortality. The receiver operating characteristic (ROC) curve served as an applied method to output cutoff values for the diagnosis and prognostic risk, and the area under the ROC curve and net reclassification improvement index (NRI), as well as integrated discrimination improvement index (IDI) were employed to assess the feasibility of multiple parameters for predictive value in 28-day mortality of septic patients.

Results: The study enrolled 274 eligible patients with sepsis. The correlation analysis indicated NLR and MHR were related to the sepsis severity. A multivariate Cox regression analysis indicated that NLR together with MHR displayed a close relation to death rate after adjusting for other potential confounders (NLR, HR = 1.404 [95% CI 1.170–1.684], $P < 0.001$; MHR, HR = 1.217 [95% CI 1.112–1.331], $P < 0.001$). The AUC of NLR, MHR, NLR_MHR was 0.827, 0.876, and 0.934, respectively. The addition on the biomarker NLR_MHR to the prediction model improved IDI by 18.5% and NRI by 37.8%.

Conclusions: Our findings suggest that NLR and MHR trend to an elevated level in non-surviving patients with sepsis. Evaluation of NLR_MHR, an independent risk factor for increased mortality, might improve the predictive efficacy for 28-day mortality risk in septic patients.

Keywords: neutrophil/lymphocyte ratio, monocyte/high-density lipoprotein cholesterol ratio, predictive value, mortality, sepsis

INTRODUCTION

Sepsis is a complicated, life-threatening disorder attributed to a dysregulated host response to infection; eventually acute multiorgan dysfunction develops with high morbidity and mortality (1–3). This syndrome, one of the major causes of death in the intensive care unit (ICU), is universally accepted as a public health issue with a considerable economic burden and tremendous concern for critical patients (4–6). According to the reports from the Centers for Disease Control, the incidence of sepsis is approximately more than 750,000 cases per year globally, and the morbidity of sepsis in all ICU admissions is as high as 27% (7, 8). Because of sepsis being the final pathway to death from most infections, it remains at a high mortality at around 25–30% in hospitalized sepsis patients that are equivalent to killing tens of millions of individuals worldwide annually (9–11). Despite constant progress in patient administration and therapeutic strategies, sepsis remains an intractable problem in clinical care because of the limitations in the gold standard of sepsis diagnosis as well as timely identification, which hinders the implement by reference in epidemiological studies.

The international consensus definition for sepsis and septic shock (Sepsis 3.0) has redefined sepsis as fatal multiple organ dysfunction with systemic interaction between excessive inflammatory response and a suppressive immune state in response to an infectious organism or tissue injury (12). The consensus of Sepsis 3.0 emphasizes the immune system as the foundation at which host-derived molecules and foreign products induced by pathogenic microorganism interact with pathogen recognition receptors expressed on immune cells, which cause unbalanced activation of innate immunity (13). Moreover, it emphasizes that the interactions between systemic inflammation and oxidative stress have particularly been accused of performing crucial impact on the pathogenesis of sepsis (14–16). Increasing evidence supports the viewpoint that both immune dysfunction and oxidative stress are critical in the pathogenesis of sepsis. Along with the continual amplification of immune dissonance, oxidative stress is exacerbated during sepsis, finally leading to the redox cascade of cell damage, impairment of mitochondrial function, and aggravation of inflammation (17). Thus, septic patients at risk of immune deterioration and oxidative storm should be identified prior to the onset of organ dysfunction. Identifications of immune and oxidative-related predictors in sepsis have great potential to improve the diagnosis, assessment, and treatment of septic complications.

Although various biomarkers have been improved and applied in evaluation of the capacity of early recognition and prediction in sepsis (18–20), their exact values are still uncertain or controversial. The neutrophil/lymphocyte ratio (NLR) is a rapidly available parameter that is previously reported as reflecting the severity of the disease in critically ill patients and notably correlates with in-hospital mortality in sepsis (21). However, whether NLR predicts septic prognosis in the long term remains controversial, and the reason is that NLR is representative only of the quantity of immune cells rather than functional and oxidative status when sepsis occurs. Monocyte/high-density lipoprotein cholesterol ratio (MHR) is proven to be a parameter of systemic inflammation and oxidative stress in many inflammatory diseases (22–24). Hence, it is speculated that MHR together with NLR might further improve predicting mortality risk in septic patients better than a single indicator. In light of this evidence, we propose to investigate the effectiveness of MHR combined with NLR in predicting 28-day mortality in patients with sepsis.

MATERIALS AND METHODS

Subject Design and Patient Enrollment

This single-center retrospective observational study was administrated in septic patients who were admitted to the emergency ICU (EICU) of the Second Hospital of Hebei Medical University between January 2015 and December 2020; 2045 adult patients (aged >18 years) who conformed to the diagnostic standard of the Surviving Sepsis Guideline (Sepsis 3.0) (12) were enrolled in this study. We excluded patients with a reference standard that included (1) younger than 18 years old, (2) EICU hospitalized <24 h, (3) immunodeficient state: systemically solid tumor or hematological malignances [active stage or decubation within 5 years; recipients of autotransplantation or allotransplantation in stem cell; solid organ transplantation, long-term application for hormonotherapy (>30 days) or high dose (>1 mg/kg/day) of steroids (>14 days)] or currently on immunosuppressive drug for more than 30 days, (4) acute or chronic liver disease, (5) using antihyperlipidemic therapy, (6) synsemantic or missing medical data registers. The enrolled participants signed informed consent forms and were observed for at least 28 days. The patients accepted professional medical care in the whole hospitalized course and normative treatment complying with the Surviving Sepsis Campaign Guideline (12). The research was conducted in accordance with the principle of the Declaration of Helsinki and approved by the Medical Ethics Committee established in the Second Hospital of Hebei Medical University, Shijiazhuang, China (**Figure 1**).

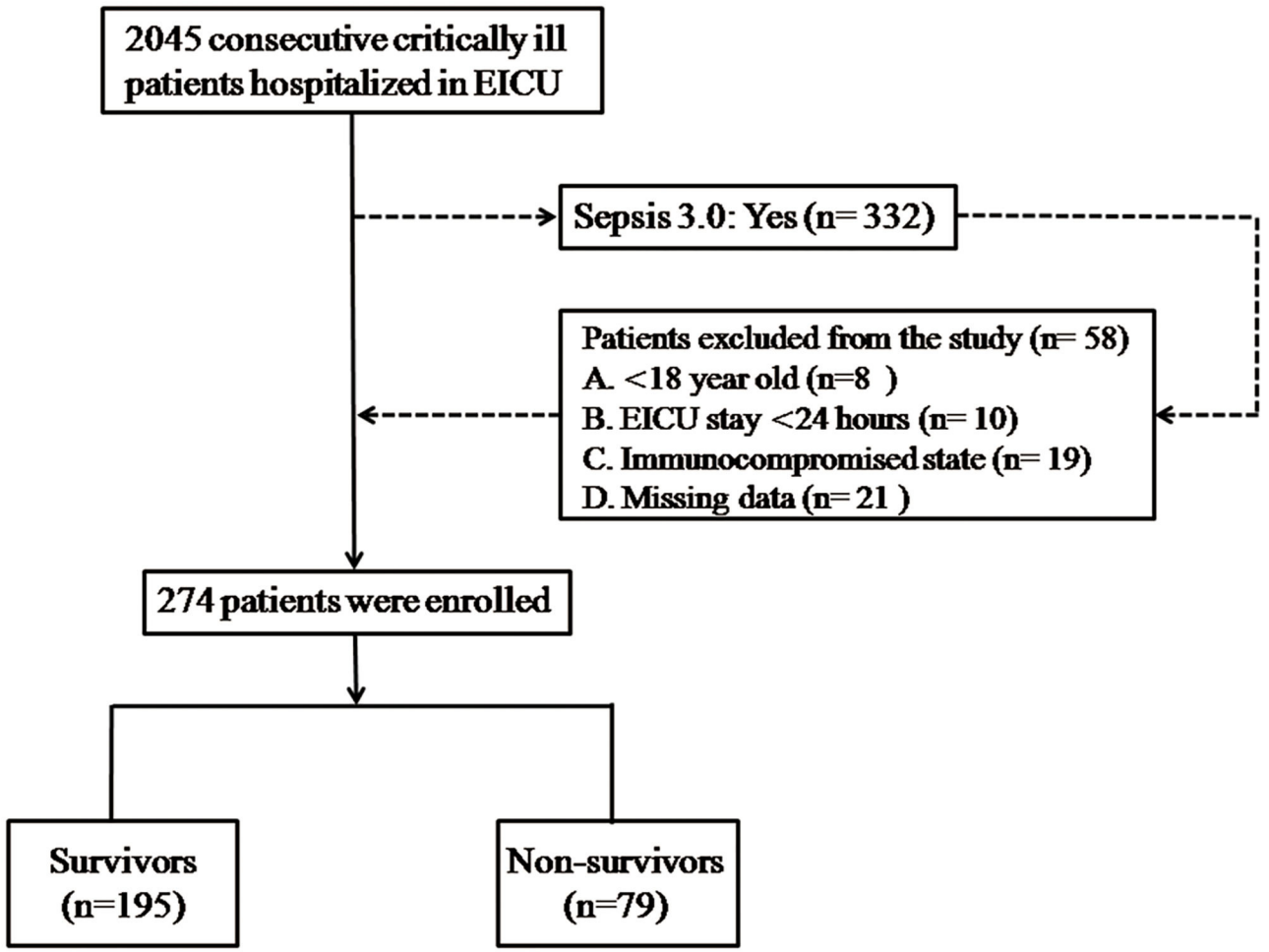

FIGURE 1 | Flowchart of the enrolled patients. There were 2,045 adult patients who met the diagnostic criteria of the Surviving Sepsis Guideline (Sepsis 3.0), who were tested in this study, and 264 enrolled patients were stratified into the survivor and non-survivor groups. Demographic data and clinical and laboratory parameters were compared between the survivor and non-survivor groups.

Data Extraction Process

Demographic data and clinical and laboratory parameters of enrolled patients were collected from the electronic medical record system in the hospital. Patients' demographic characteristics are documented in detail in the records, and complications; source of infection; and vital signs, including body temperature, systolic blood pressure (SBP), and heart rate are collected. Laboratory parameters were obtained from the examination of blood samples in the antecubital vein within 3 h after admission to the EICU. Routine hemogram was determined with the EB-10 (F4) mechanized hematology analytical facility (Sysmetix, Mobe, Japan), and procalcitonin (PCT) level was tested by the luminescence immunoassay instrument (Goche, socobas e211). Electromagnetic biochemical analysis equipment 730-128 (Mitachi High Technologies, Japan) was used to determine the biochemical parameters. C-reactive protein (CRP) level was measured by applying the CRP mensurable device (Quickly Read system). In addition, MHR was obtained by calculating a ratio of absolute monocyte count to high-density lipoprotein (HDL) cholesterol content. NLR was computed by distributing the neutrophil-to-lymphocyte count. Of note, each participant is evaluated as to severity degree by means of Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. We employed the all-cause mortality of hospitalization as a primary endpoint in the current study.

Statistical Analysis

All statistical processes were performed by using SPSS software (version 26.0; IBM Corporation, St. Louis, Missouri, USA). Enrolled patients, who were stratified into survivor and non-survivor groups in line with 28-day survival status, are compared by the baseline characteristics accordingly. Continuous data that conformed to normal distribution were expressed as mean ± standard deviation (SD), non-normally distributed variables were presented as median (interquartile range), and categorical data were shown as counts (percentages). We adopted

Student's *t*-test or the Mann–Whitney *U* test to evaluate the differences between continuous variables in the two groups, and the chi-squared test was applied to the comparison of categorical variables.

Prior to the analysis of regression on model risk factors, we selected boxplots to demonstrate the correlation between normal numerical variables (CRP, PCT, NLR, MHR) and severity of sepsis. Univariate and multivariate analyses were conducted by Cox regression model to assess the predicted potential of the abovementioned markers on 28-day mortality in sepsis. All the variables in the Cox regression models are shown as hazard ratio (HR) within 95% confidence intervals (CIs). Univariate analysis was performed preferentially, and variables with significance determined as $P < 0.01$ should subsequently be incorporated into the multivariate model, which is adjusted for the factors of age, sex, BMI, SBP, APACHE II, and SOFA scores. In a multiple Cox regression model, we compare the predictive value of PCT, CRP, NLR, and MHR.

Before further assessing the accuracy of the parameters in predicting the prognostic value of sepsis with the measure of AUC in the ROC analysis (25) and classification of mortality risk categories in the following step (26, 27), we adopted logistic regression to calculate and output a proportion of combination between NLR and MHR, which constructed a new model defined as NLR_MHR. The predictive value of each model of CRP, PCT, NLR, MHR, and NLR_MHR was evaluated by ROC analysis. Additionally, the sensitivity and specificity of the optimal cutoff value, positive predictive value (PPV) and negative predictive value (NPV) as well as Youden index were calculated to evaluate the accuracy of the predictors. The effects of classified model mortality risk categories were analyzed with net reclassification improvement index (NRI), which represents the reformative ability in differentiation and reclassification as well as the integrated discrimination improvement index (IDI) that was appropriate for the new model in prediction (27). The values of NRI and IDI were calculated by R Statistical Software (version 4.0.3, Vienna, Austria). *P* value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics and Clinical Outcomes

A total of 274 eligible patients admitted to the EICU in the period of study were enrolled with reference to the detailed flow diagram shown in **Figure 1** and should be classified into survivor ($n = 195$) and non-survivor groups ($n = 79$), according to the eventual state. The difference in demographic data of groups and comparative results are represented in **Table 1**. Of all septic patients, 195 (71.2%) patients survived more than 28 days. In comparison to those in the survivor group, patients in the non-survivor group, respectively, presented older ages (59.47 ± 7.44 vs. 56.96 ± 11.67; $P < 0.05$), higher body temperatures (38.58 ± 0.89 vs. 38.17 ± 0.88; $P < 0.05$), and lower levels of SBP (107.22 ± 15.97 vs. 112.35 ± 14.90; $P < 0.05$). Meanwhile, patients of the non-survivor group were more likely to be complicated with hypertension and coronary heart disease than those of the survivor group. With regard to the laboratory data, the levels of neutrophils (6.69 ± 1.42 vs. 6.12 ± 1.26) and monocytes (0.67 ± 0.66 vs. 0.41 ± 0.07) in the non-survivor group were significantly higher, whereas the levels of lymphocyte (1.12 ± 0.39 vs. 1.57 ± 0.65) and HDL (46.53 ± 2.4 vs. 52.11 ± 2.16) were markedly lower than those of the survivor group. For bioindicators, the levels of PCT (10.39 ± 4.21 vs. 7.71 ± 3.63; $P = 0.001$), NLR (6.28 ± 1.37 vs. 4.28 ± 1.18; $P = 0.001$), and MHR (14.29 ± 2.52 vs. 9.76 ± 2.85; $P = 0.001$) in the non-survivor group were markedly elevated than those in the survivor group. Otherwise, there was no significant difference of CRP level between the survivor and non-survivor groups. Apparently, patients in the non-survivor group presented poorer prognoses with the outcomes of APACHE II scores (27.11 ± 3.86 vs. 17.05 ± 4.13; $P = 0.001$) and SOFA scores (12 (10–14) vs. 7 (6–9); $P = 0.001$). Nevertheless, we failed to observe significant differences in terms of BMI, heart rate, and source of infection.

Correlation Analysis of Investigated Variables and Severity Scores

Scatterplots were distributed to describe the correlation between laboratory bioindicators and severity of sepsis. In antecedent of the statistical analysis, we stratified septic patients into three groups complying with the following levels of scores: (1) APACHE II scores: <16, 16–24, >24 and (2) SOFA scores: <6, 6–10, >10 (28, 29). As shown in **Figure 2**, MHR presented the closest correlation with both APACHE II and SOFA scores, followed by NLR and PCT, whereas CRP showed absence of relevance to severity scores.

Prognosticators of 28-Day Mortality Risk in Septic Patients

To identify the risk factors for 28-day mortality in patients suffering from sepsis, we implemented Cox regression analysis. As revealed in **Table 2**, high levels of PCT, NLR, and MHR potentially aggravated the 28-day mortality risk of septic patients ($P < 0.001$). In multivariate analyses, it indicated that MHR remained statistically significant after adjusting for age, sex, BMI, SBP, and APACHE II as well as SOFA scores (HR = 1.217, 95% CI 1.112–1.331, $P < 0.001$). Additionally, NLR was confirmed to be independently associated with 28-day mortality of patients diagnosed with sepsis (HR = 1.404, 95% CI 1.170–1.684, $P < 0.001$).

The Predictive Accuracy of Parameters for 28-Day Mortality in Septic Patients

We compared the model performance–discrimination, overall fit, and reclassification to further evaluate the predictive potency of 28-day mortality in sepsis. For the model discrimination displayed in **Figure 3**, outcomes in the AUC diagram indicate that the MHR_NLR model had the largest AUC (0.934 [0.898–0.960]), followed by MHR (0.876 [0.831–0.913]), NLR (0.827 [0.777–0.870]), and PCT (0.705 [0.647–0.758]). The AUC value

TABLE 1 | Baseline characteristics of studied population.

Variables	Total $n = 274$	Survivors $n = 195$	Non-survivors $n = 79$	*P*
Demographics				
Sex (male %)	168 (61.3)	117 (60.0)	51 (64.6)	0.483
Age, years	57.68 ± 10.65	56.96 ± 11.67	59.47 ± 7.44	0.035
BMI, kg/m^2	22.84 ± 2.84	22.68 ± 2.73	23.22 ± 3.09	0.148
Body temperature, °C	38.29 ± 0.90	38.17 ± 0.88	38.58 ± 0.89	0.011
SBP, mmHg	110.87 ± 15.34	112.35 ± 14.90	107.22 ± 15.97	0.012
Heart rate, bpm	98.07 ± 17.36	97.27 ± 17.23	100.04 ± 17.74	0.234
Site of primary infection				
Lower respiratory tract	101 (36.9)	68 (34.9)	33 (41.8)	0.350
Intra-abdomen	64 (23.4)	45 (23.1)	19 (24.1)	
Urinary system	45 (16.4)	37 (18.9)	8 (10.1)	
Skin and soft tissue	45 (16.4)	30 (15.4)	15 (18.9)	
Unknown origin	19 (6.9)	15 (7.7)	4 (5.1)	
Comorbidities				
Hypertension	80 (29.2)	49 (25.1)	31 (39.2)	0.020
CHD	45 (16.4)	17 (8.7)	28 (35.4)	0.001
Diabetes mellitus	53 (19.3)	32 (16.4)	21 (26.6)	0.053
COPD	19 (6.9)	11 (5.6)	8 (10.1)	0.186
Cerebrovascular disease	45 (16.4)	27 (13.8)	18 (22.8)	0.070
CRI	29 (10.6)	17 (8.7)	12 (15.2)	0.115
Malignant neoplasm	13 (4.7)	8 (4.1)	5 (6.3)	0.432
Laboratory data				
CRP, mg/L	88.84 ± 4.39	88.55 ± 3.99	89.57 ± 5.22	0.082
PCT, ng/ml	8.48 ± 3.98	7.71 ± 3.63	10.39 ± 4.21	0.001
Neutrophil, *10^9/L	6.28 ± 1.33	6.12 ± 1.26	6.69 ± 1.42	0.002
Lymphocyte, *10^9/L	1.44 ± 0.62	1.57 ± 0.65	1.12 ± 0.39	0.011
Monocyte, *10^9/L	0.48 ± 0.14	0.41 ± 0.07	0.67 ± 0.66	0.001
HDL, mg/dl	49.13 ± 2.31	52.11 ± 2.16	46.53 ± 2.4	0.015
NLR	4.86 ± 1.53	4.28 ± 1.18	6.28 ± 1.37	0.001
MHR	11.07 ± 3.43	9.76 ± 2.85	14.29 ± 2.52	0.001
Severity scores				
APACHE II	19.95 ± 6.09	17.05 ± 4.13	27.11 ± 3.86	0.001
SOFA	8 (7–10)	7 (6–9)	12 (10–14)	0.001

Data were expressed as mean ± standard deviation (SD), median (interquartile range) or No. (%). $P < 0.05$ indicates statistical significance.
CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment.

of CRP (0.569 [0.508–0.628]) was found to be smaller than the above predictors, which demonstrate the serum CRP levels might be irrelevant to the mortality risk of septic complications.

Next, the model of overall reclassification improvement was assessed by NRI and IDI, which are more sensitive tests for improving model discrimination than ROC curves. When compared with CRP, it is noteworthy that PCT failed to indicate the significantly higher NRI and IDI. NLR shows a better NRI compared with PCT. Additionally, MHR with high IDI and NRI could better regrade patients to a more proper mortality risk classification than CRP, PCT, and NLR. Notably, we identified that NLR_MRH could better reclassify patients as indicated by significantly higher NRI and IDI in comparison to the single of NLR or MHR (**Table 3**).

ROC Curve Analysis

To achieve more precise progress in predictive value for 28-day mortality of sepsis, we figured out the sensitivity, specificity, cutoff point, PPV, NPV, and Youden index in ROC analysis. As shown in **Table 4**, the sensitivity and specificity of MHR at the optimal cutoff value of 10.15 were 94.94% (87.5–98.6%) and 65.13% (58.0–71.8%), respectively. The optimal cutoff value of NLR was 5.51, which gave a sensitivity of 69.62% (58.2–79.5%) and a specificity of 89.74% (84.6–93.6%). Of note, MHR_NLR trended toward a high specificity of 91.28% (86.4–94.8%). Based on the cutoff values listed in **Table 4**, NLR_MHR obtained a best PPV (80.7, 72.5–86.9%), and MHR showed a best NPV (96.9, 92.4–98.8%). Furthermore, we found NLR_MHR presented the highest Youden index of 0.8116. Collectively, NLR_MHR was

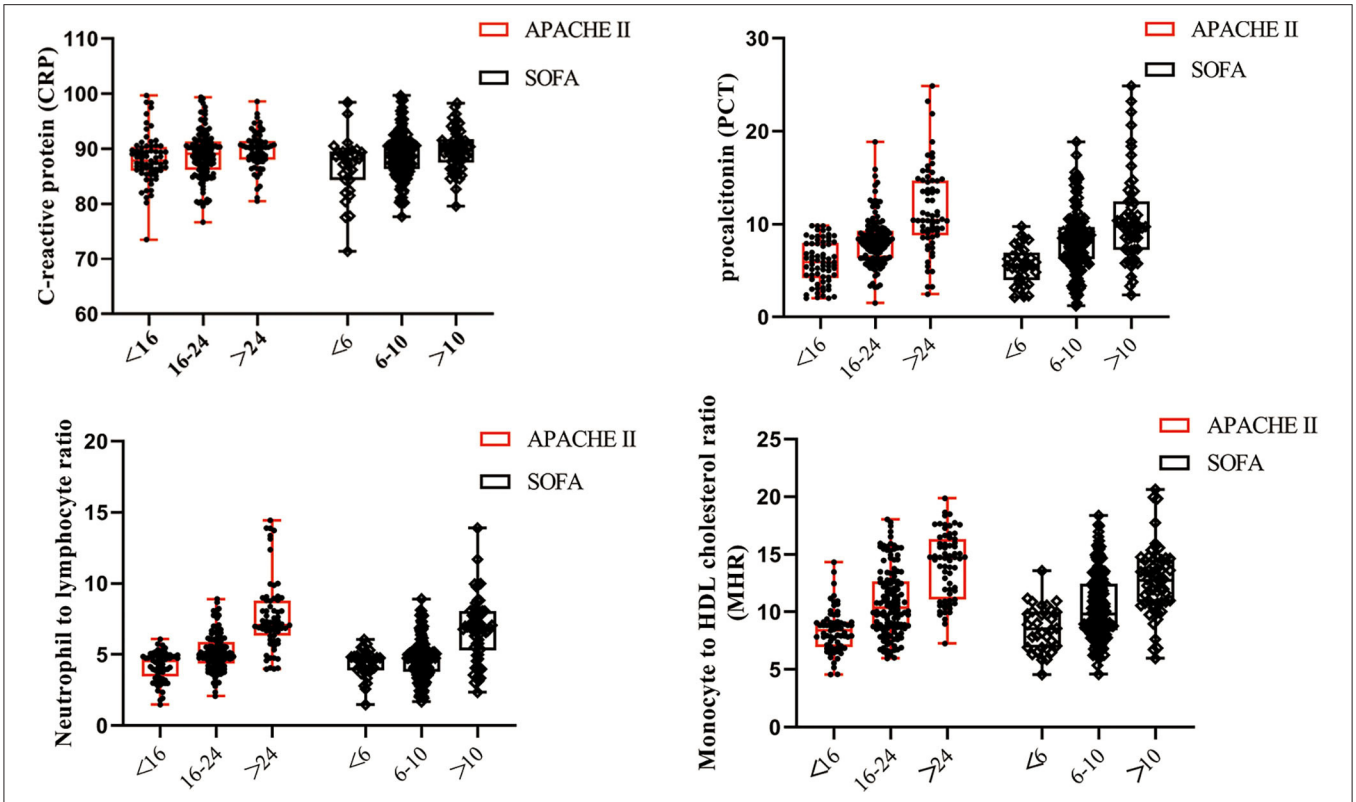

FIGURE 2 | Levels of CRP, PCT, NLR, and MHR in patients with severity classifications. Scatterplots were conducted to demonstrate the correlation between laboratory bioindicators and severity of sepsis, which was evaluated by APACHE II and SOFA scores. MHR and NLR were more closely relevant to the severity of sepsis than CRP and PCT.

TABLE 2 | Hazard ratio of predictors in univariate and multivariate Cox regression.

Variables	Univariate		Multivariate	
	HR (95% CI)	*P*	HR (95% CI)	*P*
CRP	1.047 (0.992–1.106)	0.097	1.004 (0.947–1.064)	0.900
PCT	1.096 (1.038–1.158)	0.001	1.024 (0.954–1.098)	0.517
NLR	1.960 (1.703–2.256)	<0.001	1.404 (1.170–1.684)	<0.001
MHR	1.410 (1.307–1.520)	<0.001	1.217 (1.112–1.331)	<0.001

The multivariate model included age, sex, BMI, SBP, APACHE II, and SOFA scores. P < 0.05 indicated statistical significance.
HR, hazard ratio; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; PCT, procalcitonin; MHR, monocyte/HDL cholesterol ratio.

determined to be the most reliable diagnostic accuracy for predictive value of 28-day mortality in septic patients.

DISCUSSION

Sepsis has recently been redefined as a syndrome of physiological, pathological, and biochemical abnormalities that induce an uncontrollable host reaction to inflammation that causes fatal multiple organ dysfunction (1, 12). A vicious circle of inflammation and oxidative stress ultimately inducing immunosuppression is supposed to be the essence of the pathophysiological process. The incidence of sepsis has been gradually trending toward ascension, and conservative estimates indicate that sepsis may be a leading cause of death in ICU hospitalization (30, 31). Therefore, early identification of septic risk is critical to improving the diagnosis, therapeutic intervention, and prognosis in this serious complication. Although a variety of predictive models for sepsis risk factors are established in clinical studies, the practical values of these biomarkers are still disputed. Accordingly, the current study was conducted to explore a novel death risk screening indicator defined as MHR combined with NLR in predicting 28-day mortality in sepsis, and further evaluate the predictive efficacy of the parameters.

It is demonstrated that sepsis is induced by a dysregulated host response to infection, and the innate immune system is triggered

TABLE 3 | Evaluating the efficiency of parameters in improving to predict 28-day death risk of sepsis.

Variables	CRP	PCT	NLR	MHR	NLR_MHR
AUC	0.569	0.705	0.827	0.876	0.934
	(0.508 to 0.628)	(0.647 to 0.758)	(0.777 to 0.870)	(0.831 to 0.913)	(0.898 to 0.960)
	NA	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P < 0.001$
IDI	NA	0.054	0.062	0.155	0.185
		−0.074 to 0.264	−0.028 to 0.159	0.012 to 0.326	0.019 to 0.236
		$P = 0.236$	$P = 0.127$	$P = 0.03$	$P = 0.02$
NRI	NA	0.062	0.251	0.351	0.378
		0.0068 to 0.096	0.0098 to 0.435	0.116 to 0.549	0.096 to 0.576
		$P = 0.248$	$P = 0.04$	$P < 0.001$	$P = 0.023$

Pairwise statistical comparisons were conducted from left to right. $P < 0.05$ indicated statistically significant.
AUC, area under the ROC curve; IDI, integrated discrimination improvement; NRI, net reclassification improvement.

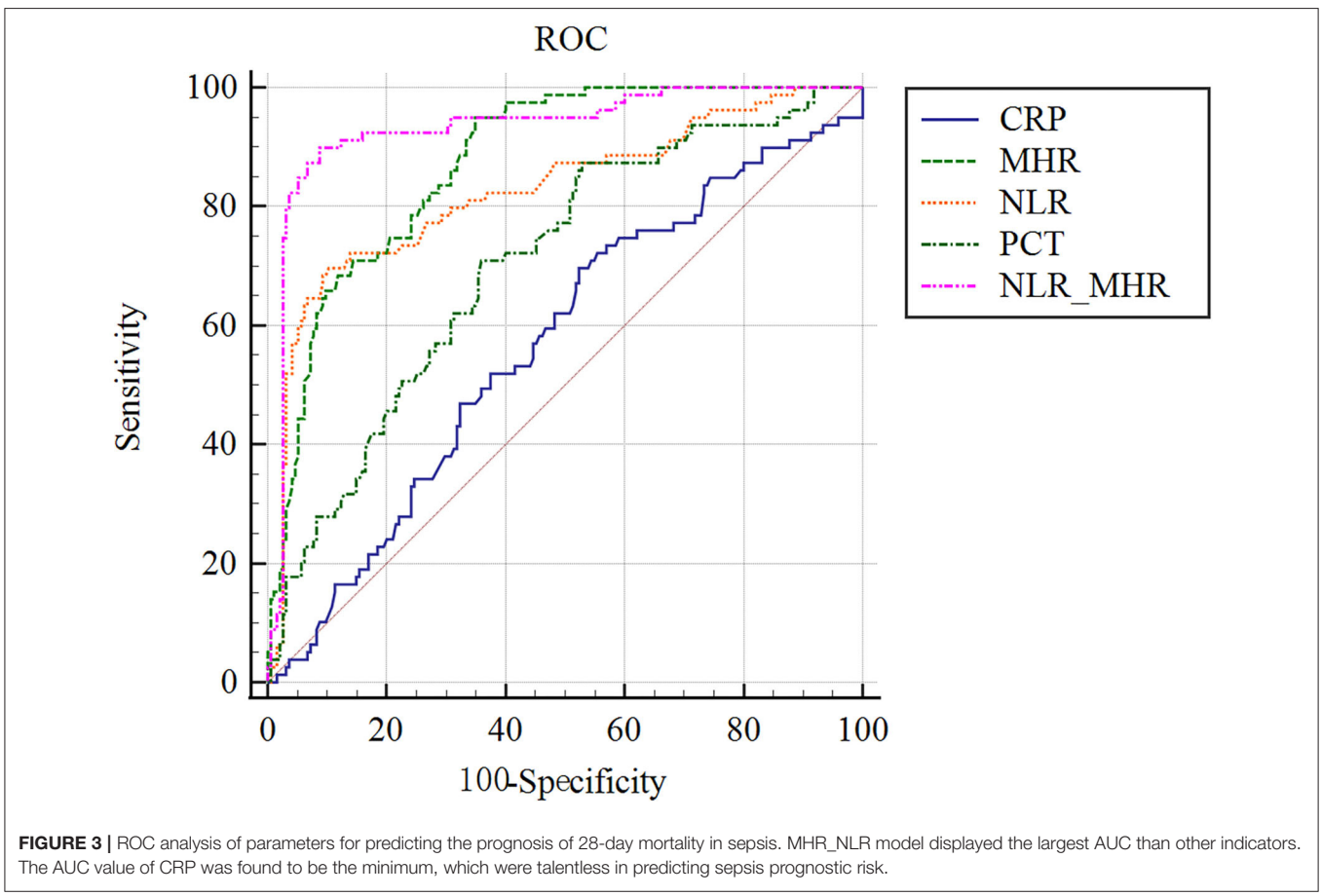

FIGURE 3 | ROC analysis of parameters for predicting the prognosis of 28-day mortality in sepsis. MHR_NLR model displayed the largest AUC than other indicators. The AUC value of CRP was found to be the minimum, which were talentless in predicting sepsis prognostic risk.

when microbial molecular patterns are identified by specific receptors expressed on immune cells (32). This interaction can activate immune cells, including neutrophils and lymphocytes, to release both proinflammatory and anti-inflammatory mediators. Neutrophils as the first line of defense play an indispensable role in elimination of pathogens by phagocytosis and T cell activation, and lymphocytes as an indicator of immunosuppression play a role in mediating apoptosis (33, 34). Therefore, NLR appears to represent a balanced state between innate and adaptive immunity. Recently, several reports have documented the potential utility of NLR as a diagnostic parameter that is closely related to miscellaneous diseases, including inflammation, ischemic cerebrovascular disease, cancer, and trauma (20, 35–40). In our observational study, we found that NLR in patients who died were remarkably elevated compared with those with mild cases ($P < 0.01$) (41), which is in accordance with the previous study showing that an inflammatory reactive state typically led to neutrophilia and relative lymphocytopenia (42). The AUC value

TABLE 4 | Diagnostic value of the predictive parameters.

Variables	Sensitivity (95% CI)	Specificity (%)	Cut-off point	PPV (95% CI)	NPV (95% CI)	Youden index
CRP	69.62	47.69	88.4	35	79.5	0.1731
	58.2–79.5	40.5–54.9		30.7–39.7	72.9–84.8	
PCT	70.89	64.10	8.51	44.4	84.5	0.3499
	59.6–80.6	56.9–70.8		38.7–50.3	79.1–88.6	
NLR	69.62	89.74	5.51	73.3	87.9	0.5936
	58.2–79.5	84.6–93.6		63.9–81.0	83.9–91.1	
MHR	94.94	65.13	10.15	52.4	96.9	0.6006
	87.5–98.6	58.0–71.8		47.5–57.4	92.4–98.8	
NLR_MHR	89.87	91.28	NLR = 5.08	80.7	95.7	0.8116
	81.0–95.5	86.4–94.8	MHR = 13.47	72.5–86.9	92.0–97.7	

of NLR corresponded to 0.827 with 69.62% sensitivity and 89.74% specificity at the optimal cutoff value of 5.51. Theoretically, increased neutrophils reflect a response to microbial infection and migration to the infected region, whereas a reduced number in apoptotic lymphopenia contributes to the development of immunosuppression (43). A high level of neutrophils in the circulation in patients with sepsis indicate overactivation of the innate immune response (44). Conversely, exhaustion of lymphopenia may induce inefficiency in initiating an adaptive immune response and activating T cells. Hence, the results in our study verify the inference that NLR could be a prognostic sign of impending sepsis and predicting mortality risk in septicemia.

Oxidative stress is considered to be another crucial element involved in progression of sepsis. Increasing evidence suggests that both the incapacity of cells to consume oxygen and accumulation of peroxide may severely exacerbate the pathological process of sepsis (45). Sepsis-induced multiple organ dysfunctions finally occur when it suffers from an imbalance of oxidants and antioxidants due to capillary penetrability damage, deteriorative organic property, and hyporespiratory function induced by mitochondrial malfunction (46). During the process of oxidative stress, monocytes, the main source of proinflammatory and oxidative mediators, reveal the responsive capacity of the innate immune system (46). Although HDL cholesterol (HDL-C) inhibits hyperoxidation of low-density lipoprotein cholesterol (LDL-C) and can exert a protective effect on the endothelium. In the early stage of sepsis, circulating monocytes migrate to vascular endothelium and mature into macrophages, which then oxidize liposomes and differentiate into foam cells to release inflammatory cytokines and activate T lyphocytes and more monocytes. In contrast, HDL-C inhibits the activation and transformation of monocytes, thereby resulting in a suppression of inflammatory response (47, 48). Based on this view, it is rational to unite these two parameters into a single index (MHR), which is cost-effective and consists of easily available laboratory parameters reflecting anti-inflammatory and antioxidant effects. Recent studies propose a high level of MHR as an unfavorable prognostic marker, indicating systemic inflammatory and oxidative diseases, including Behçet's disease, psoriasis, and spondylarthritis (49–51). The present study was consistent with the abovementioned clinical observations in that the MHR level was noticed to be significantly higher in the non-survivors group with the average level than the survivor group, which demonstrated MHR was a more precise parameter than others for evaluating systematic inflammation in sepsis. Kanbay and colleagues analyzed the level of MHR in critical patients on admission, and they suggest that MHR might be an early predictor in cardiovascular emergency in patients with chronic kidney disease (24). Similar to previous reports, the scatter diagram in our results found that a high level of MHR was significantly correlated with APACHE II and SOFA scores. The fatality in patients with a high level of MHR was more serious than in patients with a low level of MHR, which indicates that MHR was independently related to prognosis risk for a septic event. Moreover, the current data supports previous findings that MHR is better than NLR in determining prognosis due to its larger AUC. When the cutoff value of MHR was set at 10.15, a higher sensitivity was obtained, and correspondingly, 52.4% of dead patients were effectively classified in the non-survivor group, and 3.1% of the deceased could be assigned to the surviving patients group. Strikingly, the addition of MHR could efficaciously improve the early diagnosis capacity according to the high IDI and NRI. These findings illustrate that MHR may be advantageous in diagnosing sepsis and predicting prognostic risk of 28-day mortality.

Other markers, including CRP and PCT, were also analyzed in our study, and their predictive abilities appeared negative, and they failed to forecast progressive bacterial infection in terms of sepsis in early diagnostic settings. Cox analysis indicated that PCT was incapable of assessing septic mortality after adjusting partial factors (HR = 1.024, 95% CI 0.954–1.098, $P = 0.517$). Clinically, due to the trend of PCT reaching a plateau slowly at 8–24 h, the evaluated capacity of PCT in predicting septic prognosis was obviously disadvantaged with an AUC of 0.705, smaller than those of NLR and MHR. Nevertheless, CRP released in the acute phase of inflammation indicated no difference between the survivor and non-survivor groups and were irrelevant to the severity of sepsis. The potential cause might be that the CRP level peaked within only 48 h and failed to reflect the terminal state of sepsis (52).

Because MHR obtained higher sensitivity but lower specificity than NLR, we conducted model parameters of MHR together with NLR in predictive risk of sepsis, and further evaluated the efficiency in predicting 28-day mortality. In the predictive model of MHR_NLR, the AUC maximum value was 0.934 with a better sensitivity and specificity than the single variable. Moreover, we examined such parameter in terms of reclassifying improvement and discrimination by use of IDI and NRI, which showed significant improvement in the mean difference of predicted probabilities. Taken together, MHR combined with NLR as the parameter is not only appropriate for the early diagnosis of sepsis, but also for the prediction of its severity and prognosis.

There are many clinical implements in the original study. We conducted multiple indicators to evaluate their predictive efficacy to ensure the reliability and accuracy. It first illuminated the inchoate predictive value of MHR combined with NLR for prognosis in sepsis, which provided a more precise guideline for administration and management of septic patients as well as clinical follow-up during the late stage of development. Continuous monitoring of these laboratory variables contributes to enhancing septic prognosis and treatment. Nevertheless, several limitations still remain in our current study. First, this single retrospective study needs to be further proven by more prospective cohort studies or multicenter randomized clinical trials. Futhermore, we need to assess the possible impact of patient's characteristics, including dietary and smoking history, which can affect performance evaluation. Second, a larger sample size appears to be essential to reduce proportional error. Finally, we should collect more information about mechanical ventilation and hemodynamic-associated indicators to better reflect the eventual development of sepsis.

CONCLUSIONS

In summary, the current study suggests that MHR together with NLR are closely related to the severity of sepsis and might be independent predictors of 28-day mortality of septic patients. Notably, MHR combined with NLR can significantly improve the predictive efficiency of 28-day mortality in sepsis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Medical Ethic Committee of Second Hospital of Hebei Medical University, Shijiazhuang, China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

J-yL performed the major design and drafted the manuscript. R-qY and S-qL conducted the statistics. Y-fZ contributed to the data collection. Y-pT and Y-mY conceptualized, supervised, and revised. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.741015/full#supplementary-material

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Clinical Value of the Lactate/Albumin Ratio and Lactate/Albumin Ratio × Age Score in the Assessment of Prognosis in Patients With Sepsis

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Objective: To examine the clinical significance of the blood lactate (Lac)/serum albumin (Alb) ratio and the Lac/Alb × age score for assessing the severity and prognosis of patients with sepsis.

Methods: A total of 8,029 patients with sepsis, aged >18 years were enrolled between June 2001 to October 2012 from the latest version of the Medical Information Mart for Intensive Care III (MIMIC-III v.1.4). The general data of the patients were obtained from hospital records and included gender, age, body mass index (BMI), laboratory indices, the sequential organ failure assessment (SOFA) score, and simplified acute physiology score II (SAPS II). The patients were graded and scored according to their age and then divided into a survival or death group based on their prognosis. The Lac/Alb ratio after ICU admission was calculated and compared between the two groups. The risk factors for death in patients with sepsis were determined using multivariate logistic regression analysis, while mortality was examined using receiver operating characteristic (ROC) curve and survival curve plots. Finally, the values of the Lac/Alb ratio and Lac/Alb × age score for assessing prognosis of patients with sepsis were analyzed and compared.

Results: After items with default values were excluded, a total of 4,555 patients with sepsis were enrolled (2,526 males and 2,029 females). 2,843 cases were classified as the death group and 1,712 cases in the survival group. (1) The mean age, BMI, SOFA and SAPS II scores were higher in the death group than those in the survival group. Significant differences in baseline data between the two groups were also observed. (2) The patients in the death group were divided further into four subgroups according to the quartile of the Lac/Alb ratio from low to high. Comparison of the four subgroups showed that the death rate rose with an increase in the Lac/Alb ratio, while analysis of the survival curve revealed that patients with a higher Lac/Alb ratio had a worse prognosis. (3) Multivariate logistic regression analysis showed that age ≥ 60 years, overweight (BMI ≥ 24 kg/m^2), Lac/Alb ratio ≥ 0.16, SOFA score ≥ 2 points, and SAPS II ≥ 40 points were independent risk factors for death in patients with septic. (4) ROC curve analysis indicated that the SAPS II, Lac/Alb x age score, SOFA, and Lac/Alb ratio were the best predictors of death in patients with sepsis. The Lac/Alb × age score was characterized by its simple acquisition and ability to quickly analyze the prognosis of patients.

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Conclusion: (1)A high Lac/Alb ratio is an independent risk factor for death in patients with sepsis. (2) Although the prognosis of sepsis can be accurately and comprehensively assessed by multi-dimensional analysis of multiple indices, **the Lac/Alb × age score is more accurate** and convenient for providing a general assessment of prognosis, so is worthy of further clinical recognition.

Keywords: lactate, albumin, Lac/Alb ratio, sepsis, age score, disease prognosis assessment, clinical risk prediction

INTRODUCTION

Sepsis is a clinical syndrome in which the host develops a systemic inflammatory response to infection (1) and life-threatening organ dysfunction (2) resulting in the condition being the major cause of death in critically ill patients. Although the understanding of sepsis has increased continuously and medical technology has improved rapidly in recent years, the death rate of patients with sepsis remains high due to the combined effects of disorders in circulation and cellular metabolism. It is, therefore, necessary to pay close attention to assess the outcome of the disease.

In addition to the early determination of the infection site and pathogen and aggressive fluid resuscitation, there is also a need to monitor various clinical indices to examine the therapeutic effect. Currently, blood lactate (Lac), an important parameter of tissue perfusion and infection, is used widely in clinical medicine. **Lactate can be increased significantly by** cellular ischemia and hypoxia and leads to metabolic disorders as a result of a further decline in the effective circulating volume of tissues. Hypoxia and energy failure are the primary conditions for the occurrence of an injury response, which may explain the adverse outcome of sepsis. A plasma albumin (Alb) level <35 g/L in adults indicates hypoalbuminemia, which often occurs concurrently in patients with sepsis, further worsening the disease and increasing the mortality rate. Many previous studies (1–3) have shown that a decrease in serum Alb level is an independent predictor of prognosis in patients with sepsis and septic shock. Therefore, blood Alb level is not only a nutritional index in patients, but also an important marker for the incidence of complications and mortality of patients with sepsis.

Based on the above premise, we consider that the Lac/Alb ratio may be a practical measure for assessing the severity of disease in patients with sepsis. We analyzed clinical information of patients with sepsis in the American critical care medicine information database (MIMIC-III v1.4), with the aim of determining the clinical significance of the Lac/Alb ratio alone or in combination with the age score for evaluating prognosis.

MATERIALS AND METHODS

Data Source

The MIMIC-III database is an open intensive care medicine database jointly released by the Laboratory of Computational Physiology, Massachusetts Institute of Technology, Beth Israel Dikang Medical Center and Philips Healthcare under the funding of the National Institutes of Health. MIMIC-III v1.4 is the latest current version. Information on hospitalization of more than 50,000 patients admitted to the ICU of Beth Israel Dikang Medical Center from June 2001 to October 2012 was collected in the database (4), including vital signs, medications, laboratory measurements, observation results, records of nursing staff, fluid balance charts, program and diagnostic codes, imaging reports, length of stay, and survival data.

Data Acquisition Process and Permission

After the Collaborative Institution Training Initiative (CITI) course was completed, access to the database was approved by the Review Committee of the affiliated institutions of Beth Israel Dikang Medical Center and the Massachusetts Institute of Technology. At the same time, the test for Protecting Human Research Participants was passed (Certificate No: 39691827), and the right to download and use the database was obtained.

Inclusion and Exclusion Criteria

A total of 8,029 ICU patients aged >18 years and diagnosed with sepsis in accordance with the International Classification of Diseases (ICD-9) code 99591 and 99592 were included in the database. **Those with incomplete data were excluded.** For those with multiple records of hospitalization or multiple records of an ICU admission during the same hospitalization, only data from the first ICU admission during the first hospitalization were analyzed.

Data Extraction

The following data were extracted from MIMIC-III using PostgreSQL 13 software and SQL: gender, age, body mass index (BMI), sequential organ failure assessment (SOFA) score, simplified acute physiology score II (SAPS II), white blood cell count, C-reactive protein (CRP), Lac and Alb levels, and prognostic indices. The patients were divided into a survival group or death group according to the presence or absence of an in-hospital death. Patients with incomplete data were deleted from the database. According to the age scoring rules for acute physiology and chronic health evaluation II (APACHE II), the patients were then further graded and scored based on age. As shown in **Table 1**, the range in scores according to age from young to old was 1–6 points. A check was carried out to determine whether Lac and Alb levels corresponded one to one with "charttime" to ensure that they were measured at the same time point. The Lac/Alb ratio was then calculated. For multiple Lac/Alb ratios measured after blood sampling in the same patient the mean value was used in the analyses.

TABLE 1 | Age stratification and score of patients.

Age	≤44	45–54	55–64	65–74	≥74
Score	1	2	3	5	6

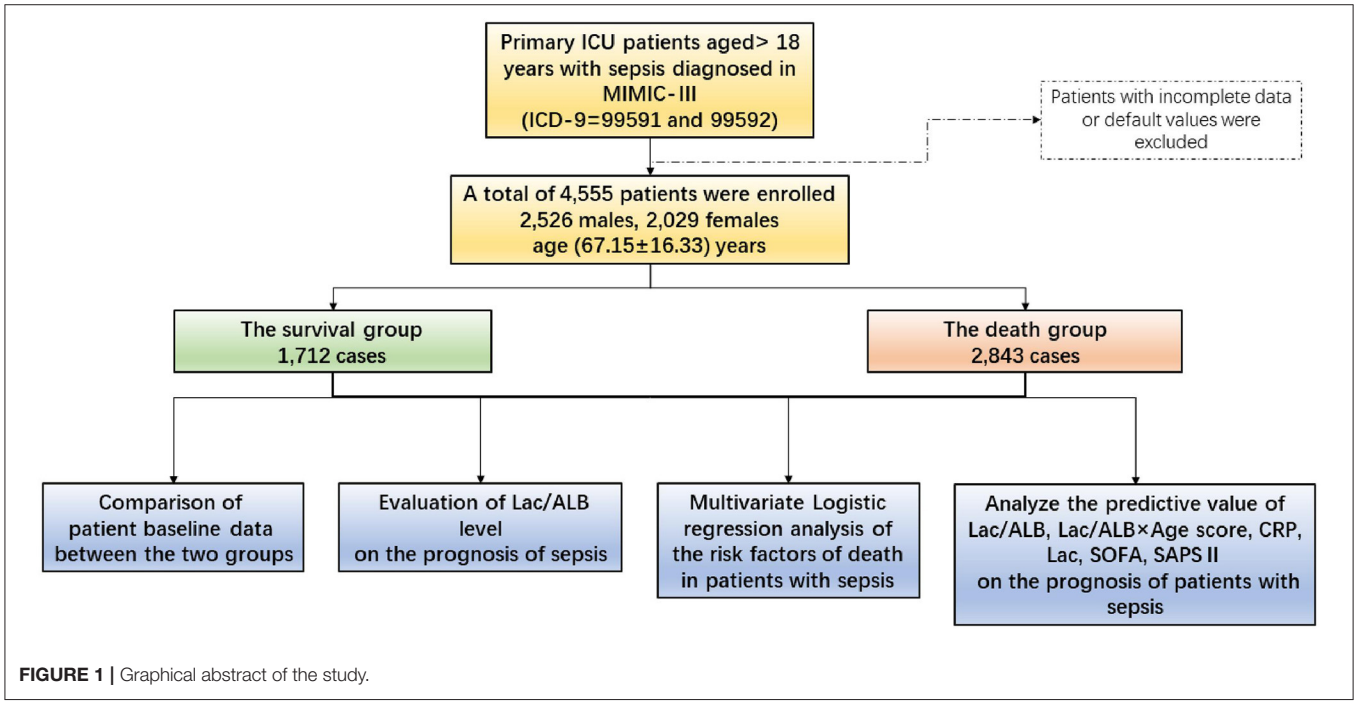

FIGURE 1 | Graphical abstract of the study.

Data Analysis

STATA 16.0 (Stata/MP for Windows, Version 16.0., StataCorp LLC, Texas, USA. Released 2019) was used for statistical analysis of the data. Continuous variables were subjected to the normality test and if they had a normal distribution they were expressed as mean ± standard deviation, with comparison between two groups carried out by independent-sample *t* tests. Variables with an non-normal distribution were expressed as median and quartiles and log-transformed for comparison of two groups using the Mann-Whitney U test. Comparison of nominal variables between two groups was carried out using the χ^2 test. The risk factors for death in patients with sepsis were determined using multivariate logistic regression analysis and receiver operating characteristic (ROC) curve plots. The value of the Lac/Alb ratio, Lac/Alb × age score, Lac, CRP, SOFA score, and SAPS II for predicting prognosis in patients with sepsis was analyzed. The area under the ROC curve (AUC) was compared using the Z test. A *P*-value <0.01 was considered to be statistically significant.

A summary of the statistical analyses is shown in **Figure 1**.

RESULTS

Baseline Data of the Patients

A total of 4,555 patients with sepsis were finally enrolled (2,526 males, 2,029 females), mean age 67.15 ± 16.33 years. The patients were divided into the survival or death groups according to the presence or absence of an in-hospital death. There were 2,843 cases in the death group and 1,712 cases in the survival group. The baseline data of patients are shown in **Table 2**. Compared to the survival group, the death group were older and had a higher BMI, while their SOFA score, SAPS II, and Lac/Alb ratio were all significantly increased (**Table 2**, **Figure 2A**). For vital signs, the death group had relatively lower body temperature and mean arterial pressure, and a higher mean heart rate and central venous pressure than that observed in the survival group. Organ function was also assessed in the two groups using the laboratory indices, with the results showing that cardiac and hepatic-renal function of patients in the death group was worse than that in the survival group (**Table 2**).

Assessment of Prognosis of Patients With Sepsis by Lac/Alb

The patients in the death group were divided into four subgroups according to the quartile of the Lac/Alb ratio from high to low. The death rate was calculated as the ratio of the number of patients in the death subgroups relative to the total number of patients enrolled (**Figure 2B**). This showed that a higher Lac/Alb ratio was associated with a significantly higher death rate, with a significant difference observed between subgroups ($P < 0.0001$). Long-term survival curve analysis also showed a close relationship between the Lac/Alb ratio and prognosis, with patients with a low ratio having longer survival (**Figure 3**).

TABLE 2 | Baseline data of patients.

Characteristics	Total	Survival (*n = 1,712*)	Death (*n = 2,843*)	*P*-value
Age (Years)	67.15 ± 16.33	61.63 ± 17.00	70.46 ± 14.97	*<0.0001*
Male (*n*)	2,526	914	1,612	*<0.0001*
Female (*n*)	2,029	798	1,231	*<0.0001*
BMI	28.91 ± 8.12	28.24 ± 7.54	29.77 ± 8.73	*<0.0001*
SAPSII score	49.32 ± 16.81	42.33 ± 15.31	52.55 ± 16.49	*<0.0001*
SOFA score	8.34 ± 4.37	7.03 ± 3.95	8.95 ± 4.42	*<0.0001*
Vital signs				
Temperature (°C)	37.09 ± 1.02	37.36 ± 1.01	36.98 ± 1.01	*<0.0001*
Heart rate (BPM)	98.19 ± 14.76	92.47 ± 12.55	103.25 ± 18.03	*<0.0001*
MAP (mmHg)	78.51 ± 18.18	84.33 ± 18.45	76.61 ± 17.68	*<0.0001*
CVP (mmHg)	41.23 ± 86.81	23.88 ± 65.21	52.38 ± 96.58	*<0.0001*
Laboratory tests				
WBC (K/uL)	12.96 ± 9.04	12.92 ± 8.37	12.98 ± 9.37	*<0.0001*
N%	74.17 ± 21.76	76.37 ± 16.21	73.12 ± 23.90	*<0.0001*
Hemoglobin (g/dL)	9.70 ± 1.57	9.72 ± 1.63	9.69 ± 1.55	*<0.0001*
Platelet (K/uL)	212.32 ± 172.52	276.58 ± 199.32	179.65 ± 146.73	*<0.0001*
Na^+ (mEq/L)	138.68 ± 5.70	139.05 ± 5.14	138.49 ± 5.96	*<0.0001*
K^+ (mEq/L)	4.10 ± 0.66	4.03 ± 0.63	4.13 ± 0.67	*<0.0001*
$HCO3^-$ (mEq/L)	23.84 ± 5.51	24.51 ± 5.15	23.50 ± 5.66	*<0.0001*
Cl^- (mEq/L)	104.43 ± 7.00	104.77 ± 6.51	104.25 ± 7.24	*<0.0001*
pH	7.36 ± 0.09	7.38 ± 0.09	7.36 ± 0.10	*<0.0001*
SaO_2 (%)	88.53 ± 14.20	89.36 ± 12.84	88.23 ± 14.65	*<0.0001*
PO_2 (mmHg)	115.41 ± 59.42	117.33 ± 58.19	114.60 ± 59.91	*<0.0001*
$PaCO_2$ (mmHg)	41.56 ± 10.96	41.34 ± 9.44	41.65 ± 11.54	*<0.0001*
ALT (IU/L)	174.69 ± 587.46	146.80 ± 545.92	188.73 ± 606.85	*<0.0001*
AST (IU/L)	282.30 ± 1,119.73	189.74 ± 789.32	328.96 ± 1251.13	*<0.0001*
CRE (mg/dL)	1.81 ± 1.58	1.69 ± 1.66	1.87 ± 1.54	*<0.0001*
BUN (mg/dL)	40.11 ± 29.46	32.83 ± 25.95	43.91 ± 30.45	*<0.0001*
BNP (pg/mL)	9,305.18 ± 12,382.45	7,835.17 ± 10,794.02	9,855.29 ± 12,894.17	*<0.0001*
TnT (ng/mL)	0.56 ± 1.55	0.51 ± 1.07	0.57 ± 1.69	*<0.0001*
CK_MB (ng/mL)	14.69 ± 34.03	12.47 ± 29.91	15.76 ± 35.79	*<0.0001*
ALB (g/dL)	3.06 ± 3.12	3.28 ± 3.39	2.60 ± 2.41	*<0.0001*
Lactate (mmol/L)	2.69 ± 0.67	2.66 ± 0.66	2.76 ± 0.69	*<0.0001*

There was a significant difference in survival between subgroups ($P < 0.0001$).

Multivariate Logistic Regression Analysis of Risk Factors for Death

Multivariate logistic regression analysis was used to compare variables in the survival and death groups. This showed that age ≥ 60 years, BMI ≥ 24 kg/m^2, SOFA score ≥ 2 points, Lac/Alb ratio ≥ 0.16 and SAPS II ≥ 40 points were independent risk factors for death in patients with sepsis (**Figure 4**, $P < 0.001$).

Predictive Value of Assessment Indices for Poor Prognosis in Patients With Sepsis

The value of the Lac/Alb ratio, Lac/Alb × age score, CRP, Lac, SOFA score, and SAPS II to predict prognosis in patients with sepsis was analyzed (**Figure 5**). The results showed that the predictive value of the Lac/Alb ratio and SOFA score were similar and not significantly different (Lac/Alb: AUC = 0.61, $P < 0.0001$, 95%CI = 0.59–0.63, cut-off value = 0.16; SOFA: AUC = 0.64, $P < 0.0001$, 95%CI = 0.63–0.66; AUC $_{Lac/Alb}$ vs. AUC $_{SOFA}$, $P = 0.7384$). It was also found that the predictive value of the Lac/Alb × age score for sepsis (AUC = 0.67, $P < 0.0001$, 95%CI = 0.65–0.68, cut-off value = 0.25) was better than that of the SOFA score, with a significant difference in AUC(AUC $_{Lac/Alb\times age}$ vs. AUC $_{SOFA}$, $P < 0.0001$). SAPS II had the highest predictive value for prognosis in patients with sepsis (AUC = 0.72, $P < 0.0001$, 95%CI = 0.70–0.73). Lactate had a relatively low predictive value (AUC = 0.56, $P < 0.0001$, 95%CI = 0.54–0.57), while CRP had no predictive value (AUC = 0.52, $P = 0.053$, 95%CI = 0.50–0.55).

The Z test was used to determine whether the predictive value of SAPS II and the Lac/Alb × age score was significantly different.

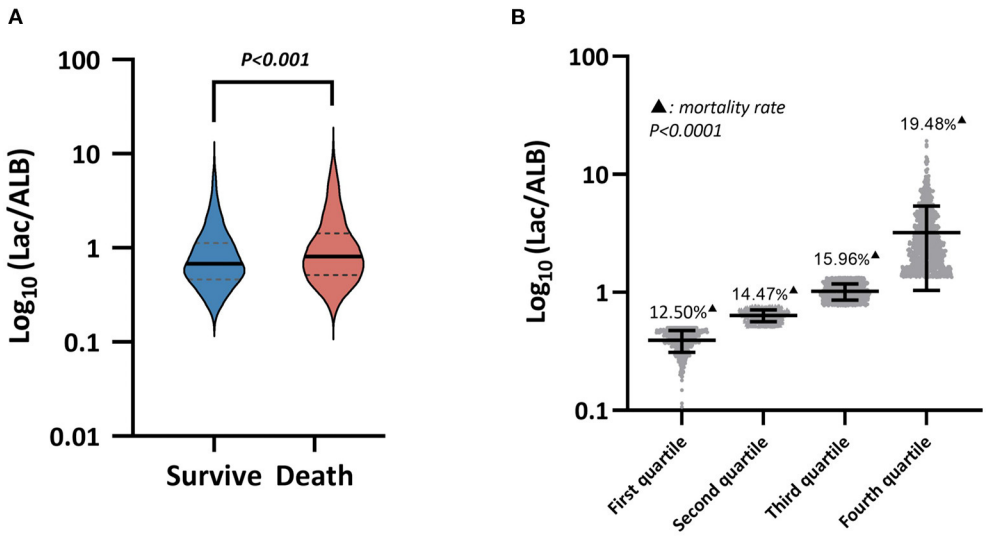

FIGURE 2 | (A) Lac/A1b levels between the survival group and the death group, **(B)** Mortality among the four subgroups in the death group.

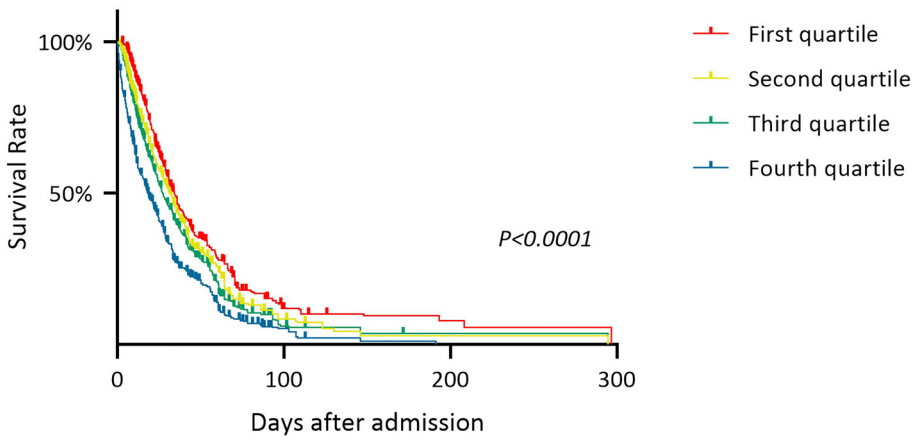

FIGURE 3 | Overall survival expectations of sepsis patients with different Lac/A1b levels.

The results showed no significant difference in the predictive potential of the two indices ($P = 0.3266$).

DISCUSSION

Sepsis is the main cause of death in severely ill patients in ICU units. Recent studies in China and other countries have reported that the morbidity and mortality rates of sepsis remain high. These studies showed there are more than 30 million people in the world who suffer from sepsis every year, with any infected person possibly developing the condition The incidence rate of sepsis in hospital in-patients is 1–2% (5). Septic shock will develop in about 15% of these patients, occurring in about 10% of ICU patients, with a mortality rate above 50% (6). An epidemiological survey in China reported that the mortality rate of patients with sepsis was 48.7% (7), while a retrospective review of 419 patients with sepsis in a teaching hospital showed that the mortality rate of ICU patients was as high as 43.9% (8). These findings emphasize the importance of diagnosing and treating sepsis. Our results demonstrated that the in-hospital mortality rate in sepsis patients was as high as 62.4% with baseline data of the mortality group showing an association between death and older age, higher BMI, poorer organ function, and lower disease tolerance. Other factors possibly causing poor prognosis include more obvious progression of disease and greater organ dysfunction. Sepsis progresses very rapidly and its morbidity and mortality rates remain high despite good monitoring processes and diagnostic and treatment techniques, making it a major medical problem worldwide. In recent years, the guidelines

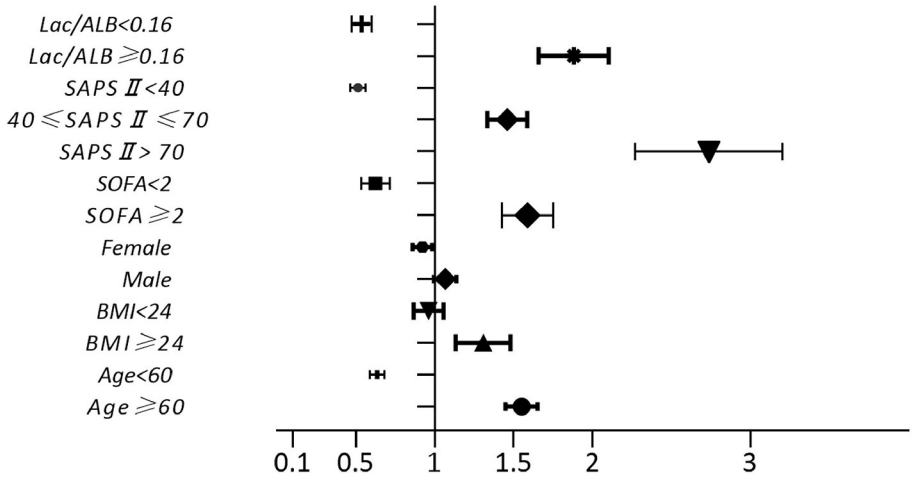

FIGURE 4 | Mortality risk factors of patients with severe sepsis.

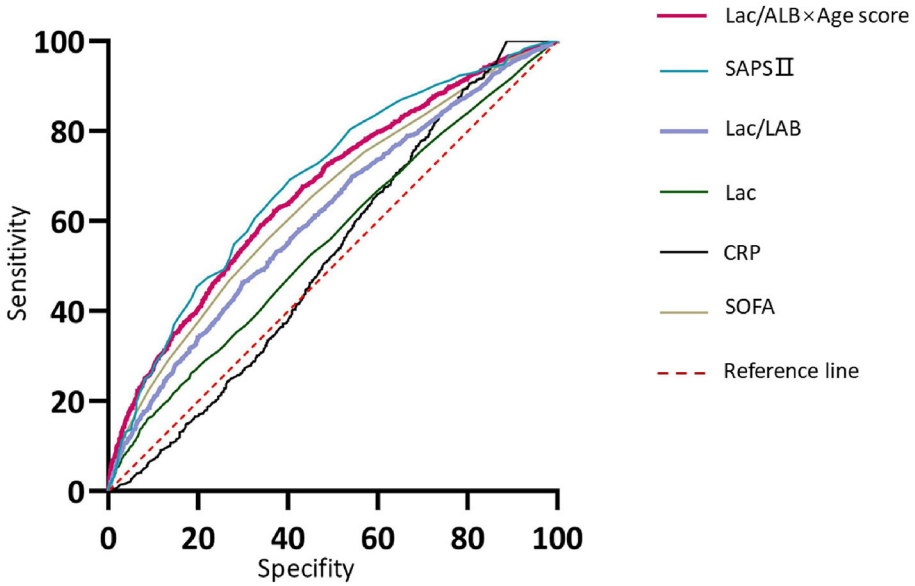

FIGURE 5 | Prognostic value of indicators for predicting adverse outcomes in sepsis patients.

on treatment for sepsis have been updated continuously, with the focus always on early identification of the pathogen and effective antibacterial medication. However, these etiological examinations are time-consuming and have a high false-negative rate, while the pathophysiological mechanism of sepsis is complex, involving immuno-inflammatory responses, cell function and metabolism, and blood coagulation abnormalities in the microcirculation. It is, therefore necessary for intervention strategies to combine anti-infection, organ protection, and fluid resuscitation. When changes in the condition of patients with sepsis are not assessed sufficiently early, the disease often leads rapidly to multiple organ and system failures, resulting in death.

Sepsis is a systemic inflammatory response syndrome caused by infection that is assessed usually by measuring body temperature, peripheral white blood cell count, percentage of neutrophils, CRP level, and organ function. However, these indices have very poor sensitivity and specificity, with our results confirming that these indices have low value for assessing the severity of sepsis and do not identify patients with a potentially poor prognosis. As a product of tissue anaerobic metabolism, Lac is an indicator of tissue hypoperfusion and cell hypoxia sensitivity, and also aerobic glycolysis, a key marker of the stress response and mitochondrial dysfunction. Coast et al. (9) showed that the Lac level in the early stage of trauma correlated with the severity of trauma and that an increase in level indicated

an increased risk of mortality in patients, with a mortality rate of 0, 22, 78 and up to 100% when the level was lower than 1.4, 4.4, and 8.7 mmol/L and higher than 13 mmol/L, respectively. Clinically, blood Lac levels are usually monitored dynamically to assess the perfusion metabolism of tissue cells and the patient's response to treatment. During treatment of shock patients, the mortality rate will rise dramatically if their Lac level is high (10–12). The results of the current study showed that the Lac level in patients with sepsis was higher in the death group than that in survival group, suggesting that Lac levels reflect the severity of disease to some degree. In addition, Alb levels have a major effect on the maintenance of plasma colloid osmotic pressure. In an inflammatory storm, large quantities of inflammatory mediators are produced due to over-activation of the mononuclear phagocyte system, endothelial cells and neutrophils, that act on hepatocytes to inhibit expression of mRNA for Alb, triggering hypoproteinemia (13, 14). In addition, stress caused by severe infection accelerates the catabolism of serum albumin, significantly shortening its half-life. An increased distribution rate of Alb from intravascular to extravascular regions also reduces its serum levels (15). Our study, also found that Alb levels in the death group were markedly lower than those in the survival group, possibly as a consequence of its production and metabolism being adversely affected by other factors such as organ function and peripheral circulation. For example, clearance disorders and hepatic or renal insufficiency lead to abnormal levels of Lac and Alb. However, ROC curve analysis in our study showed that the Lac level alone could not be used to determine the severity or prognosis of the disease.

To help clinicians make treatment decisions for patients with sepsis, the severity or prognosis of the disease should be assessed as early as possible using multiple indices and prognostic scoring systems such as APACHE II, SOFA, and SAPS II (16, 17). APACHE II is used often to assess prognosis of respiratory, circulatory, and neurological diseases while SOFA provides an accurate assessment of the severity of sepsis and degree of organ damage. SAPS II is a modification of APACHE II but has fewer variables making it easier to collect. Recently, more attention has been paid to the value of the Lac/Alb ratio for assessing prognosis in critically ill patients as it reflects opposite changes caused by two different mechanisms with a normal or lower ratio indicating good prognosis. Shin et al. (18) carried out a multi-center retrospective study of patients with severe sepsis presenting to emergency departments of 10 teaching hospitals to evaluate the value of Lac/ALB to predict patient outcome and confirmed that the AUC of the Lac/Alb ratio was greater than that of Lac alone. Moustafa et al. (19) also studied pediatric patients with severe sepsis and found that the Lac/Alb ratio performed better than the Lac clearance rate for predicting the occurrence of the multiple organ dysfunction syndrome and death of patients. In addition, other studies confirmed that the Lac/Alb ratio is useful for risk stratification and predicting the risk of in-hospital death in patients with sepsis (20, 21). In early ICU hospitalization, the Lac/Alb ratio was also superior to APACHE II for predicting the development of MODS and mortality in septic patients (22, 23). The Lac/Alb ratio also plays a role in predicting the prognosis of other severe diseases. With similar Lac levels, the Lac/Alb ratio has been used to identify critically ill patients with heart failure (24), and as an early prognostic marker in ICU patients with different initial Lac levels or hepatic-renal insufficiency (25). Therefore, monitoring the Lac/Alb ratio may help to detect sepsis and initiate early treatment of critically ill patients.

The results of our detailed correlation analyses showed that an increase in the Lac/Alb ratio in patients with sepsis was associated with a gradual increase in the mortality rate and a corresponding decrease in survival rate. Because the levels of Lac and Alb show opposite changes with sepsis, the Lac/Alb ratio by integrating the two indices is able to sensitively reflect small changes in the condition of patients and therefore is an independent risk factor with good predictive potential for a poor prognosis. Because the MIMIC-III database did not contain the APACHE II scoring system data, SOFA and SAPS II were included as controls in the current study to assess the value of the Lac/Alb ratio for predicting the development of sepsis. The results showed that SAPS II had the strongest association with sepsis mortality, followed by SOFA and then the Lac/Alb ratio. These results indicate that although the Lac/Alb ratio can be used as an independent risk factor for death in patients with sepsis its predictive value is not greatly different from that of SOFA, and that it is best to use multiple indices for predicting a poor prognosis. Furthermore, when the Lac/Alb ratio was combined with the age score, the value of the Lac/Alb × age score to predict a poor prognosis from sepsis was further improved in that it was not only superior to SOFA but also comparable to SAPS II. The need for early detection and diagnosis of sepsis is the reason for carrying out these clinical measures, with a study reporting that treatment of a large number of patients with sepsis was delayed during an emergency due to failure of early identification and diagnosis, resulting in negative impact on prognosis (26). In clinical practice, indices that accurately assess the degree of sepsis and are easy and quick to acquire are extremely important. Several recent studies have compared different assessment modes and also developed new assessment tools for sepsis (27, 28) with the aim of obtaining a screening plan with good sensitivity and specificity. However, the effectiveness of these assessments remains to be validated by large-sample, multi-center studies. The SOFA score assesses six important system functions, while SAPS II evaluates 17 variables. Although multi-dimensional assessment integrating multiple variables greatly improves the predictive accuracy for sepsis, it is inconvenient to collect so many variables which is not conducive for early and rapid judgment of disease prognosis and treatment. The quick SOFA (qSOFA), a simpler scoring system, is therefore used commonly in clinics. This score incorporates systolic blood pressure, respiratory rate, and consciousness changes, making it easy to acquire and rapidly judge changes in a patient's condition. However, there is evidence that the specificity of qSOFA for assessing sepsis is unsatisfactory (29–31). The information of lactate and albumin is easy to obtain and can be reviewed in time with the changes of the disease. Lac/Alb × age score is also relatively accurate in the prediction of sepsis, which can be used as a convenient auxiliary means for early diagnosis and can also be used to closely evaluate the progress of sepsis.

LIMITATIONS

Despite a large sample size and a long duration of retrospective data collection this study had some limitations. First, it was a single-center, retrospective study that limits the generalizability of the results. Large-sample multi-center prospective studies are therefore needed to validate the assessment potential of the indices. Second, no screening was carried out on underlying diseases that may possibly have affected the metabolism of Lac and Alb. Therefore, targeted studies on specific underlying disease groups are needed in the future. Finally, the APACHE II and qSOFA scoring systems and other prognostic indexes, such as procalcitonin used commonly to assess sepsis were not included in MIMIC-III. This may have caused certain deficiencies in the comparison and validation of the assessment ability of the Lac/Alb ratio and Lac/Alb × age score.

CONCLUSION

In conclusion, the Lac/Alb ratio is an independent risk factor for death in patients with sepsis, and to a certain extent can be used to assess the severity of sepsis. Although the prognosis of sepsis can be assessed accurately and comprehensively by multi-dimensional analysis including multiple indexes, Lac/Alb × age score can give consideration to the accuracy and convenience of assessment to a certain extent, which has the value of further promotion in clinical practice.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

ETHICS STATEMENT

All information related to the patients in MIMIC-III was anonymous, so informed consent was not needed. A review by the Ethics Committee of Huashan Hospital approved the study as it met all the conditions for exemption from review.

AUTHOR CONTRIBUTIONS

XC, HP, and HZ: conceptualization. XZ, YW, and KM: methodology. YW and XC: validation. XC: investigation and writing—original draft preparation. ZX: resources and funding acquisition. XZ and HZ: data curation. XC and HP: writing—review and editing. KM: project administration. All authors have read and agreed to the published version of the manuscript.

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Early Fresh Frozen Plasma Transfusion: Is It Associated With Improved Outcomes of Patients With Sepsis?

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Background: So far, no study has investigated the effects of plasma transfusion in the patients with sepsis, especially in the terms of prognosis. Therefore, we aimed to explore the association of early fresh frozen plasma (FFP) transfusion with the outcomes of patients with sepsis.

Methods: We performed a cohort study using data extracted from the Medical Information Mart for Intensive Care III database (v1.4). External validation was obtained from the First Affiliated Hospital of Wenzhou Medical University, China. We adopted the Sepsis-3 criteria to extract the patients with sepsis and septic shock. The occurrence of transfusion during the first 3-days of intensive care unit (ICU) stay was regarded as early FFP transfusion. The primary outcome was 28-day mortality. We assessed the association of early FFP transfusion with the patient outcomes using a Cox regression analysis. Furthermore, we performed the sensitivity analysis, subset analysis, and external validation to verify the true strength of the results.

Results: After adjusting for the covariates in the three models, respectively, the significantly higher risk of death in the FFP transfusion group at 28-days [e.g., Model 2: hazard ratio (*HR*) = 1.361, *P* = 0.018, 95% *CI* = 1.054–1.756] and 90-days (e.g., Model 2: *HR* = 1.368, *P* = 0.005, 95% *CI* = 1.099–1.704) remained distinct. Contrarily, the mortality increased significantly with the increase of FFP transfusion volume. The outcomes of the patients with sepsis with hypocoagulable state after early FFP transfusion were not significantly improved. Similar results can also be found in the subset analysis of the septic shock cohort. The results of external validation exhibited good consistency.

Conclusions: Our study provides a new understanding of the rationale and effectiveness of FFP transfusion for the patients with sepsis. After recognizing the evidence of risk-benefit and cost-benefit, it is important to reduce the inappropriate use of FFP and avoid unnecessary adverse transfusion reactions.

Keywords: fresh frozen plasma, international normalized ratio, partial thromboplastin time, sepsis, septic shock

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INTRODUCTION

Sepsis, a syndrome of pathophysiological abnormalities and severe organ dysfunction induced by infection, leads to high incidence and mortality rates worldwide (1–4). Since 2002, the Surviving Sepsis Campaign has made a highly successful international effort to decrease sepsis mortality by the therapeutic strategies of bundle elements (5). In its 2018 update, it is believed that the early effective fluid therapies with intravenous injection are crucial for the stabilization of sepsis-induced tissue hypoperfusion (6). The ideal fluid management in sepsis should improve euvolemia without causing edema, potentially by rebuilding the damaged endothelial glycocalyx layer and repairing the injured endothelium (7). The crystalloids are recommended as first-line therapy, however, the benefit following the administration of colloids compared with crystalloids in the patients with sepsis remains unclear (6–8).

Plasma, as a "super-colloid," is rich of proteins, such as albumin, coagulation factors, fibrin, immunoglobulins, antithrombin, protein C, and protein S (9). The studies regarding the effects of plasma transfusion in the patients with a critical illness are limited, and the conclusions have not reached an agreement. Much of what we know about the plasma-based fluid management comes from the studies performed in the setting of trauma. Early plasma transfusion instead of other blood products is associated with the decreased mortality in trauma patients (10, 11). In traditional clinical practice, the patients with critical illness who have abnormal coagulation may benefit from plasma transfusion at intensive care unit (ICU) admission. However, Dara SI et al. considered that the risk-benefit ratio of fresh frozen plasma (FFP) transfusion in the patients with critical illness with coagulopathy may not be favorable (12). This contradiction may attribute to the adverse effects accompanied by plasma transfusion in aspects of infections, immunomodulation, allergic reactions, circulatory overload, and citrate toxicity (13).

As no previous studies for reference, the effects of plasma transfusion in the patients with sepsis remain unknown. Therefore, we aimed to explore the potential relationship of early FFP transfusion with the outcomes of the patients with sepsis at ICU admission. Furthermore, we hypothesize that early FFP transfusion does not benefit the short-term survival of most patients with sepsis.

METHODS

Data Source

We performed a retrospective cohort study using data extracted from the Medical Information Mart for Intensive Care III (MIMIC III) database (v1.4) which integrated deidentified and comprehensive clinical data of the patients admitted to the Beth Israel Deaconess Medical Center (BIDMC) in Boston, Massachusetts, United States (14). MIMIC III database contains over 58,000 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 MIMIC III database for authorized users. Wei Zhou was allowed to download data from the database, having completed the "Data or Specimens Only Research" course (record identity: 25222342).

External validation was collected from the First Affiliated Hospital of Wenzhou Medical University (Wenzhou, Zhejiang, China) after approval from the First Affiliated Hospital Ethics Committee.

The informed consents of all the patients were not required because the present study neither contained any protected health information nor impacted clinical care.

Study Cohort

A flowchart of the inclusion and exclusion procedure for the MIMIC III is depicted in **Figure 1**. We adopted the third international consensus definitions (Sepsis-3, a diagnosis flowchart is presented in **Supplementary Figure 1**) to extract the patients with sepsis and septic shock from the database (1). Based on the Sepsis-3 criteria, patients with suspected infection and evidence of organ dysfunction [Sequential Organ Failure Assessment (SOFA) score ≥ 2] were identified as the patients with sepsis (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 h, whereas if the antibiotic was first, the culture was required within 24 h (1). Moreover, we defined the period of suspected infection as ranging between 24 h before and 24 h after admission to an ICU. The 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 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 the simplest option for us to limit the cohort to the MetaVision system, because the resulting sample size was sufficient. Additionally, the exclusion criteria for the initial sepsis cohort were as follows: (1) repeat hospitalization at ICU, (2) aged 16 years or younger, and (3) current service relating to cardiac, vascular, or thoracic surgery. We assumed that these sub-populations had physiological abnormalities yet caused by the factors unrelated to sepsis. Furthermore, we excluded the patients who had incomplete covariate data for further multivariate analysis.

External validation data were collected between September 15, 2018 and December 31, 2020 according to the same inclusion and exclusion criteria. The main diagnosis of these patients clearly met the Sepsis-3 criteria within 24 h of ICU admission. The clinical outcomes were followed-up for 90-days after admission (13 patients were excluded due to loss to follow-up).

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; BIDMC, Beth Israel Deaconess Medical Center; CIs, confidence intervals; FFP, fresh frozen plasma; GCS, Glasgow coma scale; HRs, hazard ratios; ICU, intensive care unit; INR, international normalized ratio; IQRs, interquartile ranges; K–M, Kaplan–Meier; LOS, length of stay; MIMIC III, Medical Information Mart for Intensive Care III; ORs, odds ratios; PTT, partial thromboplastin time; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; and TRALI, transfusion-related acute lung injury.

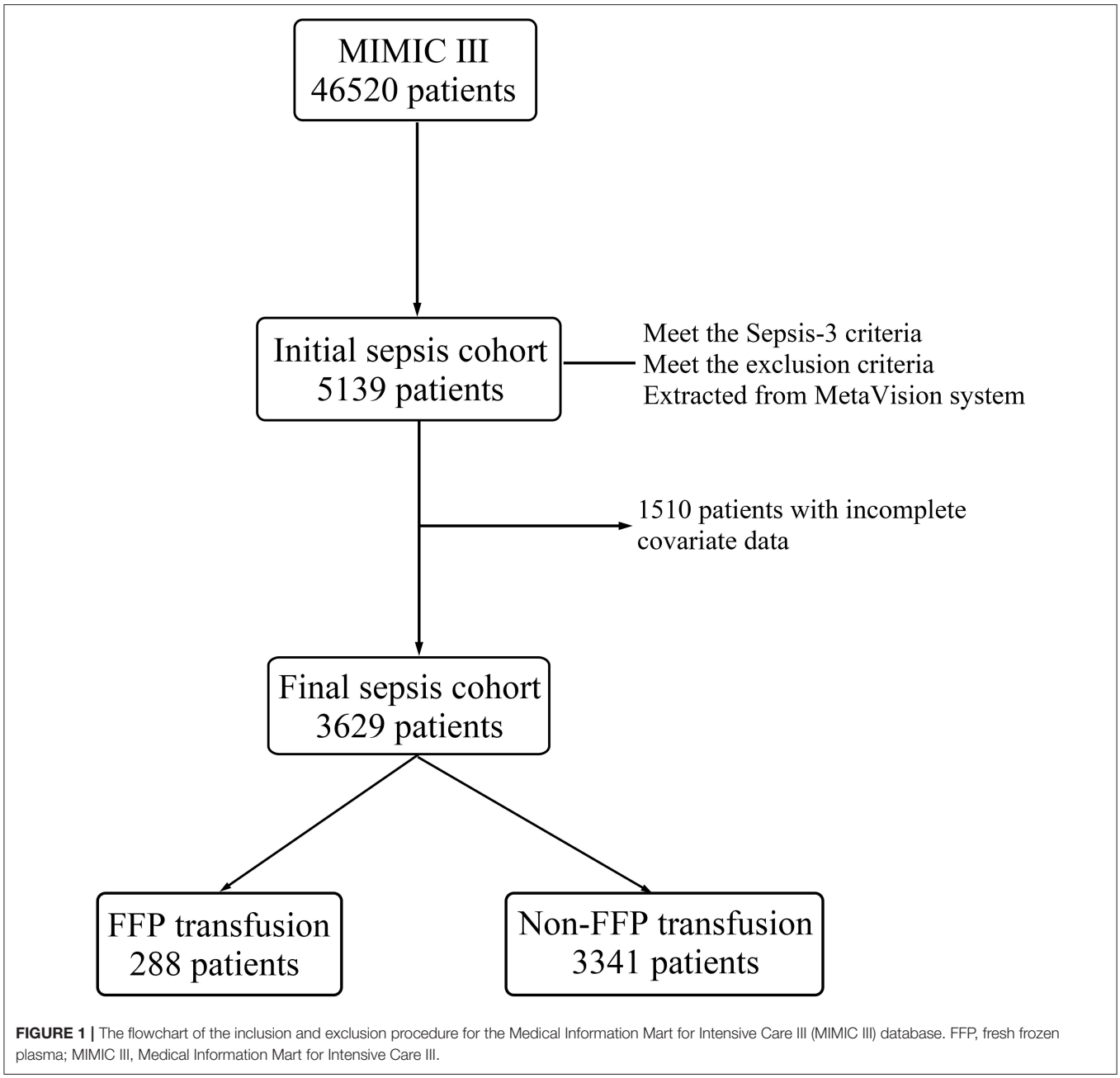

FIGURE 1 | The flowchart of the inclusion and exclusion procedure for the Medical Information Mart for Intensive Care III (MIMIC III) database. FFP, fresh frozen plasma; MIMIC III, Medical Information Mart for Intensive Care III.

Data Extraction

The data were extracted from MIMIC III and our hospital system, such as gender, age, laboratory data, vital statistics, comorbidities, ICU interventions, and hospital length of stay (LOS). The severity scores of illness, such as Simplified Acute Physiology Score II (SAPS II), Acute Physiology and Chronic Health Evaluation II (APACHE II), and SOFA were calculated on the basis of their predefined criteria (15–17). The mean values of laboratory data and vital statistics during the first 24 h of ICU stay were regarded as baseline data. The scores of Glasgow coma scale (GCS), SAPS II, APACHE II, and SOFA as well as the necessity to perform interventions with vasopressor and mechanical ventilation were evaluated during the first 24 h of ICU stay. Additionally, SAPS II and APACHE II were used for MIMIC III and the external validation data analysis, respectively.

Predictor and Outcome Variables

We recorded the FFP transfusion status of each patient during the first 3-days of their ICU stays. To minimize the potential bias, the values of international normalized ratio (INR) and partial thromboplastin time (PTT) were obtained before FFP transfusion.

The primary end point was 28-day mortality. The secondary end points were 90-day and in-hospital mortality. Mortality

information in the MIMIC III was calculated based on the dates of admission and death obtained from the social security records.

Statistical Analysis

The Kolmogorov–Smirnov normality test was used to check the normality assumption for the numerical variables. Differences in the normally and non-normally distributed variables were compared using the unpaired Student's *t*-test and Wilcoxon's rank-sum test, respectively. Comparisons for the categorical variables were performed by Pearson's χ^2 test and Fisher's exact test. Normally distributed data were expressed as the means with SDs, and non-normally distributed data were expressed as the medians with inter-quartile ranges (IQRs). The categorical variables were expressed as frequencies with percentages.

We assessed the association of early FFP transfusion with survival in the patients with sepsis using the logistic regression and Kaplan–Meier (K–M) analysis. The results were presented in form of odds ratios (*OR*s) with 95% *CI*s and survival curve, respectively.

For the Cox regression analysis, three multivariate models were constructed as follows: Model 1, adjusting only for gender and age; Model 2, adjusting for gender, age, and scores of SAPS II (APACHE II for external validation) and SOFA; Model 3, adjusting for gender, age, laboratory data (white blood cell, platelet, hemoglobin, lactate, and creatinine), vital statistics (heart rate, mean blood pressure, respiration rate, temperature, pulse oxygen saturation, and glucose), scores of GCS, SOFA, and SAPS II (APACHE II for external validation), ICU interventions (vasopressor, mechanical ventilation, and renal replacement therapy), history of alcohol abuse, comorbidities, and hospital LOS. The hazard ratios (*HR*s) and 95% *CI*s were calculated for these models.

A sensitivity analysis was performed to further validate the effects of early FFP transfusion in the patients with sepsis with hypocoagulable and non-hypocoagulable state. Moreover, a subset analysis was performed for the patients with FFP transfusion ($N = 288$) to evaluate the relationship between the transfusion volume of FFP and survival. Subsequently, we performed an additional subset analysis to establish whether similar results also existed in the septic shock cohort ($N = 625$). Finally, external validation was introduced to verify whether similar results can be observed in the East Asian population.

A two-sided $P < 0.05$ was regarded as representing statistical significance. The statistical analyses were performed using the SPSS software 20.0 (SPSS, Chicago, IL, USA) and MedCalc software 19.0.5 (MedCalc, Ostend, Belgium).

RESULTS

Baseline Data of Study Cohort

A total of 3,629 patients with sepsis from the MIMIC-III database were included in final sepsis cohort (**Figure 1**). The baseline characteristics of final sepsis cohort are summarized in **Table 1**. The median transfusion volume in FFP transfusion group was 627 ml (IQR: 532–1,169 ml). Additionally, the baseline laboratory data and vital statistics for further multivariate analysis are shown in **Table 2**.

Comparison of the baseline characteristics of the initial sepsis cohort vs. final sepsis cohort is presented in **Supplementary Table 1**. Similar baseline data were found between the two cohorts.

Associations of Early FFP Transfusion With Primary and Secondary Outcomes

The rates of 28-, 90-day, and in-hospital mortality of the two groups were as follows: FFP transfusion group = 24.3, 32.6, and 22.2%, respectively, and non-FFP transfusion group = 14.7, 20.3, and 11.1%, respectively. For the univariate logistic regression analysis, the mortality of FFP transfusion group was significantly higher than the non-FFP transfusion group in 28-, 90-day, and in-hospital ($OR = 1.859$, $P < 0.001$, 95% $CI = 1.397$–2.474; $OR = 1.907$, $P < 0.001$, 95% $CI = 1.470$–2.474; and $OR = 2.287$, $P < 0.001$, 95% $CI = 1.698$–3.081, respectively).

Moreover, based on the K–M survival analysis of 28- and 90-day, the patients of non-FFP transfusion conferred more favorable prognosis than those of FFP transfusion ($P < 0.001$, both) (**Figures 2A,B**).

Multivariate Analysis, Sensitivity Analysis, and Subset Analysis

In clinical practice, the patients with FFP transfusion are often more serious and accompanied by the coagulation abnormalities, thus, the multivariate analysis, sensitivity analysis, and subset analysis still need to be performed to verify the true intrinsic relationship on the premise of excluding potentially relevant bias.

The actual associations of FFP transfusion with 28- and 90-day mortality were evaluated by the Cox regression models. As shown in **Table 3**, after adjusting for the covariates of Model 1, Model 2, and Model 3, respectively, the significantly higher risk of death in the FFP transfusion group at 28 and 90-days remained distinct. Additionally, for the in-hospital mortality, a similar result can be found using a multivariate logistic regression analysis (Model 1: $OR = 2.282$, $P < 0.001$, 95% $CI = 1.685$–3.091; Model 2: $OR = 1.887$, $P < 0.001$, 95% $CI = 1.366$–2.606; and Model 3: $OR = 1.899$, $P < 0.001$, 95% $CI = 1.350$–2.672).

The sensitivity analysis on the basis of two different coagulation indexes was performed in our study. INR and PTT, representing exogenous and endogenous coagulation function, respectively, were divided into hypocoagulable and non-hypocoagulable state according to the upper limit of their normal range (18, 19). As presented in **Table 4**, after correcting for the same covariates (Model 2), the outcomes of the patients with sepsis with hypocoagulable state after early FFP transfusion were not significantly improved in the Cox regression models. Contrarily, for the patients with PTT $\leq$ 40, there was a statistically significant increasing trend for the patients with sepsis of early FFP transfusion in the risk of death at 28- and 90-days.

The distribution of transfusion volume in the FFP transfusion group ($N = 288$) during the first 3-days of ICU stay was as follows: the lowest tertile range from 220 to 567 ml; the

TABLE 1 | The baseline characteristics of study cohort.

Characteristics	Total (*N* = 3,629)	FFP transfusion (*N* = 288)	Non-FFP transfusion (*N* = 3,341)
Gender (men/women)	2,023/1,606	182/106	1,841/1,500**
Age (years)	66.6 (53.8–79.7)	68.4 (54.4–80.6)	66.4 (53.8–79.6)
≤30, *n* (%)	175 (4.8)	10 (3.5)	165 (4.9)
>30, ≤60, *n* (%)	1,132 (31.2)	87 (30.2)	1,045 (31.3)
>60, *n* (%)	2,322 (64.0)	191 (66.3)	2,131 (63.8)
Alcohol abuse, *n* (%)	388 (10.7)	41 (14.2)	347 (10.4)*
Culture specimen types			
Blood, *n* (%)	1,572 (43.3)	109 (37.8)	1,463 (43.8)
Lung, *n* (%)	122 (3.4)	8 (2.8)	114 (3.4)
Urinary system, *n* (%)	610 (16.8)	49 (17.0)	561 (16.8)
Gastrointestinal system, *n* (%)	11 (0.3)	0 (0)	11 (0.3)
Others, *n* (%)	1,314 (36.2)	122 (42.4)	1,192 (35.7)*
Culture positive, *n* (%)	476 (13.1)	46 (16.0)	430 (12.9)
Vasopressor (first 24 h), *n* (%)	1,082 (29.8)	101 (35.1)	981 (29.4)*
Mechanical ventilation (first 24 h), *n* (%)	1,884 (51.9)	177 (61.5)	1,707 (51.1)**
Renal replacement therapy, *n* (%)	173 (4.8)	27 (9.4)	146 (4.4)**
GCS score	15 (13–15)	15 (14–15)	15 (13–15)**
SOFA score	5 (3–6)	6 (4–7)	4 (3–6)**
SAPS II score	37.0 (30.0–46.0)	40.5 (34.0–50.0)	37.0 (29.0–46.0)**
Comorbidities			
Congestive heart failure, *n* (%)	850 (23.4)	72 (25.0)	778 (23.3)
Cardiac arrhythmias, *n* (%)	1,089 (30.0)	135 (46.9)	954 (28.6)**
Hypertension, *n* (%)	2,140 (59.0)	159 (55.2)	1,981 (59.3)
Chronic pulmonary, *n* (%)	788 (21.7)	55 (19.1)	733 (21.9)
Renal failure, *n* (%)	634 (17.5)	55 (19.1)	579 (17.3)
Liver disease, *n* (%)	347 (9.6)	57 (19.8)	290 (8.7)**
Solid tumor, *n* (%)	231 (6.4)	23 (8.0)	208 (6.2)
Diabetes, *n* (%)	1,043 (28.7)	78 (27.1)	965 (28.9)
Hospital LOS (days)	7.7 (4.9–12.7)	10.4 (6.2–16.5)	7.6 (4.8–12.4)**

**P-value < 0.05; **P-value < 0.01. The data were expressed as median (inter-quartile range) or frequency (percentage). FFP, fresh frozen plasma; GCS, Glasgow coma scale; LOS, length of stay; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.*

medium tertile from 567 to 926 ml; the highest tertile from 926 to 8,148 ml. There seemed to be an increasing trend from the lowest tertile to the highest tertile in the risk of death at both 28-days ($HR = 1.783$, $P = 0.055$, 95% $CI = 0.987–3.219$) and 90-days ($HR = 1.710$, $P = 0.035$, 95% $CI = 1.039–2.813$) after correcting for the covariates of Model 2. Meanwhile, the survival curves of the three groups are presented in **Figures 3A,B**. The detailed distribution of FFP transfusion volume is shown in **Supplementary Figure 2**.

The comparison of baseline characteristics of septic shock cohort vs. sepsis cohort is summarized in **Supplementary Table 2**. There were significant differences between the septic shock cohort ($N = 625$) and sepsis cohort ($N = 3,629$) in the severity of disease ($P < 0.001$ for SOFA and SAPS II, both). For the subset analysis of septic shock cohort (**Supplementary Table 3**), early FFP transfusion was not associated with the improved 28- and 90-day survival, even in the hypocoagulable group. Similarly, no significant dose-effect relationship was found between the transfusion volume and prognosis.

External Validation

The baseline characteristics of the external validation cohort ($N = 294$) were presented in **Supplementary Tables 4**, **5**. New data collected from our hospital also led to similar results (**Table 5**) as in the primary analysis, indicating that even in the hypocoagulable group, early FFP transfusion cannot improve the outcomes of patients with sepsis, even was unfavorable. Additionally, in the subset analysis of the septic shock cohort (**Supplementary Table 6**), early FFP transfusion was not associated with the improved 28- and 90-day survival. Contrarily, the mortality of high transfusion volume was higher than that of low transfusion volume.

DISCUSSION

The present study revealed that regardless of whether the patients were in hypocoagulable or non-hypocoagulable state, early FFP transfusion was not associated with improved survival of 28-, 90-day, and in-hospital for the patients with sepsis, was unfavorable. Contrarily, both 28- and 90-day mortality increased significantly with the increase of FFP transfusion volume. Additionally, for the subset analysis of septic shock, early FFP transfusion was not associated with the improved 28- and 90-day survival, even in the hypocoagulable group. Similarly, the results of external validation exhibited good consistency, which suggests the conclusions of our study have a certain generalization value.

Sepsis, a syndrome of immense clinical importance, accounts for high incidence, high mortality, and high ICU admission rate in recent years (3, 20, 21). The latest Sepsis-3 definition, replacing the previous definitions of sepsis gradually, is defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection (1, 22). Johnson et al. performed a comparative analysis of sepsis identification methods in the MIMIC III database (v1.4), indicating that Sepsis-3 criteria had several advantages over the previous methods as follows: (1) less susceptibility to the coding practices changes, (2) provision of temporal context because of extracting sepsis cohort by suspected 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 (23). Therefore, it is appropriate to extract the patients with sepsis from the MIMIC III database *via* Sepsis-3 criteria.

Early effective fluid management is a mainstay in the initial treatment of sepsis. The controversy for the effects of fluid therapies with colloids vs. crystalloids on mortality in the patients with sepsis has always attracted much attention. As lack of any clear benefit following the administration of colloids compared with crystalloids in the patients with sepsis, the crystalloids are still recommended as first-line therapy (6). However, a systematic review suggested that the patients with severe sepsis might benefit from the fluid therapies with albumin (24). The relevant study on sepsis concerning plasma involved in the fluid therapies has, to the best of our knowledge, not been previously reported.

TABLE 2 | The baseline laboratory data and vital statistics.

Parameters	FFP transfusion (*N* = 288)	Non-FFP transfusion (*N* = 3,341)
Laboratory data		
WBC (10^9/L)	11.3 (7.9–15.2)	11.6 (8.4–15.6)
Platelet (10^9/L)	166.3 (108.8–240.0)	209.7 (153.0–277.7)**
Hemoglobin (g/dL)	10.1 (9.0–11.5)	10.9 (9.6–12.3)**
Lactate (mmol/L)	2.2 (1.6–3.2)	1.8 (1.3–2.5)**
Creatinine (mg/dL)	1.1 (0.8–1.6)	1.0 (0.8–1.5)*
PTT (s)	34.1 (28.6–43.1)	28.3 (25.0–33.4)**
INR	1.8 (1.4–2.8)	1.2 (1.1–1.4)**
Vital statistics		
Heart rate (bpm)	89.2 (75.1–100.4)	87.2 (76.0–98.8)
Mean blood pressure (mmHg)	74.7 (69.8–82.9)	75.7 (69.5–83.3)
Respiration rate (times/min)	18.7 (16.4–21.6)	19.0 (16.6–22.1)
Temperature (°C)	36.7 (36.3–37.2)	36.8 (36.5–37.3)**
SpO_2 (%)	97.8 (96.2–99.1)	97.3 (95.9–98.6)**
Glucose (mg/dL)	138.2 (112.8–166.4)	133.3 (112.3–163.1)

**P-value < 0.05; **P-value < 0.01. The data were expressed as median (interquartile range). FFP, fresh frozen plasma; INR, international normalized ratio; PTT, partial thromboplastin time; SpO_2, pulse oxygen saturation; WBC, white blood cell.*

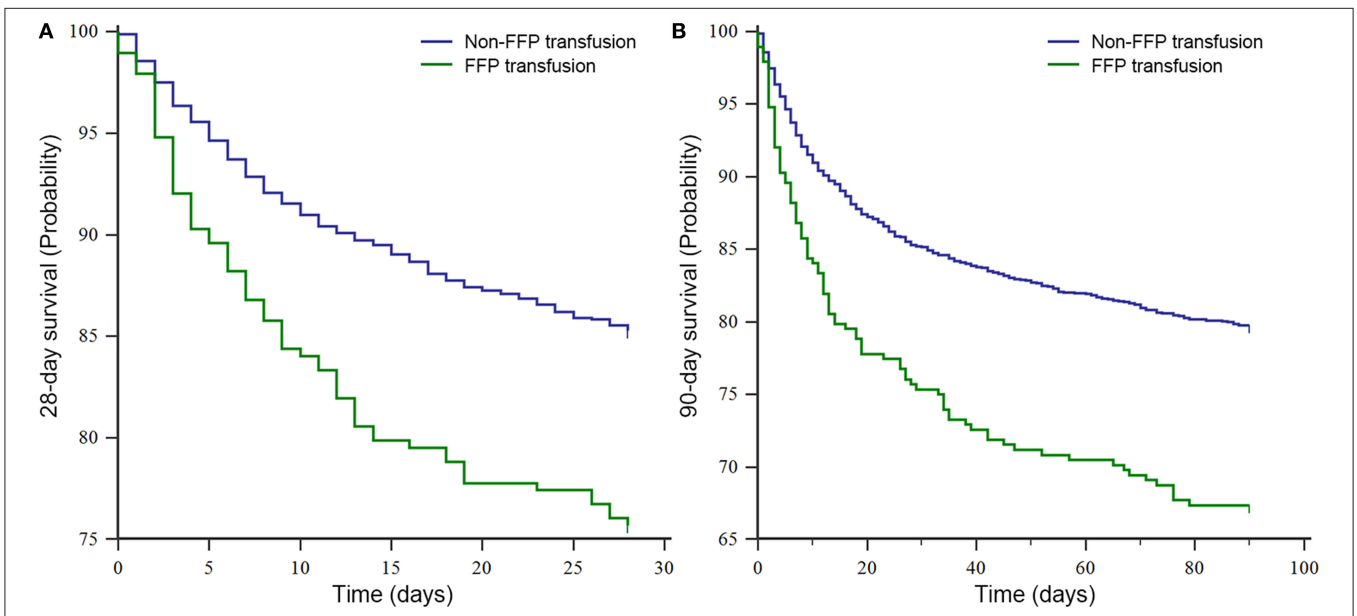

FIGURE 2 | The Kaplan–Meier survival analysis of sepsis cohort in the MIMIC III database. **(A)** 28-day survival curve and **(B)** 90-day survival curve. FFP, fresh frozen plasma; and MIMIC III, Medical Information Mart for Intensive Care III.

TABLE 3 | A multivariate Cox regression analysis of 28- and 90-day mortality.

Research variables	28-day mortality			90-day mortality		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Model 1						
FFP transfusion vs. non-FFP transfusion	1.716	1.336–2.206	**<0.001**	1.692	1.363–2.100	**<0.001**
Model 2						
FFP transfusion vs. non-FFP transfusion	1.361	1.054–1.756	**0.018**	1.368	1.099–1.704	**0.005**
Model 3						
FFP transfusion vs. non-FFP transfusion	1.597	1.224–2.082	**0.001**	1.387	1.107–1.738	**0.004**

The significant P-value was indicated in bold. Model 1, adjusting for gender and age; Model 2, adjusting for gender, age, and scores of SAPS II and SOFA; Model 3, adjusting for all covariates. CI, confidence interval; FFP, fresh frozen plasma; HR, hazard ratio; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

TABLE 4 | The sensitivity analysis with INR and PTT by the Cox regression models.

Research subgroups	28-day mortality			90-day mortality		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Non-hypocoagulable group (INR ≤ 1.20)*	1.000	0.371–2.693	0.999	1.494	0.739–3.021	0.264
Hypocoagulable group (INR > 1.20)*	1.264	0.960–1.664	0.095	1.188	0.936–1.509	0.157
Non-hypocoagulable group (PTT ≤ 40)*	1.373	1.013–1.862	**0.041**	1.336	1.027–1.736	**0.031**
Hypocoagulable group (PTT > 40)*	1.217	0.746–1.986	0.431	1.347	0.881–2.060	0.169

*The significant P-value was indicated in bold. *Adjusting for the covariates of Model 2. CI, confidence interval; HR, hazard ratio; INR, international normalized ratio; and PTT, partial thromboplastin time.*

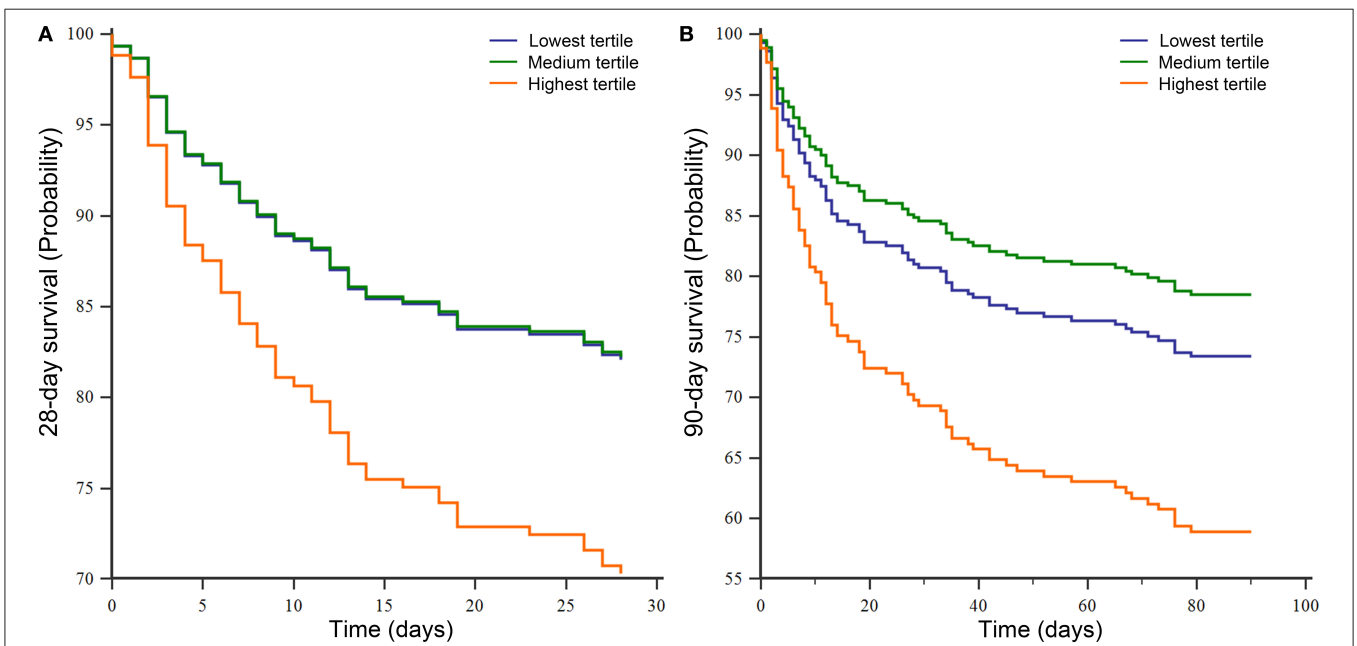

FIGURE 3 | The survival curves of Cox regression analysis for subset analysis in the MIMIC III database. **(A)** 28-day survival curve and **(B)** 90-day survival curve. MIMIC III, Medical Information Mart for Intensive Care III.

Plasma, a biological product containing the acellular portion of blood after centrifugation or by plasmapheresis, has important clinical effects, such as volume expansion, correction of abnormal coagulation tests, and transfusion-associated immunomodulation (13). The studies regarding the effects of plasma transfusion in the patients with a critical illness are limited, and the conclusions have not reached an agreement. Much of what we know about the effects of plasma transfusion

TABLE 5 | External validation with our hospital data.

Research variables	28-day mortality			90-day mortality		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Model 1						
FFP transfusion vs. non-FFP transfusion	3.572	1.956–6.524	**<0.001**	2.758	1.690–4.500	**<0.001**
Model 2						
FFP transfusion vs. non-FFP transfusion	2.470	1.272–4.795	**0.008**	1.979	1.142–3.429	**0.015**
Model 3						
FFP transfusion vs. non-FFP transfusion	2.493	1.273–4.884	**0.008**	2.386	1.363–4.175	**0.002**
Sensitivity analysis with different coagulation indexes						
Non-hypocoagulable group (INR ≤ 1.20)*	1.313	0.175–9.856	0.791	0.793	0.172–3.658	0.767
Hypocoagulable group (INR > 1.20)*	1.931	0.905–4.119	0.089	1.608	0.853–3.030	0.142
Non-hypocoagulable group (PTT ≤ 40)*	2.775	0.617–12.472	0.183	2.748	0.805–9.379	0.107
Hypocoagulable group (PTT > 40)*	2.426	1.133–5.193	**0.023**	1.814	0.974–3.379	0.061
Subgroup analysis in FFP transfusion group (*N* = 174)						
Low transfusion volume vs. high transfusion volume*#	1.884	1.040–3.414	**0.037**	1.882	1.096–3.232	**0.022**

*The significant P-value was indicated in bold. *Adjusting for the covariates of Model 2. #Median as cutoff value. CI, confidence interval; FFP, fresh frozen plasma; HR, hazard ratio; INR, international normalized ratio; and PTT, partial thromboplastin time.*

come from the studies performed in the setting of trauma. With the deep understanding of trauma-induced coagulopathy, many studies advocated that early FFP transfusion of high ratio was associated with the improved survival in severe traumatic patients (10, 11, 25, 26). However, as to systemic meningococcal disease, a study by Busund et al. revealed that the use of FFP may negatively influence the outcomes (27). Similarly, in the children with critical illness, plasma transfusion seemed to be independently associated with an increased occurrence of new or progressive multiple organ dysfunction syndrome, nosocomial infections, prolonged length of stay, and risk of mortality (28, 29). Moreover, with regard to the rat and foal models of sepsis, several studies discovered that plasma transfusion was beneficial for the survival of septic animals (30, 31).

For the traditional clinical experience, the patients with critical illness with coagulation disorder may benefit from an early FFP transfusion, thus, it is worthy to verify this hypothesis by the setting of sensitivity analysis with different coagulation indexes. Obviously, early FFP transfusion cannot improve survival for the patients with sepsis with hypocoagulable state in our study. Similarly, Dara SI et al. study showed that the outcomes of the FFP transfusion group in the patients with critical illness with coagulopathy had no statistically significant improvement (12). Additionally, as failing to induce a more procoagulant state, Müller et al. did not advocate FFP transfusion in the non-bleeding patients with critical illness with coagulopathy (32). The prophylactic use of FFP before invasive procedures to correct abnormal INR or PTT is never shown to reduce bleeding, because there is no correlation between the coagulation tests and risk of bleeding (33, 34). These previous studies support our findings in a sense.

As to the septic shock, Nanna et al. study showed that ICU mortality, 30-day mortality, 90-day mortality, and 365-day mortality were comparable between the patients with FFP transfused and non-transfused patients (35), which was consistent with our results of subset analysis. Due to the lack of sufficient references and guidelines, the role of FFP in fluid therapy of septic shock remains to be further studied.

In trauma patients, plasma can decrease the edema-mediated and inflammatory-mediated complications which are the detrimental processes that contribute to the organ failure and increased mortality (36). Several studies hypothesized that plasma also had similar effects on sepsis, because sepsis produced trauma-like changes on the endothelial glycocalyx layer which was a matrix of membrane-bound glycoproteins and proteoglycans projecting from the luminal surface of endothelial cells (7). However, as no definitive data that state plasma mitigates endothelial injury in sepsis, it is too early to draw this conclusion. Contrarily, there may be factors in the donor plasma that are deleterious to the host. The passive transfusion of antileukocyte antibodies from the alloimmunized donors and biological response modifiers accumulated during the storage of cellular blood products lead to the development of transfusion-related acute lung injury (TRALI) (37). Several previous studies suggested that FFP transfusion for the patients with critical illness was associated with an increased risk of the development of TRALI, which was regarded as the most serious transfusion complication (37, 38). Moreover, FFP transfusion was associated with an increased risk of infection and systemic inflammatory response syndrome (39, 40), thus, the double strike for the patients with sepsis may not conducive to the recovery of inflammatory response. In addition to TRALI and infection, there are other adverse reactions with the FFP transfusion as follows: allergic reactions, febrile reactions, citrate toxicity, circulatory overload, graft vs. host disease, and inhibitors against deficient proteins (41–43). As we can imagine, the FFP transfusion may not conducive to survival on the patients with sepsis when the effects of adverse reactions play a dominant role. As lack of relevant studies, the exact mechanisms remain to be elucidated.

Our study has several limitations. First, there may be existing potential bias caused by the factors in the patients with FFP transfusion who tend to be more serious. Thus, we adjusted the severity scores of illness in Model 2 to eliminate the influence of confounding factors and make the research variables comparable. Second, our main study from MIMIC III, due to its retrospective design, was vulnerable to the selection bias as a result of the inclusion of only a single-center sample and the exclusion of patients with missing data. Additionally, there is no denying that the lack of records for the causes of FFP transfusion is a limitation in our study. This is a preliminary exploratory study, thus, further prospective studies are warranted to validate our findings *via* a randomized controlled trial with different intervention groups.

CONCLUSIONS

Through the data analyses of dual centers and dual populations, the present study uncovered for the first time that for the patients with sepsis with coagulopathy, early FFP transfusion cannot improve the outcomes and was unfavorable. Contrarily, the mortality increased significantly with the increase of FFP transfusion volume. Similar results can also be found in the subset analysis of the septic shock cohort.

Significantly, our study provides a new understanding of the rationale and effectiveness of FFP transfusion for the patients with sepsis in a different perspective. In the clinical practice, there may be two existing misunderstandings that the patients with sepsis can benefit from early FFP transfusion as follows: (1) FFP can be used as a volume replacement, and (2) FFP should be used to correct abnormal INR or PTT in the patients with non-bleeding who have no planned invasive procedures. After recognizing the evidence of risk-benefit and cost-benefit, it is important to reduce the inappropriate use of FFP and avoid unnecessary adverse transfusion reactions. However, it is too early to deny the role of plasma completely, further studies are warranted to explore the guidelines for optimizing the rational use of FFP in the patients with sepsis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

XQ and WZho conceived and designed this study. WZha, XZ, and XH helped with the collection and assembly of data. All the authors contributed toward data analysis, drafting, critically revising the paper, agreed to be accountable for all aspects of the work, and read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.754859/full#supplementary-material

Supplementary Figure 1 | The diagnosis flowchart of Sepsis-3 criteria. *Vasopressors initiation (e.g., dopamine, norepinephrine, epinephrine, vasopressin, and phenylephrine). MAP, mean arterial pressure; qSOFA, quick Sequential Organ Failure Assessment; and SOFA, Sequential Organ Failure Assessment.

Supplementary Figure 2 | The detailed distribution of fresh frozen plasma (FFP) transfusion volume in the MIMIC III database. FFP, fresh frozen plasma and MIMIC III, Medical Information Mart for Intensive Care III.

Supplementary Table 1 | The baseline characteristics of final sepsis cohort and initial sepsis cohort.

Supplementary Table 2 | Comparison of the baseline characteristics of septic shock cohort vs. sepsis cohort.

Supplementary Table 3 | A subset analysis for septic shock cohort in the MIMIC III database.

Supplementary Table 4 | The baseline characteristics of external validation cohort.

Supplementary Table 5 | The baseline laboratory data and vital statistics of external validation cohort.

Supplementary Table 6 | A subset analysis for septic shock cohort with external validation.

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Mortality Prediction in Sepsis With an Immune-Related Transcriptomics Signature: A Multi-Cohort Analysis

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Background: Novel biomarkers are needed to progress toward individualized patient care in sepsis. The immune profiling panel (IPP) prototype has been designed as a fully-automated multiplex tool measuring expression levels of 26 genes in sepsis patients to explore immune functions, determine sepsis endotypes and guide personalized clinical management. The performance of the IPP gene set to predict 30-day mortality has not been extensively characterized in heterogeneous cohorts of sepsis patients.

Methods: Publicly available microarray data of sepsis patients with widely variable demographics, clinical characteristics and ethnical background were co-normalized, and the performance of the IPP gene set to predict 30-day mortality was assessed using a combination of machine learning algorithms.

Results: We collected data from 1,801 arrays sampled on sepsis patients and 598 sampled on controls in 17 studies. When gene expression was assayed at day 1 following admission (1,437 arrays sampled on sepsis patients, of whom 1,161 were alive and 276 (19.2%) were dead at day 30), the IPP gene set showed good performance to predict 30-day mortality, with an area under the receiving operating characteristics curve (AUROC) of 0.710 (CI 0.652–0.768). Importantly, there was no statistically significant improvement in predictive performance when training the same models with all genes common to the 17 microarray studies (n = 7,122 genes), with an AUROC = 0.755 (CI 0.697–0.813, p = 0.286). In patients with gene expression data sampled at day 3 following admission or later, the IPP gene set had higher performance, with an AUROC = 0.804 (CI 0.643–0.964), while the total gene pool had an AUROC = 0.787 (CI 0.610–0.965, p = 0.811).

Conclusion: Using pooled publicly-available gene expression data from multiple cohorts, we showed that the IPP gene set, an immune-related transcriptomics signature conveys relevant information to predict 30-day mortality when sampled at day 1

following admission. Our data also suggests that higher predictive performance could be obtained when assaying gene expression at later time points during the course of sepsis. Prospective studies are needed to confirm these findings using the IPP gene set on its dedicated measurement platform.

Keywords: sepsis, transcriptomics, predictive modeling, gene expression analysis, mortality, biomarker discovery

INTRODUCTION

Sepsis – a dysregulated immune response to severe infection leading to acute organ dysfunction (1) – is the third leading cause of death worldwide and the main cause of in-hospital mortality (2, 3). Despite more than 100 randomized clinical trials attempting to manipulate the host response to improve sepsis outcomes, sepsis care remains mainly supportive, limited to hemodynamic support, early antibiotic treatment and source control (4). In contrast to what is seen in the treatment of cancer, the aim of delivering precision medicine in sepsis remains far from attained: new tools and strategies are urgently needed to progress toward individualized patient care in sepsis (5, 6).

Why have all clinical trials in sepsis failed? (7). One reason is that they have not taken into account the significant heterogeneity in the epidemiology, microbiology and immunology of this syndrome. The immune response in sepsis is highly complex and dynamic, involving both pro- and anti-inflammatory mechanisms, with substantial intra- and inter-individual variability (8, 9). While its initial phase is characterized by uncontrolled inflammation responsible for tissue injury, sepsis patients also display markers of a profound immunosuppression (10), linked to a high prevalence of secondary opportunistic infections (11, 12) and contributing to significant mortality in sepsis survivors (13). Thus, trials are investigating whether immune-suppressing therapies such as interleukine (IL) 1 receptor antagonist (IL-1Ra) and anti–IL-6 could dampen the early cytokine storm, and conversely whether immune-stimulatory agents such as IL-7, granulocyte macrophage-colony stimulating factor (GM-CSF), and interferon gamma (IFN-γ) could reverse sepsis-induced immunosuppression (14).

To identify sub-groups of patients with reduced heterogeneity and a higher likelihood to respond favorably to such targeted therapies, it is crucial to use appropriate biomarkers (15, 16). For example, a low expression of human leukocyte antigen–DR on monocytes (mHLA-DR) can be used as a surrogate marker for monocyte anergy and decreased antigen presentation (17), and has been used as an inclusion criterion in the GM-CSF trial (18). However, its dissemination at the point-of-care has been limited, mainly because its accurate measurement is time-consuming and requires dedicated specialized personnel and equipment, and also because – as a univariate biomarker – it may fail to capture the global complexity of sepsis immunology.

More recent biotechnological and analytical advances have prompted the use of -omics technologies - mostly transcriptomics - to probe the immune response in sepsis, hoping that this approach could uncover important mechanisms of immune regulation and help identify biomarkers to inform targeted therapeutic strategies in sepsis (16, 19). By assaying messenger RNA (mRNA) transcripts in peripheral blood leukocytes and using unsupervised machine learning (ML) methods, sub-groups of sepsis patients whose distinct patterns of gene expression (GE) can be linked to distinct immune states, so-called « endotypes », have been identified. For instance, the Dutch Molecular Diagnosis and Risk Stratification of Sepsis (MARS) project identified four distinct sepsis endotypes named MARS 1 to 4, with patients in the MARS 1 cluster showing a pronounced decrease in expression of genes corresponding to key innate and adaptive immune cell functions and a decreased 28-day survival (20); and the United Kingdom Genomic Advances in Sepsis (GAinS) study identified two distinct sepsis response signatures named SRS 1 and SRS 2, with SRS 1 patients having an immunosuppressed status and higher 14-day mortality (21).

Importantly, there is only partial overlap in differentially expressed genes of the MARS 1 and SRS 1 clusters, raising the question of the generalizability of these signatures. This could be explained by the limited sample size of both studies; the redundancy in the information carried by multiples genes belonging to common biological pathways; and the sampling of patients from restricted ethnic backgrounds and geographic areas. In order to increase the potential to generalize transcriptomics studies in sepsis, one strategy is to leverage biological and technical heterogeneity across a large number of studies taken from diverse clinical backgrounds and profiled using different platforms (22). To this end, Stanford-based investigators have collected publicly available GE data sets sampled from sepsis patients, implemented a modified type of array normalization that uses the ComBat empirical Bayes normalization method (an algorithm called COCONUT, for COmbat CO-normalization Using coNTrols) and used a supervised learning approach to identify a gene signature predictive of 30-day sepsis mortality (23).

However, while this approach has focused on finding a gene signature with the broadest generalizability across populations and the highest predictive performance, it does not provide a mechanistic insight into the pathways involved in disease trajectories. Further, none of the above-mentioned

Abbreviations: AUPRC, area under the precision recall curve; AUROC, area under the receiving operating characteristics curve; COCONUT, COmbat CO-normalization Using coNTrols; GE, gene expression; GM-CSF, granulocyte macrophage-colony stimulating factor; IFN-γ, interferon gamma; IL, interleukin; IPP, immune profiling panel; mHLA-DR, human leukocyte antigen–DR; ML, machine learning; PCR, polymerase chain reaction.

signatures have incorporated prior knowledge on immunological abnormalities in sepsis, nor was devised precisely to discriminate between sub-groups of sepsis patients that could be targeted by specific immunomodulatory agents. Finally, they were devised using microarray data, while a point-of-care device targeting these gene sets would most likely use another technology to measure gene expression, raising the question of the transferability across platforms.

To circumvent these obstacles, we are working on an Immune Profiling Panel (IPP) prototype, a multiplexed transcriptomic assay that uses the FilmArray technology to quantify mRNA expression in whole blood and deliver results in less than an hour (24, 25). This prototype test, which has not been submitted for regulatory review at the time of this writing, may someday be able to provide clinicians with timely information about the immune system of sepsis patients and potentially aid in providing appropriate care. Selection of the IPP gene set was based on existing knowledge on genes related to relevant outcomes in sepsis (mortality prediction, sepsis-associated immunosuppression, susceptibility to secondary infections); technical performance of the selected targets in multiplex quantitative polymerase chain reaction (qPCR); and the goal to attain a balanced representation of pathways involved in sepsis immunopathology (such as monocyte anergy, antigen presentation, lymphocyte exhaustion, etc.) (26–29).

However, the performance of the whole IPP gene set to predict 30-day mortality in sepsis has not been evaluated in a large heterogeneous cohort of sepsis patients. To this end, we decided to: 1) collect publicly available microarray data sets of sepsis patients with patient-level information on mortality; (2) co-normalize data sets using COCONUT; (3) optimize ML models using the expression of the IPP gene set on day 1 following admission as input and 30-day mortality as the outcome of interest to evaluate the predictive performance of the IPP signature. Additional objectives were to evaluate if better predictive performances could be attained either by using another gene signature, or by using GE data sampled more than 2 days after hospital admission.

METHODS

Data Collection and Pre-processing

We searched NCBI GEO and EMBL-EBI ArrayExpress databases for studies with the following inclusion criteria: (1) publicly available GE data from micro-array experiments collected by whole blood sampling, with at least one sample collected at day 1 following hospital or intensive care unit (ICU) admission; (2) adult or pediatric patients with sepsis, according to Sepsis-1 (30), Sepsis-2 (31) or Sepsis-3 (32) definitions; (3) individual patient data on mortality (assessed between 28 and 30 days after blood sampling); (4) at least 5 control patients (healthy volunteers or patients with non-septic inflammation), which was mandatory for co-normalization across studies. Data sets using endotoxin or lipopolysaccharide infusion as a model for inflammation or sepsis, as well as datasets derived from sorted cells and RNAseq experiments were excluded.

We collected normalized GE data from selected studies when it was available, and inspected normalization visually by plotting individual patient data for each study. In case normalized data was not available, raw GE data was downloaded and normalized using the gcRMA method (R package affy) for *Affymetrix* chips, and normal-exponential background corrected and quantile normalized (R package limma) for *Agilent* and *Illumina* chips. When several microarray probe sets pointed toward one common gene under the HUGO gene nomenclature data base, we used the collapseRows function in the R package WGCNA to select the probe set with the highest mean value (MaxMean method) (33).

Individual patient data related to demographics and clinical characteristics were also extracted when available, including data on age, gender, ethnicity, clinical severity scores, and bacterial vs. viral origin of sepsis.

Co-normalization Using COCONUT

Comparison of GE data from different microarray studies is limited by different background measurements for each gene between microarrays, and potential batch effects among studies using the same types of microarrays. To analyze pooled data from different studies, co-normalization methods must be applied in such a way that: (1) no bias is introduced that could influence final classification; (2) there should be no change in the distribution of a gene within a study; and (3) a gene should show the same range of distributions between studies after normalization (34). To this end, we used the R package COCONUT (35), which implements a modified version of the ComBat empirical Bayes normalization method (36), using the assumption that all healthy/control patients from different studies come from the same distribution. All cohorts are split into healthy/control and diseased (sepsis) patients; the healthy components undergo parametric ComBat co-normalization without covariates; the ComBat estimated parameters are obtained for each data set for the healthy/control component and then applied to the diseased component.

Model Selection, Performance Metrics, Hyperparameter Tuning

Prior to model training, we randomly split the ComBat-corrected GE data into a discovery data set (70%) and a validation data set (30%). The discovery set was used to train several classification algorithms, taking GE data related to the IPP genes as input and 30-day mortality as outcome: logistic regression with L1 (lasso), L2 (ridge) and mixed (elastic net) regularization, random forest, support vector machines with linear and radial kernels and partial least squares-discriminant analysis. Mortality was considered as a binary variable because time-to-event data were not available in most public data sets.

Hyperparameter optimization was performed to select models with the highest mean area under the receiver operating characteristic (ROC) curve (AUROC) using 5 repetitions of 10-fold cross-validation. Alternatively, the area under the precision recall curve (AUPRC) was used as a performance scoring metric because our discovery data set had an imbalanced distribution of the outcome (with ∼19% mortality) (37). Furthermore, to

mitigate the negative impact of data imbalance on model training, we used several oversampling strategies, including the Synthetic Minority Oversampling Technique (SMOTE) on the discovery data set prior to hyperparameter tuning (38).

For each optimized model, we evaluated performance by computing the AUROC and its confidence interval (DeLong method) on the validation set.

Models and Feature Sets Comparisons

The IPP gene set contains 26 immune-related genes and 3 genes used for normalization, and we used those the total of 29 as input in the IPP models (**Supplementary Table 1**). To compare the predictive performance of the IPP gene set to that of the best possible signature derived from the pooled data set assembled from publicly available microarray data, we trained the same machine learning (ML) models, taking all genes common to all included studies as input ("all genes" models, $n = 7{,}122$ genes). To see if improvement in predictive performance from the IPP gene set to the total gene pool was due to the fact that the IPP gene set did not contain the best set of predictors, or solely a consequence of it having a limited number of predictors, we selected the 29 genes with the highest feature importance in the best performing "total gene pool" model and re-ran ML models using the "top 29 genes" set as input. Finally, we compared the IPP gene set to the "all genes" and "top 29 genes" sets by comparing ROC curves obtained by prediction on the validation set.

To determine if gene expression data could yield different predictive information on mortality if mRNA is sampled at time points beyond patient admission, we trained models on 2 data sets: (1) the "day 1" data set was a subset of the whole co-normalized data set, restricted to cohorts with available GE data for all the IPP genes, sampled at day 1 following enrolment; (2) the "day > 2" data set was a subset of the whole co-normalized data set, restricted to cohorts with available GE data for all the IPP genes, sampled at time points 3 to 7 days following enrolment. Each of these 2 data sets were split in discovery and validation sets as described above.

Finally, we sought to assess how IPP could be used as a tool for prognostication at the patient level. We used IPP models and found optimal thresholds of sensitivity and specificity using the top-left method on the "day 1" and "day > 2" data sets, enabling us to define 2 groups based on the predicted probability of death (low- and high-risk groups). Finally we computed and compared observed 30-day mortality rates in the low- and high-risk groups using appropriate statistical tests (see below).

Statistical Analysis and Software

To compare demographics and clinical features in the discovery and validation data sets, we used the Wilcoxon rank sum test. To compare predictive performance between models, we compared ROC curves computed using the same test set with DeLong's test for correlated data. To compare proportions of dead patients between different risk groups obtained with IPP genes, we used the chi-squared test or Fisher's exact test, as appropriate. Significance levels for p-values were set at 0.05 and analyses were two-tailed. Statistical analyses were performed using R (v3.6.2) with packages from the BioConductor library, the tidyverse collection, caret and COCONUT, as well as on Python 3 with the scikit-learn machine learning library.

RESULTS

Studies Included in the Analysis, Discovery and Validation Sets

Twenty studies fulfilled our inclusion criteria (20, 39–58). Of these, three studies (40, 48, 56) did not contain data on three genes included in the IPP gene set (TDRD9, CD274 and ARL14EP) because associated probes were not on the chip used in these studies (Affymetrix Human Genome U133A 2.0 Array), and were subsequently removed from analysis.

The remaining 17 studies included 2,399 arrays, with 1,801 arrays from sepsis patients and 598 arrays from controls (**Table 1**). The "day 1" data set included 1,437 arrays sampled on sepsis patients at day 1, of whom 1,161 were alive and 276 (19.2%) were deceased at day 30 following enrolment. As presented in **Table 2**, demographics and clinical characteristics were similar in the discovery ($n = 1{,}007$) and validation ($n = 430$) sets obtained after random splitting of the "day 1" data set.

In the 7 studies (43, 45, 46, 51–53, 58) with GE data collected at time points 3 to 7, there were 270 arrays sampled on 173 patients, of whom 134 were alive and 39 (22.5%) deceased at day 30; 122 were used for training and 51 for testing models (**Supplementary Tables 2, 3**).

We ran the COCONUT algorithm on the 17 studies selected for analysis and assessed the effect of co-normalization: (1) on patient-level GE data across studies (**Figure 1** and **Supplementary Figure 1**); (2) at the gene level in controls and cases (**Supplementary Figure 2** presenting data for CD3D); (3) for 2 genes in controls and cases, here with CLDN8 (a housekeeping gene, with minimal difference in mean GE between controls and cases and minimal overall GE variance) and CEACAM1, up-regulated during sepsis (**Supplementary Figure 3**). As expected, visual inspection of these plots confirmed the effect of COCONUT to attenuate the "batch effect" across the selected 17 studies.

Predictive Performances of the IPP Gene Set at Day 1 Following Admission

First, we sought to determine the performance of the IPP gene set to predict 30-day mortality using GE data sampled on the day of patient admission. As shown in **Figures 2**, **3**, the highest predictive performance was obtained by training of a random forest classifier, with an AUROC computed on the validation set of 0.710 (CI 0.652–0.768). Next, to determine if better predictive performance could be extracted from other genes, we ran the same models using all the genes common to the 17 selected studies as input. We found that the highest predictive performance of the "all genes" set ($n = 7{,}122$ genes) was obtained by training of an L2-penalized logistic regression classifier, with an AUROC computed on the validation set of 0.755 (CI 0.697–0.813), which was not statistically different from the performance obtained with the IPP gene set ($p = 0.286$). In such a logistic

TABLE 1 | Characteristics of the cohorts, patients and microarray data included in the study.

Dataset accession	First author	Country	CA vs. HCA**	Time points	Age	Sex (%males)	Arrays	Patients	Controls	Sepsis	Bacterial	Viral	Alive	Deceased	Chip	Normalization method
GSE27131	Berdal	Norway	CA	d1 d6 d7	41.1	85.7	21	14	7	7	0	7	5	2	Affymetrix	RMA
GSE32707	Dolinay	United States	CA	d1	57.1	54.2	103	103	55	48	NA	NA	86	17	Illumina	Quantile
GSE40586	Lill	Estonia	CA	d1	46.1	NA	39	39	18	21	21	0	19	2	Affymetrix	RMA
GSE66099	Wong	United States	CA	d1	3.7	63.1	276	276	77	199	NA	NA	248	28	Affymetrix	gcRMA
GSE21802	Bermejo-Martin	Canada	CA	d1	NA	NA	15	15	4	11	0	11	7	4	Illumina	Quantile
GSE54514	Parnell	Australia	CA	d1-d5	59.8	41.7	163	54	18	36	36	0	26	10	Illumina	Quantile
GSE20346	Parnell	Australia	CA	d1-d7	NA	NA	55	22	18	4	0	4	22	0	Illumina	Cubic spline
GSE40012	Parnell	Australia	CA	d1-d5	NA	45.5	129	42	31	11	3	11	42	0	Illumina	Quantile
GSE57065	Cazalis	France	CA HCA	d1 d2 d3	62.7	67.9	107	53	25	28	28	0	22	6	Affymetrix	RMA
GSE60244	Suarez	United States	CA	d1	62.1	41.5	158	158	40	118	47	96	158	0	Illumina	Quantile*
GSE65682	Scicluna	Netherland	CA HCA	d1	61	56.8	521	521	42	479	NA	NA	365	114	Affymetrix	RMA + quantile
GSE95233	Tabone	France	CA	d1 d2 d3	62.1	64.7	124	71	20	51	NA	NA	56	17	Illumina	Quantile
E-MEXP-3589	Almansa	Spain	CA	d1	NA	50	16	16	4	12	5	3	16	0	Agilent	Normexp
E-MTAB-1548	Almansa	Spain	HCA	d1	69.2	67.1	155	155	73	82	NA	NA	138	17	Agilent	Normexp
E-MTAB-5273/5274	Burnham	United Kingdom	CA	d1 d3 d5	65.4	53	337	253	10	243	NA	NA	204	39	Illumina	VSN
GSE13015	Planka	Thailand	CA HCA	d1	53.7	54.7	92	92	29	63	63	0	52	20	Illumina	Quantile*
GSE25504	Smith	United Kingdom	CA HCA	d1	0.25	56.8	88	88	44	44	37	5	84	4	Illumina + Affymetrix	Spline
Total							**2,399**	**1,972**	**515**	**1,457**	**240**	**137**	**1,181**	**276**		

**Normalization method was not specified in the original study but was verified graphically and assumed to follow the method specified in the table based on usual methods for the associated chip.*
***Community- vs. healthcare associated sepsis cases: CA is for community-acquired and HCA for healthcare-associated infections.*

regression classifier, it is possible to extract the genes with the highest absolute value of regression coefficients, indicative of the highest predictive performance. Thus, we subsequently trained ML algorithms with the 29 genes with the highest feature importance in the "all genes" model, and obtained an AUROC of 0.727 (CI 0.670–0.785, $p = 0.610$ in comparison to the IPP gene set). In conclusion, we found that the IPP gene set conveyed useful information to predict 30-day mortality with GE data assayed upon patient admission. Furthermore, we found evidence that the predictive power of the IPP gene set was equivalent to the best performing signature extracted from the 17 studies included in our multi-cohort ComBat-normalized data set.

Predictive Performances at Time Points > Day 2 Following Admission

Because most of the existing literature on sepsis immunology has shown that more relevant information can be obtained when assessing biomarkers later in the course of disease, we sought to investigate the predictive performance of the IPP gene set when GE data is measured on day 3 following admission or later. As shown in **Figure 4**, the highest performance of the IPP gene set at days > 2 following admission to predict 30-day mortality was obtained by training of a random forest classifier, with an AUROC computed on the validation set of 0.804 (CI 0.643–0.964). Here again, we found that the IPP gene set yielded similar information to the total gene pool, as we obtained an AUROC on the validation set of 0.787 (CI 0.610–0.965, $p = 0.811$) in the "all genes" best model.

TABLE 2 | Demographics and clinical characteristics in the discovery and validation sets computed with microarray data sampled at day 1 following study enrolment.

	Discovery set (*n* = 1007)	Validation set (*n* = 430)	*P*-value
Age [mean (SD)]	52.09 (26.35)	49.79 (26.83)	0.138
Gender (n,%)			0.142
Female	419 (41.6)	189 (44.0)	
Male	566 (56.2)	225 (52.3)	
NA	22 (2.2)	16 (3.7)	
Infection setting (n,%)			0.133
Community-associated	685 (68.0)	313 (72.8)	
Healthcare-associated	69 (6.9)	30 (7.0)	
NA	253 (25.1)	87 (20.2)	
Microbiology (n,%)			0.972
Viral sepsis	79 (7.8)	33 (7.7)	
bacterial sepsis	143 (14.2)	63 (14.7)	
NA	785 (78.0)	334 (77.7)	
Ethnic background (n,%)			0.976
Asian	46 (4.6)	19 (4.4)	
Black	17 (1.7)	6 (1.4)	
Latino	13 (1.3)	7 (1.6)	
White	52 (5.2)	21 (4.9)	
NA	879 (87.3)	377 (87.7)	
Platform (n,%)			0.708
Affymetrix	552 (54.8)	226 (52.6)	
Agilent	66 (6.6)	28 (6.5)	
Illumina	389 (38.6)	176 (40.9)	
Survival (n,%)	816 (81.0)	349 (81.2)	> 0.999

NA indicates values missing in the original studies.

Interest of IPP for Prognostic Enrichment

The ROC curve provides generic information on the performance of a binary classifier over a range of possible thresholds, but this information might be of limited relevance to clinicians aiming to determine the probability of an event for a specific patient, given the result of the test. To investigate how IPP could be used for prognostic enrichment, we used the optimized ML models obtained with the "day 1" and "days > 2" discovery data sets, computed ROC curves based on predictions on the validation sets, extracted thresholds based on the closest top-left method, and calculated the mortality rates in patients of the validation sets below (low-risk group) and above (high-risk group) this threshold.

As shown in **Figure 5**, using gene expression data from the "day 1" data set, 30.2% (CI 24.2–36.8%) of patients in the high-risk group were dead at day 30, as compared to 7.4% (CI 4.3–11.8%, p-value < 10E-8) in the low-risk group. Furthermore, using gene expression data from the "days > 2" data set, we found that 63.6% (CI 30.8–89.1%) of patients in the high-risk group were dead at day 30, compared to 8.5% (CI 2.8–18.7%, p-value < 10E-4) in the low-risk group. This indicated that using IPP at the bedside could help clinicians identify a sub-group of patients with higher 30-day mortality early-on during the course of sepsis.

DISCUSSION

The main finding of our study is that the IPP gene set has good overall performance to predict 30-day mortality, as assessed using microarray data sampled at day 1 following admission in a large and heterogeneous cohort of sepsis patients, with best model showing an AUROC of 0.710 (95% CI 0.652–0.768). IPP was designed using existing knowledge on sepsis immunology and pathophysiology, with the aim to assess the immune system of sepsis patients in a multifaceted manner, and this study demonstrates that the selected immune-related genes also provide predictive information on all-cause mortality. Furthermore, this information can be captured using retrospective and highly heterogeneous data collected on microarrays, even though the IPP tool is based on a PCR assay.

Importantly, predictive performance obtained with all the genes common to all microarrays (>7,000 genes) was not statistically different from that obtained with the IPP genes. It is still possible that the IPP gene set does not capture all the information available in GE data to predict 30-day mortality, but for important technical reasons (e.g., the limited multiplexing capabilities of most commercially available PCR-based assays), models including a large feature set would not be easy to implement at the bedside. This would mandate finding the optimal trade-off between statistical performance and technical

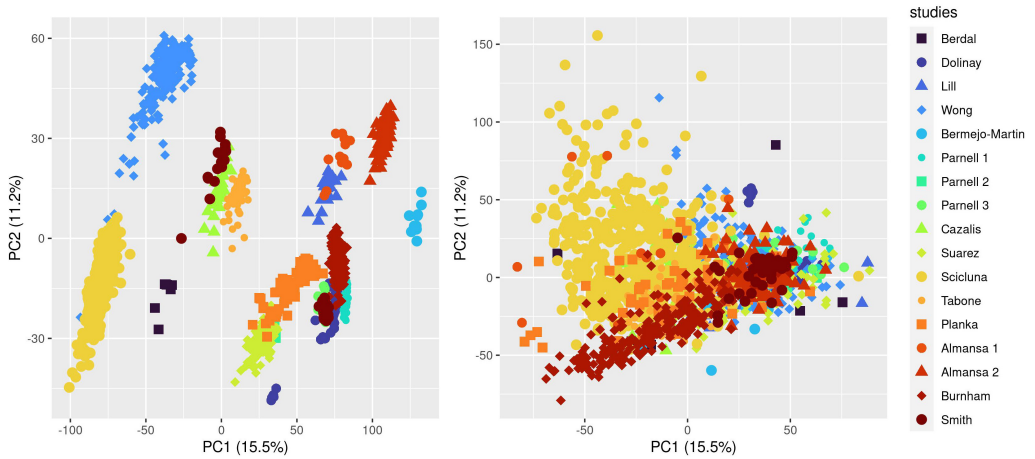

FIGURE 1 | Effect of ComBat co-normalization on patient-level gene expression data assessed by principal component analysis (PCA) across 17 microarray studies. We computed a 2-dimensional PCA plot of individual gene expression data from sepsis patients at day 1 following admission (7,122 genes assessed on 1,437 arrays sampled on 1,437 patients) before (left panel) and after (right panel) ComBat co-normalization using controls with the COCONUT R package. Each of the 17 studies maps to one color, showing how co-normalization attenuates the segregation of individual data points in clusters determined by the study to which they belong.

constraints to identify the best number of features to include in the assay. Furthermore, models with a high number of predictors are prone to overfitting, which could limit the prognostic accuracy of gene sets across different technological platforms or in different clinical settings. Overall, these results demonstrate that the IPP gene set can capture similar information on 30-day mortality in sepsis as the total gene pool common to 17 microarrays, but with the potential to deliver actionable results in less than an hour, directly at the point of care.

One key aspect of our analysis pipeline is the use of publicly available GE data and batch-effect correction using the ComBat algorithm, which follows a strategy developed by a group from Stanford University (22, 34, 39, 59). Conceptually, pooling together highly heterogeneous data collected in different clinical settings has the potential to increase the generalizability of gene signatures to populations with different ethnic backgrounds and disease phenotypes. However, one can question the relevance of this approach when looking in detail at the wide variability in the demographics and clinical characteristics of the patients included in our multi-cohort analysis. Whether or not there are in fact shared pathophysiological mechanisms and common immunological pathways in children vs. adults, in viral vs. bacterial sepsis, or in ICU vs. ward patients, remains to be fully investigated to demonstrate the usefulness of this strategy.

The IPP prototype has been designed to be run on a dedicated real-time multiplex PCR platform, whereas GE data used in our analysis was collected on microarrays, which raises the question of cross-platform transferability of transcriptomics assays. Given the sometimes weak correlation in expression levels of the same gene target measured on one given sample but different technology, it is highly possible that the real association between our gene signature (as measured with the IPP tool) and 30-day mortality might not be accurately recapitulated in our study. While many gene signatures have been devised for diagnosis and prediction in sepsis, none so far has been proven robust enough to be translated into a clinically usable tool, in part because good statistical performance seen during the conception phase was not reproduced on prospectively collected new patient data, especially if analyzed on a different platform (60). In recent studies for instance, a gene signature devised using microarray data did not show major improvement in predictive power compared to usual severity scores (SAPS 3 and APACHE II) when tested on prospectively collected patient samples processed on the NanoString nCounter platform (60, 61). In line with this, a prospective multicenter study [IMPACCT (62)] is currently enrolling sepsis patients to better evaluate the predictive performance of the IPP gene set when used on its dedicated platform.

Independent of the question of cross-platform transferability, transcriptomics-based diagnostic tools in sepsis might fail to take into account all the relevant information available to predict key outcomes. For instance, there are validated and widely-used clinical severity scores that can predict mortality in intensive care patients with moderate discrimination but wide generalizability and at virtually no added cost. Thus, when evaluating a transcriptomics-based tool, we should verify that GE data provide information independently of the clinical scores. This question was assessed in the Stanford multi-cohort analysis on mortality prediction by running models including both clinical and transcriptomics data, and evaluating the independent effect of GE data on mortality prediction. These analyses showed a consistent (yet not always large) improvement in AUROCs when using genes in addition to clinical data as input (23). Unfortunately, we were not able to run the same analyses, as the majority of publicly available data sets we used did not report patient-level clinical severity data (and because studies that did report data on clinical severity used a wide range of severity scores, limiting their use in our multi-cohort analysis framework). In the same line, it can be argued that for both, clinical and methodological considerations, it would be

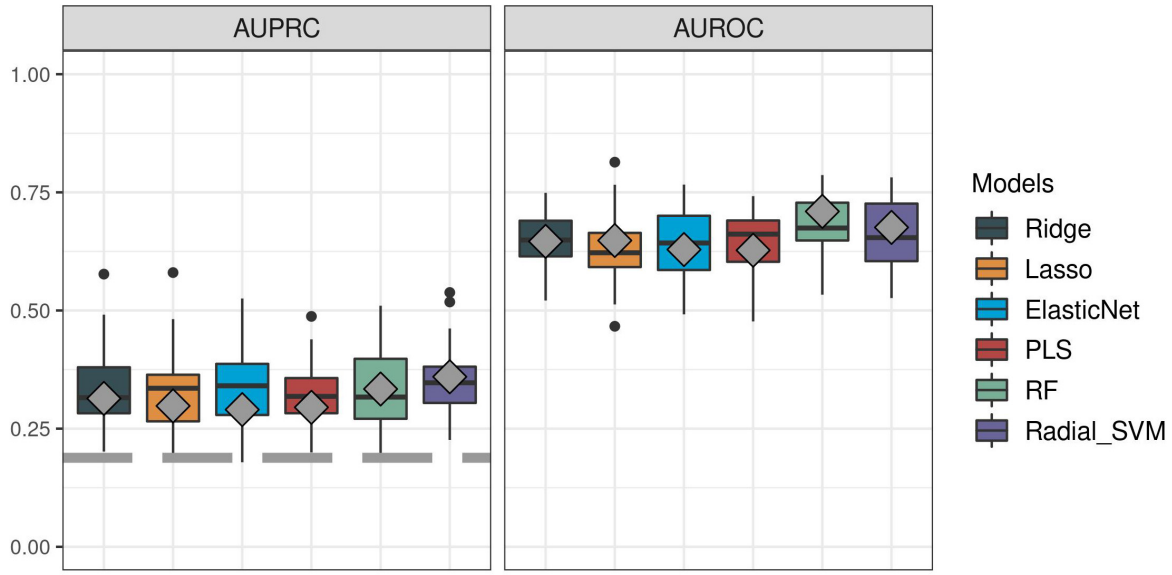

FIGURE 2 | Predictive performance of the IPP gene set on "day 1" discovery and validation sets. We trained machine learning models on the "day 1" discovery (n = 1,007) and validation (n = 430) data sets by 5 repeats of 10-fold cross-validation, and computed areas under the receiver operating characteristic (AUROC, right panel) and precision-recall curves (AUPRC, left panel) on the resampled discovery set (box plots) and by prediction on the validation set (gray diamonds). Gray dashed line on the AUPRC facet indicates baseline probability of the outcome (death).

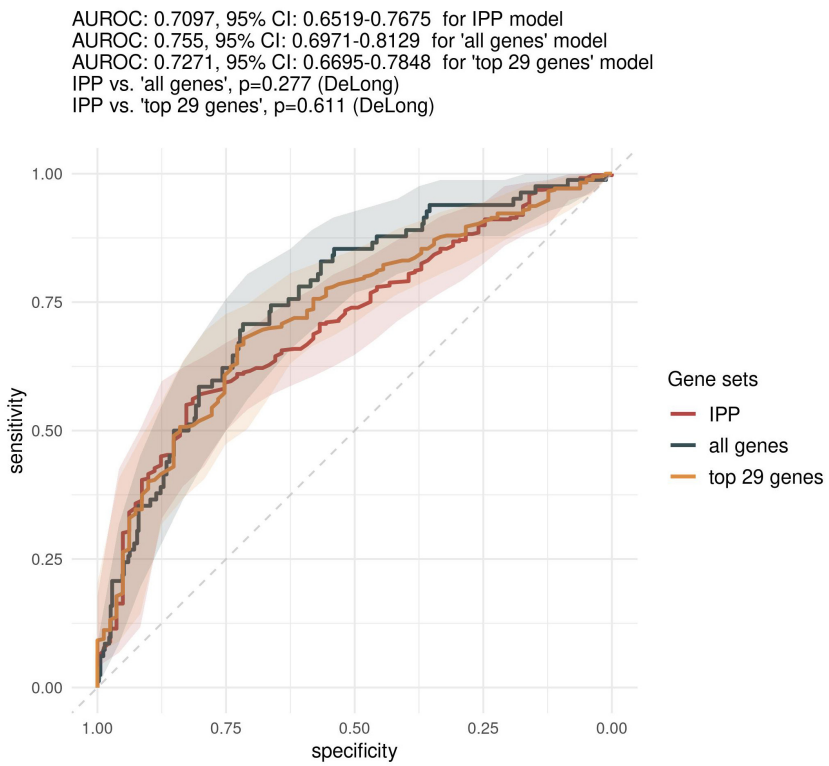

FIGURE 3 | Comparison of predictive performances of the IPP gene set with that obtained with other genes on the "day 1" data set. We compared the predictive performance of the IPP gene set to that obtained with other genes common to the 17 microarray studies by computing ROC curves obtained by prediction on the validation set with IPP, "all genes" and "top 29 genes" models trained on GE data collected at day 1 following admission. Gray areas indicate 95% confidence intervals of corresponding AUROCs.

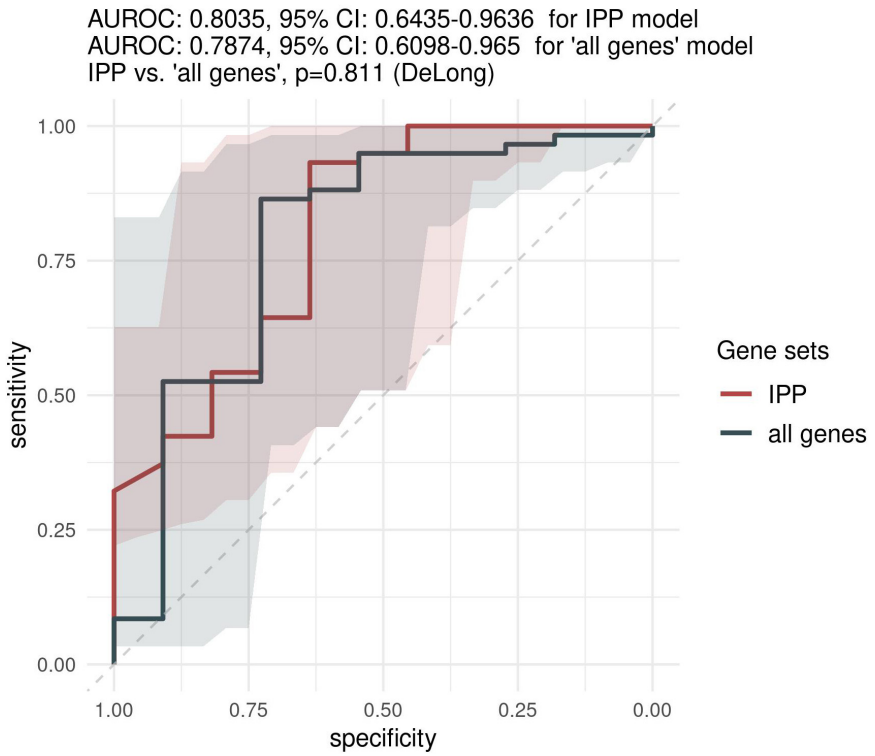

FIGURE 4 | Predictive performance of the IPP gene set on the "days > 2" data set. We assessed the predictive performance of the IPP and "all genes" set by computing ROC curves on the validation set.

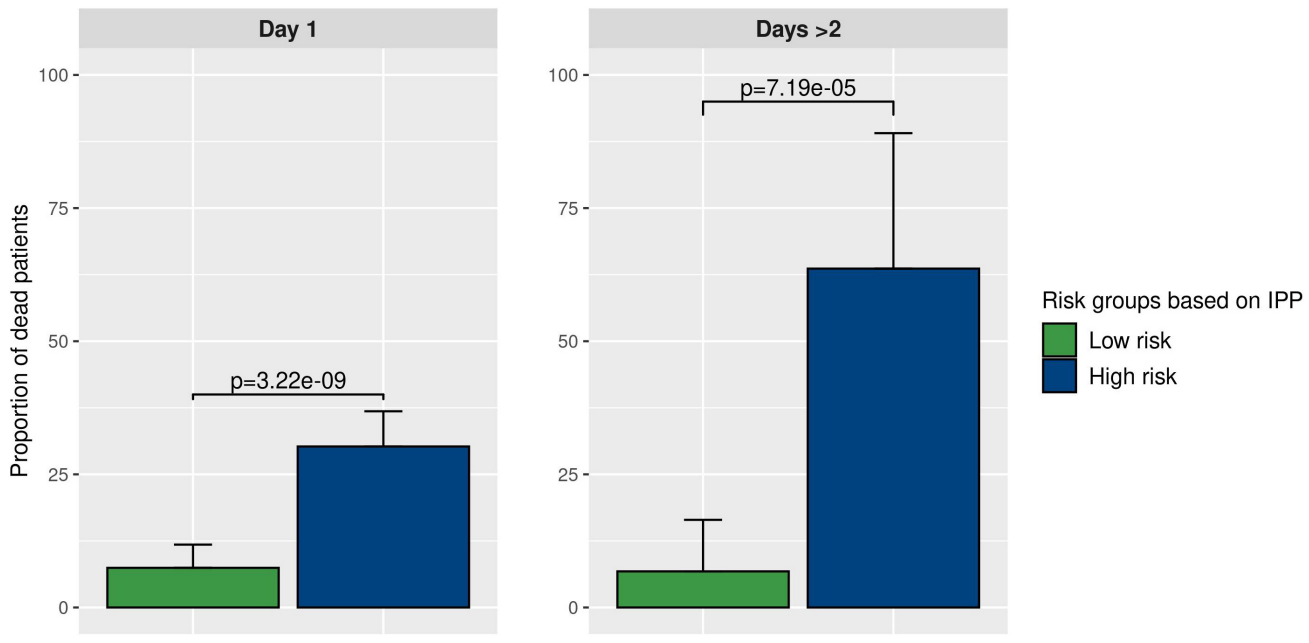

FIGURE 5 | Prognostic enrichment with the IPP tool. We used the best IPP models (trained on the "day 1" and "days > 2" discovery sets) and computed a test threshold using the top-left method on corresponding validation sets. This enabled us to divide the validation sets in 2 sub-groups with a low and a high predicted risk of death. Then, we compared the actual proportion of sepsis patients deceased at day 30 in both sub-groups, to assess if IPP could be used for prognostic enrichment at the bedside.

interesting to include in our prediction models patient-level data on demographics, clinical characteristics and therapeutics (such a steroids, which are known to influence shock severity and sepsis mortality (63), and are also potentially responsible for a change in immune-related GE profile). This argues in favor of prospectively collecting more high quality data on sepsis patients to refine prediction models that would include all relevant information, including clinical and biological, but also genetic, epigenetic, microbiological (etc.), data.

Another inherent limitation of this work is that even though mortality is widely considered an important patient-centered outcome, it is influenced by myriad factors, including many that are not easily modified through medical intervention, which makes it difficult to predict accurately using easily available patient data. Furthermore, it can be argued that even a perfectly calibrated mortality prediction model would fall short of having a positive impact on an individual patient's care if not coupled with a set of clinical measures meant to improve patient outcomes. In line with this, models designed to predict healthcare-associated infections (HAIs) may be more valuable to clinicians, as they could enable identification of high-risk patients that could be targeted by preventive bundles of cares [e.g., early removal of invasive devices, which are associated with the occurrence of HAIs (12)]. Maybe even more importantly, models designed to identify sepsis endotypes could lead to targeted immune stimulating therapies (10, 64).

Finally, our study suggests that GE data has better performance to predict mortality when mRNA is sampled on day 3 or later following hospital admission. This finding is in line with numerous reports on sepsis biomarkers used to predict mortality or hospital-acquired infections, which consistently show higher performances when biomarkers are assayed after day 3–4 (17, 65). This is also consistent with accumulating data on sepsis immunology, indicating that sepsis-acquired immunosuppression develops in a subset of patients with a worse prognosis only after a few days of acute inflammation (10, 66, 67). Thus, our findings confirm that a transcriptomics tool assessing the host response of sepsis patients to predict mortality could yield more reliable information if assayed at later time points. However, our data must be interpreted with caution, as there were a limited number of patients with GE data available at time points > 2 days, with only 122 patients in the discovery set and 51 (including 11 deaths) in the validation set. In line with this, evaluating if serial measurements of biomarkers can be used to recapitulate disease trajectories in sepsis, and whether this information can be helpful in refining the definition of sepsis endotypes, is the subject of active research (68).

CONCLUSION

Through multi-cohort analysis using ComBat co-normalization on microarray data in a heterogeneous group of sepsis patients, we found that the IPP gene set, when assayed at day 1 following hospital admission, can reliably predict all-cause 30-day mortality. Our data also suggest that more information could be extracted from mRNA data if sampled at later time points, when immunological trajectories begin to diverge between sepsis survivors and patients who will eventually die. Since mortality prediction in sepsis is of limited interest to clinicians if not coupled with specific interventions meant to influence disease trajectory and prognosis, using IPP to identify sepsis endotypes or predict HAI is more likely to have a positive impact on the care of patients with sepsis.

DATA AVAILABILITY STATEMENT

The raw and normalized gene expression data sets analyzed in this study, data on patient demographics, clinical characteristics and outcomes have been deposited publicly and are available from referenced studies and from Synapse (doi: 10.7303/syn5612563). The code written for co-normalization across studies and assessment of predictive performance of gene signatures is available at: https://github.com/lkreitmann-bmx/IPP_mortality_2022.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

SB, KB-P, and LK: study conception and design. LK, MB, KI, and SB: statistical analysis. M-AC, EP, and EC: data curation. LK: manuscript drafting. AF, CT, FC, J-FL, JT, and GM: critical revision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.930043/full#supplementary-material

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In-Hospital Mortality of Sepsis Differs Depending on the Origin of Infection: An Investigation of Predisposing Factors

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Sepsis is a heterogeneous syndrome characterized by a variety of clinical features. Analysis of large clinical datasets may serve to define groups of sepsis with different risks of adverse outcomes. Clinical experience supports the concept that prognosis, treatment, severity, and time course of sepsis vary depending on the source of infection. We analyzed a large publicly available database to test this hypothesis. In addition, we developed prognostic models for the three main types of sepsis: pulmonary, urinary, and abdominal sepsis. We used logistic regression using routinely available clinical data for mortality prediction in each of these groups. The data was extracted from the eICU collaborative research database, a multi-center intensive care unit with over 200,000 admissions. Sepsis cohorts were defined using admission diagnosis codes. We used univariate and multivariate analyses to establish factors relevant for outcome prediction in all three cohorts of sepsis (pulmonary, urinary and abdominal). For logistic regression, input variables were automatically selected using a sequential forward search algorithm over 10 dataset instances. Receiver operator characteristics were generated for each model and compared with established prognostication tools (APACHE IV and SOFA). A total of 3,958 sepsis admissions were included in the analysis. Sepsis in-hospital mortality differed depending on the cause of infection: abdominal 18.93%, pulmonary 19.27%, and renal 12.81%. Higher average heart rate was associated with increased mortality risk. Increased average Mean Arterial Pressure (MAP) showed a reduced mortality risk across all sepsis groups. Results from the LR models found significant factors that were relevant for specific sepsis groups. Our models outperformed APACHE IV and SOFA scores with AUC between 0.63 and 0.74. Predictive power decreased over time, with the best results achieved for data extracted for the first 24 h of admission. Mortality varied significantly between the three sepsis groups. We also demonstrate that factors of importance show considerable heterogeneity depending on the source of infection. The factors influencing in-hospital mortality vary depending on the source

of sepsis which may explain why most sepsis trials have failed to identify an effective treatment. The source of infection should be considered when considering mortality risk. Planning of sepsis treatment trials may benefit from risk stratification based on the source of infection.

Keywords: sepsis, intensive care medicine, mortality risk, prognostic factors, origin of infection, logistic regression

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (1). It is not a uniform disease, but a complex syndrome of physiologic and biochemical abnormalities. Clinical experience supports the concept that prognosis, treatment, severity and time course vary depending on the source of infection (2, 3). Consequently, attempts have been made to characterize different types of sepsis based on clinical data, routine blood results and biomarkers (4). Mortality of sepsis ranges from 15% in patients with sepsis without shock to 56% in patients with sepsis with shock (5). However, mortality prediction for sepsis remains satisfactory at best (4).

Although numerous trials have been designed to explore treatment options for sepsis, so far, none of these has resulted in new therapies (6). A major shortcoming of many of these multi-center randomized clinical trials is the patient cohort investigated. Patients with sepsis manifest striking heterogeneity, not only with respect to the site or microbiology of the inciting infection but also with respect to the comorbid conditions present in the patient at the time of onset (7). Comorbidities, site of infection and pathogen factors impact the mortality attributed to sepsis. However, in most clinical trials differentiation between groups of sepsis is lacking and may have contributed to the negative outcome of these studies. Recently, attempts have been made to discriminate sub-phenotypes of sepsis based on panels of immunological markers. Although promising, these clinical phenotypes for sepsis (4) are complex, rely on measurement of biomarker profiles, and are thus not easy to implement into routine clinical applications.

Electronic health records are now commonly used to record all routine clinical data. This allows the construction of large databases, which not only structure and aggregate clinical data but also record outcome measures such as mortality, length of stay, and duration of ventilation. Alongside with routinely applied scoring systems such as the Acute Physiology and Chronic Health Evaluation (APACHE), the Sequential Organ Failure Assessment (SOFA), or the Simplified Acute Physiology Score (SAPS), novel outcome prediction models are being developed based on these large patient populations.

In this research, we investigate in-hospital mortality and predictors thereof in different cohorts of sepsis based on the origin of infection using data from the eICU Collaborative Research Database, a freely available multi-center database for critical care research (8). We hypothesize that mortality and factors influencing mortality risk differ between pulmonary, urinary, and abdominal sepsis as the three most relevant clinical presentations. We aim to identify unifying and distinct features in these groups. Comparisons will be made with established outcome prediction scores such as APACHE IV and SOFA to determine if more sophisticated models show superior performance in predicting hospital mortality in these different groups of septic patients.

MATERIALS AND METHODS

Data Source

In this study, we used the eICU Collaborative Research Database (eICU) (8). The eICU is a multi-center intensive care unit (ICU) database with highly granular data for over 200,000 ICU admissions collected *via* eICU programs across the United States (US) (8). The eICU (V2.0) database comprises 200,859 ICU encounters for 139,369 unique patients admitted to hospitals between 2014 and 2015 to one of the 335 intensive care units across 208 hospitals in the US. All tables are deidentified to meet the safe harbor provisions of the US Health Insurance Portability and Accountability Act (HIPAA). This includes the removal of all protected health information and the assignment of random unique identifiers. The database includes demographic/hospital level records, vital signs and laboratory measurements, medications, APACHE components, care plan documentation, severity illness measures, diagnosis information, and treatment details.

Data Extraction

We extracted data from the medical ICUs (MICU), surgical ICUs (SICU), and medical-surgical ICUs (Med-Surg ICU). Specialist critical care units such as cardiothoracic and cardio-surgical ICUs were excluded because of their specific patient cohorts with distinct presentations of sepsis. Patients after elective surgery and those with an underlying hematology diagnosis were also excluded, as their clinical presentation and course are distinct from patients with sepsis as the primary diagnosis. We then used the admission diagnosis codes, which are coded using the APACHE IV diagnosis system, to extract the admissions related to sepsis, and excluded patients < 18 years of age and with an ICU stay < 72 h. Lastly, all records with more than 35% missing data were excluded. These inclusion and exclusion criteria are represented in **Figure 1**.

We collected all electronic health record data from the acute phase of the ICU admission, defined as the first 72 h after admission. From this dataset, we excluded the first 6 h (resuscitation phase), where the priority is to stabilize the patient. Previous studies have used data from different time windows for outcome prediction, e.g., the first 24 h of the ICU admission (9).

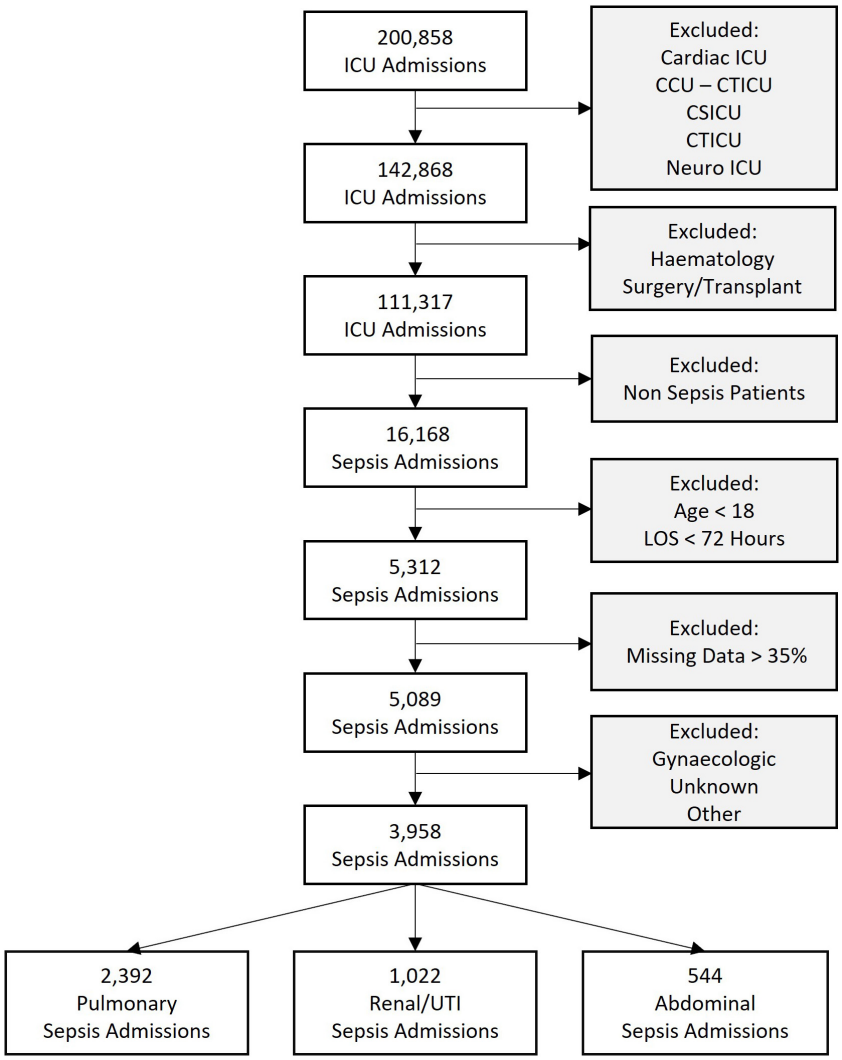


FIGURE 1 | Flowchart of sepsis cohorts analyzed showing the inclusion and exclusion criteria. ICU, intensive care unit; CCU-CTICU, critical care unit-cardiothoracic intensive care unit, CSICU, cardio-surgical intensive care unit; LOS, length of stay; UTI, urinary tract infection.

All dynamic features were organized into 1-h non-overlapping time series bins when extracting the data from the eICU database. This was to accommodate for different sampling frequencies of available data and the balance between missing data points and bin size. All time-varying variables were converted into tabular representations by extracting their means and standard deviations. The mean value of these time-varying variables, which represents the average of each time series, was named "Average" (Avg), e.g., the mean of the heart rate signal was coded as "Avg Heart Rate." Similarly, the standard deviation, which is representing the variation in the time series, was coded as "Variations" (Var), e.g., Heart Rate Var.

Outcome

The primary outcome was In-Hospital Mortality, which was coded as a binary variable to indicate whether the patient was dead ("1") or alive ("0").

Study Aim

The aims of this study were (1). to define in-hospital mortality depending on the origin of infection and (2). To investigate predictors of in-hospital mortality for each of the most common types of sepsis: abdominal, urinary and chest sepsis.

Definition of Sepsis Types

A cohort of patients with sepsis was extracted based upon the ICU admission diagnosis, which is coded using the APACHE IV diagnosis system (10) routinely recorded in the eICU database. From here, the following septic groups were identified: pulmonary, abdominal, and renal/urinary tract infection (UTI). Other smaller cohorts of septic patient groups were excluded either because of a lack of clarity regarding their clinical source (e.g., those encoded as "unknown" or "others") or because of their considerably smaller number of cases (e.g., gynaecologic sepsis with less than 20 admissions). The prevalence in these groups was

also reviewed against the encoded ICD codes for these patients to ensure that the relevant cohorts were well defined.

Univariate Analysis

We used non-parametric statistical tests for continuous and categorical variables for univariate analysis of the three main groups of sepsis. The univariate analysis aims to compare variable distributions for significant differences amongst the sepsis groups. The Kruskal-Wallis test was applied to assess the differences among the sepsis groups for all continuous variables. Similarly, Pearson's Chi-Square was used to assess differences for all categorical variables. P-values < 0.05 were considered statistically significant.

Multiple Logistic Regression

Multiple logistic regression (LR) was used throughout the experiments. LR models the outcome probability or risk to be "1" (positive class) as $P(Y = 1) = 1/\left(1 + \exp\left[-\sum_{k=0}^{K} \beta_k X_k\right]\right)$, where $\{\beta_0, ..., \beta_K\}$ are the model coefficients which are estimated by maximum likelihood (11). The LR coefficients are the logarithm odds ratios (OR) between the factors and the outcome. If a factor increased by one unit, its coefficient measures how much the outcome odd would increase or decrease, depending on whether the coefficient is positive or negative.

Variable Selection and Cross-Validation

For LR, input variables were automatically selected using a sequential forward search algorithm over 10 dataset instances (10-fold cross-validation). For each iteration, an inner cycle of fivefold cross-validation was used to select relevant variables. Collectively this is referred to as nested cross-validation (**Supplementary Figure 1**). The selection algorithm starts with a baseline model (i.e., all coefficients but the intercept set to zero, $\beta_{k\neq 0} = 0$), and in each step, the variable which most improves the performance on the validation set is added (12).

Model Performance

Model performance was measured using the area under the receiver operator characteristic (AUC) curve. AUC means and confidence intervals (CI) were calculated for each sepsis type.

Model Explainability

To provide model explainability, we developed a forest plot for each sepsis type and a Sankey network diagram. The forest plots display the ORs and CIs associated with each clinical feature relevant to the developed LR models. The Sankey network diagram was used in a novel way to visualize the interactions between the significant clinical features and sepsis groups. For this, we selected the significant variables ($P < 0.05$) from the LR models (nodes on the left-hand side of the diagram) and generated links between them and the sepsis groups (nodes on the right-hand side of the diagram). Additionally, the absolute value of the OR interactions between clinical features and sepsis groups was represented by the height of the nodes, to provide further information regarding the relevance of each clinical feature.

Comparisons of the Novel Models Against Established Critical Care Deterioration Scores

We compared the performance of two commonly used clinical scoring systems, the APACHE IV and SOFA score, which are typically used to predict in-hospital mortality for patients in critical care. We used the SOFA and APACHE IV scores as independent variables in a univariate LR model to produce the mortality risk estimate for the outcome. The purpose was to allow for a fair comparison between the developed models and the scores using the same methodology to evaluate how well each of them can predict the outcome.

The APACHE IV and SOFA scores are readily available in the eICU database. The APACHE IV scores were calculated based upon data collected on admission to the ICU, these values were available and listed in the eICU table "apachePatientResults." Individual components of the SOFA score were calculated (13) for the first 3 days and then averaged. qSOFA scores were calculated by assigning points for (1). altered mental state (< 15 in the Glasgow Coma Scale), (2). Fast respiratory rate (> 22 breaths per minute) 3. Low blood pressure (systolic blood pressure < 100 mmHg).

RESULTS

Sepsis Groups

A total of 3,958 ICU admissions were analyzed. A total of 2,393 patients were admitted with pulmonary sepsis, 1,044 with urinary sepsis and 544 with abdominal sepsis (**Figure 1**). Unadjusted statistical comparisons between the three sepsis groups are displayed in **Table 1**. Patients with urinary sepsis were older than patients with pulmonary and abdominal sepsis.

With the exception of hypertension, there were no significant differences in cardiovascular comorbidities between the groups. We found group differences that were statistically significant (p-value < 0.05) for comorbidities such as mild and severe liver disease, dementia and respiratory diseases (COPD, asthma). We also observed significant group differences in vital signs (average heart rate, average mean arterial pressure (MAP), average saturation, average respiratory rate and average temperature) and blood counts (average lymphocyte count, average white blood cell count, average platelet count, and hematocrit). Blood gas results differed between groups with regards to average pH, average pO_2 and average pCO_2. Liver and kidney function was also significantly different between groups. Compared to patients with pulmonary or abdominal sepsis, a smaller proportion of patients with urinary sepsis required inotropes during their stay.

While there was a significant difference between SOFA and qSOFA scores between the groups, Charlson comorbidity index and APACHE IV score were comparable between abdominal, urinary and pulmonary sepsis.

Evaluation of Model Performances

Figure 2 displays the results of the comparison between the developed multivariate models and the APACHE IV and SOFA

scores. These AUC results show that, for pulmonary and abdominal sepsis, the novel models outperformed APACHE IV and SOFA scores (AUC 0.74 and 0.71, respectively), but were not superior in urinary sepsis (AUC 0.63).

Comparisons using different time windows for data extraction was performed to assess (a) how this decision impacts model performances, and (b) how our analysis compares to previous studies. **Figure 3** compiles the results obtained for the first 24, 48, and 72 h, with or without the inclusion of the first 6 h. The best results were obtained when using the first 24 h, where the cohort sizes were generally twice the size of those at 72 h (see the bottom of **Figure 3**), as a great proportion of patients either died or were discharged between 24 and 72 h after ICU admission.

TABLE 1 | Demographics, comorbidities, vital signs, and routine prognostic scores used for modeling.

	Abdominal (*N* = 544)	Pulmonary (*N* = 2,392)	Renal/UTI (*N* = 1,022)	*P*-value
Outcome				
In-hospital mortality	103 (18.9%)	461 (19.3%)	131 (12.8%)	<0.001
Demographics				
Age	67.0 (56.0, 76.0)	67.0 (56.0, 77.0)	71.0 (60.0, 81.0)	<0.001
Gender (Male)	276 (50.7%)	1,281 (53.6%)	437 (42.8%)	<0.001
Comorbidities				
Myocardial infarction	45 (8.3%)	184 (7.7%)	85 (8.3%)	0.7862
CHF	85 (15.6%)	461 (19.3%)	204 (20.0%)	0.0932
PVD	27 (5.0%)	116 (4.8%)	53 (5.2%)	0.9172
Dementia	14 (2.6%)	166 (6.9%)	104 (10.2%)	<0.001
COPD	81 (14.9%)	600 (25.1%)	136 (13.3%)	<0.001
CTD	16 (2.9%)	70 (2.9%)	35 (3.4%)	0.7302
Peptic ulcer disease	14 (2.6%)	75 (3.1%)	35 (3.4%)	0.6552
Mild liver disease	31 (5.7%)	55 (2.3%)	26 (2.5%)	<0.001
Uncomplicated DM	146 (26.8%)	713 (29.8%)	407 (39.8%)	<0.001
Renal disease	94 (17.3%)	334 (14.0%)	165 (16.1%)	0.0712
Hemiplegia	45 (8.3%)	246 (10.3%)	146 (14.3%)	<0.001
Severe liver disease	32 (5.9%)	49 (2.0%)	18 (1.8%)	<0.001
Hypertension	269 (49.4%)	1,143 (47.8%)	564 (55.2%)	<0.001
Hypothyroidism	16 (2.9%)	100 (4.2%)	43 (4.2%)	0.3882
Atrial fibrillation	70 (12.9%)	307 (12.8%)	144 (14.1%)	0.5962
Asthma	38 (7.0%)	219 (9.2%)	70 (6.8%)	0.0412
Seizures	32 (5.9%)	166 (6.9%)	83 (8.1%)	0.2312
Respiratory failure	10 (1.8%)	126 (5.3%)	46 (4.5%)	0.0032
CABG	25 (4.6%)	139 (5.8%)	46 (4.5%)	0.2142
Cancer	116 (21.3%)	422 (17.6%)	169 (16.5%)	0.0572
Admission diagnosis				
Pulmonary	181 (33.3%)	2,109 (88.2%)	350 (34.2%)	<0.001
Cardiovascular	423 (77.8%)	1,788 (74.7%)	787 (77.0%)	0.1852
Infectious diseases	165 (30.3%)	569 (23.8%)	361 (35.3%)	<0.001
Renal	205 (37.7%)	730 (30.5%)	662 (64.8%)	<0.001
Gastrointestinal	323 (59.4%)	211 (8.8%)	91 (8.9%)	<0.001
Oncology	20 (3.7%)	114 (4.8%)	24 (2.3%)	0.0042
Neurologic	85 (15.6%)	443 (18.5%)	270 (26.4%)	<0.001
Endocrine	63 (11.6%)	330 (13.8%)	169 (16.5%)	0.0192
Vitals				
Avg heart rate	94.0 (81.9, 105.0)	90.2 (79.8, 100.8)	89.0 (78.1, 98.7)	<0.001
Heart rate var	9.5 (6.9, 12.6)	10.0 (7.3, 13.5)	9.7 (7.1, 13.4)	0.0201
Avg SaO_2	96.6 (95.3, 98.2)	96.6 (95.1, 98.0)	97.1 (95.9, 98.5)	<0.001
SaO_2 var	1.9 (1.4, 2.5)	2.1 (1.6, 2.7)	1.8 (1.3, 2.5)	<0.001
Avg GCS total	13.8 (10.5, 14.9)	11.3 (9.0, 14.3)	13.6 (10.0, 14.8)	<0.001
GCS total var	0.7 (0.2, 1.7)	0.9 (0.4, 1.9)	0.6 (0.3, 1.5)	<0.001
Avg respiratory rate	20.5 (18.0, 23.9)	21.4 (18.6, 24.8)	20.1 (17.6, 23.3)	<0.001
Respiratory rate var	3.8 (2.9, 5.0)	4.0 (2.9, 5.2)	3.7 (2.9, 4.9)	0.0171

(Continued)

TABLE 1 | (Continued)

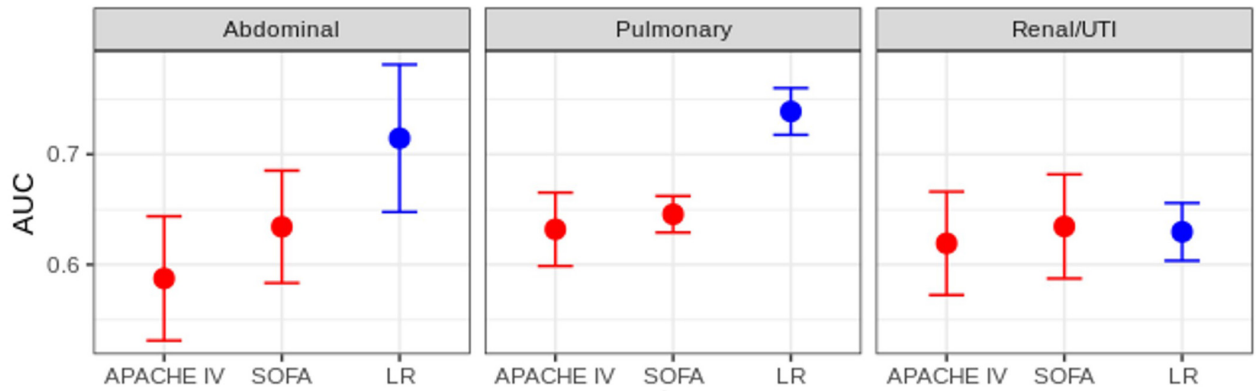
	Abdominal (*N* = 544)	Pulmonary (*N* = 2,392)	Renal/UTI (*N* = 1,022)	*P*-value
Vitals				
Avg temperature °C	36.8 (36.6, 37.2)	36.9 (36.6, 37.2)	36.8 (36.6, 37.2)	0.0431
Temperature °C var	0.4 (0.3, 0.6)	0.4 (0.3, 0.6)	0.4 (0.3, 0.6)	0.0411
Avg MAP	76.8 (72.4, 84.3)	80.1 (74.4, 87.6)	78.6 (73.2, 86.4)	<0.001
MAP var	9.1 (7.3, 11.6)	9.6 (7.5, 12.1)	9.9 (7.9, 12.5)	<0.001
Avg WBC	13.5 (9.3, 19.1)	12.2 (8.6, 16.9)	12.6 (8.7, 18.0)	<0.001
WBC var	2.5 (1.3, 4.5)	2.0 (1.1, 3.6)	2.3 (1.1, 4.2)	<0.001
Avg albumin	2.3 (1.9, 2.6)	2.3 (2.0, 2.7)	2.3 (2.0, 2.7)	0.0161
Albumin var	0.2 (0.1, 0.3)	0.1 (0.1, 0.3)	0.1 (0.1, 0.2)	0.0041
Avg platelets	163.8 (100.7, 239.8)	180.0 (124.0, 249.0)	164.6 (106.0, 230.8)	<0.001
Platelets var	21.2 (12.0, 37.1)	18.6 (9.2, 31.8)	17.7 (9.2, 29.8)	0.0071
Avg PaO_2	92.4 (75.9, 115.4)	91.0 (75.8, 113.1)	97.0 (79.4, 120.0)	0.0181
PaO_2 var	20.6 (11.2, 43.4)	20.6 (11.1, 37.8)	19.3 (9.2, 34.3)	0.3321
Avg $PaCO_2$	36.3 (31.6, 42.0)	39.3 (34.0, 46.3)	35.8 (30.2, 41.2)	<0.001
$PaCO_2$ var	4.1 (2.6, 6.4)	4.0 (2.2, 7.1)	3.5 (2.1, 5.8)	0.0821
Avg FiO_2	43.0 (35.0, 60.0)	50.0 (40.0, 70.0)	40.0 (33.3, 53.6)	<0.001
FiO_2 Var	7.5 (0.0, 17.9)	9.5 (3.5, 18.3)	7.1 (0.7, 15.2)	0.1121
Avg total bilirubin	0.9 (0.5, 2.3)	0.6 (0.4, 1.0)	0.6 (0.4, 1.2)	<0.001
Total bilirubin var	0.2 (0.1, 0.5)	0.1 (0.1, 0.3)	0.1 (0.1, 0.3)	<0.001
Avg creatinine	1.4 (0.9, 2.6)	1.0 (0.7, 1.8)	1.4 (0.9, 2.3)	<0.001
Creatinine var	0.2 (0.1, 0.4)	0.1 (0.1, 0.3)	0.2 (0.1, 0.4)	<0.001
Avg BUN	29.6 (17.7, 49.8)	25.5 (16.0, 41.0)	31.0 (18.3, 48.9)	<0.001
BUN var	4.8 (2.4, 8.8)	4.0 (2.1, 7.3)	4.2 (2.1, 8.6)	<0.001
Avg PH	7.4 (7.3, 7.4)	7.4 (7.3, 7.4)	7.4 (7.3, 7.4)	<0.001
pH Var	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.0 (0.0, 0.1)	0.0681
Avg sodium	139.0 (136.0, 142.7)	139.8 (136.7, 143.0)	140.0 (136.9, 144.0)	<0.001
Sodium var	1.8 (1.2, 3.1)	1.9 (1.2, 2.8)	2.1 (1.3, 3.1)	0.0171
Avg glucose	130.8 (110.0, 161.5)	141.0 (114.6, 170.6)	139.2 (115.8, 170.5)	<0.001
Glucose var	24.7 (15.3, 37.7)	26.8 (17.1, 41.4)	29.8 (19.5, 45.8)	<0.001
Avg hematocrit	28.9 (25.6, 32.8)	29.9 (26.5, 34.0)	29.5 (26.5, 33.3)	<0.001
Hematocrit var	2.1 (1.2, 3.1)	1.6 (0.9, 2.6)	1.5 (0.9, 2.5)	<0.001
Avg urine	161.1 (68.8, 364.1)	226.2 (96.3, 475.0)	224.2 (91.4, 551.0)	<0.001
Urine var	70.6 (33.3, 158.9)	108.9 (54.5, 208.9)	106.1 (50.3, 226.3)	<0.001
Respiration				
Intubated	289 (53.1%)	1,914 (80.0%)	486 (47.6%)	<0.001
Drugs				
Norepinephrine	241 (44.3%)	861 (36.0%)	436 (42.7%)	<0.001
Vasopressin	80 (14.7%)	225 (9.4%)	111 (10.9%)	0.0012
Phenylephrine	56 (10.3%)	147 (6.1%)	60 (5.9%)	0.0012
Dopamine	18 (3.3%)	60 (2.5%)	44 (4.3%)	0.0202
Epinephrine	15 (2.8%)	36 (1.5%)	15 (1.5%)	0.1022
Dobutamine	16 (2.9%)	43 (1.8%)	24 (2.3%)	0.1972
Scores				
Charlson CI	2.0 (0.0, 3.0)	2.0 (0.0, 3.0)	2.0 (1.0, 3.0)	0.4031
SOFA	4.0 (1.0, 7.0)	4.0 (2.0, 7.0)	3.0 (1.0, 6.0)	<0.001
APACHE IV	73.0 (61.0, 88.0)	73.0 (58.0, 89.0)	73.0 (62.0, 87.0)	0.8951
SIRS	2.0 (1.0, 2.0)	2.0 (1.0, 2.0)	1.0 (1.0, 2.0)	<0.001
qSOFA	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)	<0.001
Unit stay type				<0.001
Admit	453 (83.3%)	1,991 (83.2%)	863 (84.4%)	
Other/Stepdown/Transfer	67 (12.3%)	277 (11.6%)	138 (13.5%)	
Readmit	24 (4.4%)	124 (5.2%)	21 (2.1%)	

(Continued)

TABLE 1 | (Continued)

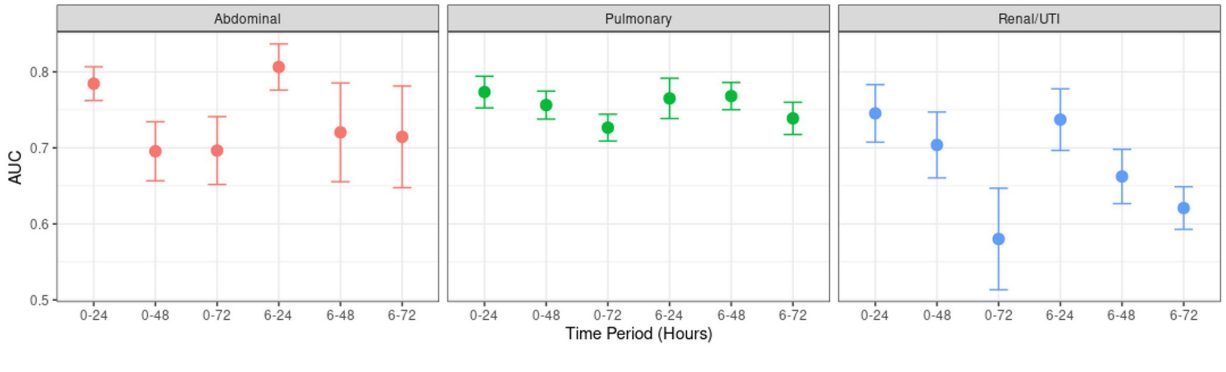
	Abdominal (*N* = 544)	Pulmonary (*N* = 2,392)	Renal/UTI (*N* = 1,022)	*P*-value
Unit type				<0.001
Med-surg ICU	386 (71.0%)	1,830 (76.5%)	785 (76.8%)	
MICU	104 (19.1%)	440 (18.4%)	197 (19.3%)	
SICU	54 (9.9%)	122 (5.1%)	40 (3.9%)	
Admission duration				
Hospital LOS	287.3 (190.7, 470.7)	264.4 (172.7, 400.2)	222.7 (159.6, 343.7)	<0.001
ICU LOS	125.9 (92.1, 209.0)	140.7 (97.7, 228.8)	112.1 (87.5, 159.3)	<0.001

The first column displays the data characteristics (variables). Columns second to fourth show summary statistics of all the variables for each sepsis group. Sepsis group cohort sizes are reported under the group name. Numeric variables are reported with the median and IQR (in parentheses), while categorical variables are reported with the frequency and proportion (in parenthesis). The resulting statistical tests are reported in the fifth column in the form of p-values. Any p-value smaller than 0.001 was indicated as " < 0.001." CHF, congestive heart failure; PVD, Peripheral vascular disease; COPD, Chronic obstructive pulmonary disease; CTD, Connective tissue diseases; DM, diabetes mellitus; CABG, Coronary artery bypass graft surgery; SaO_2, oxygen saturation; GCS, Glasgow coma scale; MAP, Mean Arterial Pressure; WBC, white blood cells count; PaO_2, partial pressure of oxygen; FiO_2, Fraction of Inspired Oxygen; BUN, blood urea nitrogen; SOFA, Sequential Organ Failure Assessment; qSOFA, quick SOFA; APACHE, Acute Physiology And Chronic Health Evaluation; SIRS, Systemic Inflammatory Response Syndrome; ICU, Intensive Care Unit; Med-Surg ICU, medical-surgical ICU; MICU, medical ICU, SICU, surgical ICU; LOS, length of stay; Avg, average (mean); Var, variation (standard deviation).



Sepsis Type	Algorithms	AUC	Sensitivity	Specificity
Abdominal	APACHE IV	0.59 (0.53-0.64)	0.54 (0.45 0.63)	0.65 (0.60-0.70)
	SOFA	0.63 (0.58-0.69)	0.57 (0.44-0.69)	0.61 (0.56-0.66)
	LR	0.71 (0.65-0.78)	0.54 (0.43-0.65)	0.73 (0.68-0.79)
Pulmonary	APACHE IV	0.63 (0.60-0.67)	0.54 (0.48-0.59)	0.66 (0.64-0.68)
	SOFA	0.65 (0.63-0.66)	0.60 (0.57-0.64)	0.60 (0.59-0.61)
	LR	0.74 (0.72-0.76)	0.65 (0.61-0.70)	0.70 (0.67-0.73)
Renal/UTI	APACHE IV	0.62 (0.57-0.67)	0.53 (0.45-0.61)	0.65 (0.63-0.66)
	SOFA	0.63 (0.59-0.68)	0.54 (0.45-0.63)	0.69 (0.67-0.72)
	LR	0.63 (0.60-0.66)	0.48 (0.41-0.55)	0.70 (0.66-0.73)

FIGURE 2 | Model performance comparisons. (Top) Area under the ROC curve (AUC) for each sepsis group. Average AUC (filled circles) and confidence intervals (vertical bars) estimated after the 10 repetitions of the outer cross-validation. Deterioration scores (APACHE IV and SOFA) models are represented in red, LR models in blue. (Bottom) Detailed comparison, also including sensitivity and specificity. APACHE IV, Acute Physiology And Chronic Health Evaluation IV; SOFA, Sequential Organ Failure Assessment; LR, multiple logistic regression.



Sepsis Type	Time Split	Cohort Size	Discharged	Died	Prevalence	Lost in the first 24h	Discharged	Died	Lost in the first 48h	Discharged	Died
Pulmonary	0-24	4,856	4046 [83%]	810 [17%]	16.7	-	-	-	-	-	-
	0-48	3,442	2833 [82%]	609 [18%]	17.7	1,414	1213 [86%]	201 [14%]	-	-	-
	0-72	2,414	1948 [81%]	466 [19%]	19.3	-	-	-	2,442	2098 [86%]	344[14%]
	6-24	4,475	3715 [83%]	760 [17%]	17.0	-	-	-	-	-	-
	6-48	3,393	2790 [82%]	603 [18%]	17.8	1082	925 [85%]	157 [15%]	-	-	-
	6-72	2,392	1931 [81%]	461 [19%]	19.3	-	-	-	2083	1784 [86%]	299 [14%]
Renal	0-24	2,772	2511 [91%]	261 [9%]	9.4	-	-	-	-	-	-
	0-48	1,713	1535 [90%]	178 [10%]	10.4	1059	976 [92%]	83 [8%]	-	-	-
	0-72	1,028	897 [87%]	131 [13%]	12.7	-	-	-	1744	1614 [93%]	130 [7%]
	6-24	2,546	2295 [90%]	251 [10%]	9.9	-	-	-	-	-	-
	6-48	1,692	1514 [89%]	178 [11%]	10.5	854	781 [91%]	73 [9%]	-	-	-
	6-72	1,022	891 [87%]	131 [13%]	12.8	-	-	-	1524	1404 [92%]	120 [8%]
Abdominal	0-24	1,408	1156 [82%]	252 [18%]	17.9	-	-	-	-	-	-
	0-48	884	730 [83%]	154 [17%]	17.4	524	426 [81%]	98 [19%]	-	-	-
	0-72	546	443 [81%]	103 [19%]	18.9	-	-	-	862	713 [83%]	149 [17%]
	6-24	1,344	1101 [82%]	243 [18%]	18.1	-	-	-	-	-	-
	6-48	876	723 [83%]	153 [17%]	17.5	468	378 [81%]	90 [19%]	-	-	-
	6-72	544	441 [81%]	103 [19%]	18.9	-	-	-	800	660 [83%]	140 [17%]

FIGURE 3 | Model performance measures on several time windows. (Top) Model performance comparisons as measured using the AUC for each sepsis group at several time intervals. The figure shows AUC means and confidence intervals estimated after the 10 repetitions of the outer cross-validation with logistic regression. (Bottom) Effects of different time windows on cohort size and mortality rates.

Explanatory Analysis

Figure 4 displays the ORs for risk factors in the three sepsis groups as estimated across the 10 dataset instances. Higher age and higher average heart rate were associated with increased mortality risk. Increased values in average MAP were associated with a reduced mortality risk across all sepsis groups. Our LR models identified significant factors that were relevant only for certain sepsis groups. For instance, atrial fibrillation and cancer were associated with an increased mortality risk only in pulmonary sepsis, but not in urinary or abdominal sepsis. Contrastingly, in abdominal sepsis hypertension represented a relevant risk factor of mortality. Interestingly, abdominal sepsis was the only group for which uncomplicated diabetes represented a significant protective factor regarding mortality risk.

A number of factors were relevant to more than one sepsis group. For instance, the most influential factor for increased mortality risk was "intubation" for urinary and pulmonary sepsis groups, however, in abdominal sepsis "readmitted to ICU" represented the most important factor. A rise in risk was associated with higher "average FiO_2" and "average total bilirubin" values in both abdominal and pulmonary sepsis, but not in urinary sepsis. Distinctively, in pulmonary and renal sepsis lower average temperature was indicative of reduced mortality risk. The average albumin was associated with the greatest risk reduction in pulmonary sepsis, whereas in renal and abdominal sepsis "average temperature" and "unit stay type (other/stepdown/transfer)" represented important variables.

Moreover, results illustrated that the average value for certain parameters was relevant while for other variables, the average variation played a greater role in mortality risk prediction. For instance, mortality risk reduces in renal sepsis when there is an increase in "average SaO_2." This is dissimilar to pulmonary sepsis, for which higher "SaO_2 variation" increased the risk of mortality.

Figure 5 presents a Sankey network diagram displaying the relationship between several clinical features and the sepsis groups. It shows that "intubation," "average total bilirubin," "average FiO_2," "average urine output," "average heart rate" and "average MAP" had the greatest overlap between sepsis groups. In abdominal sepsis, readmission had the greatest influence on the risk of in-hospital mortality compared to any other variables included in the model.

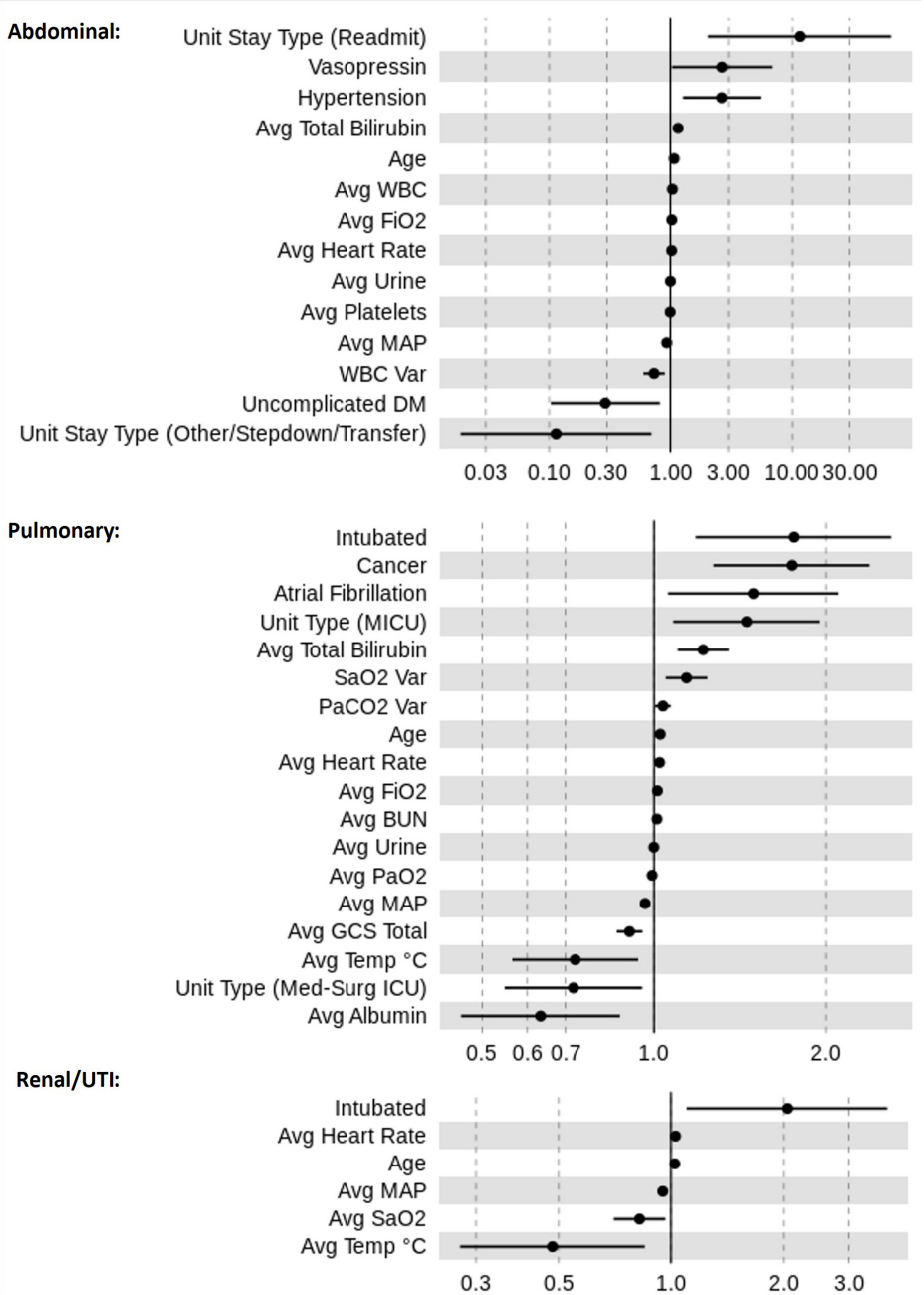


FIGURE 4 | Odds ratio (OR) estimates for LR. The figure displays the pooled ORs average (filled circles) and confidence intervals (vertical bars) for all significant features ($p < 0.05$) selected by the feature selection algorithms for the sepsis groups: pulmonary, abdominal, and renal/UTI. An OR of 1 represents a baseline risk, with values < 1 indicating a reduction in risk for the outcome, and > 1 indicating an increased risk in relation to the outcome.

DISCUSSION

In this study, we conduct a LR analysis of several types of sepsis based on the origin of infection. Our results showed that using LR as a relatively simple approach to ML was sufficient to obtain good to very good models for renal, abdominal and pulmonary sepsis that consistently outperformed the established risk scores for predicting in-hospital mortality. Biomedical and social scientists are usually familiar with the results provided by LR models, hence their great popularity. The major drawbacks of LR are the linearity and normality assumptions of the data which could yield biased models.

Traditionally, outcome prediction in sepsis is based on clinical scores, such as SOFA, APACHE, or SAPS. Such mortality prediction scores for critically ill patients are used worldwide and have been extensively validated (14). These models, however, may

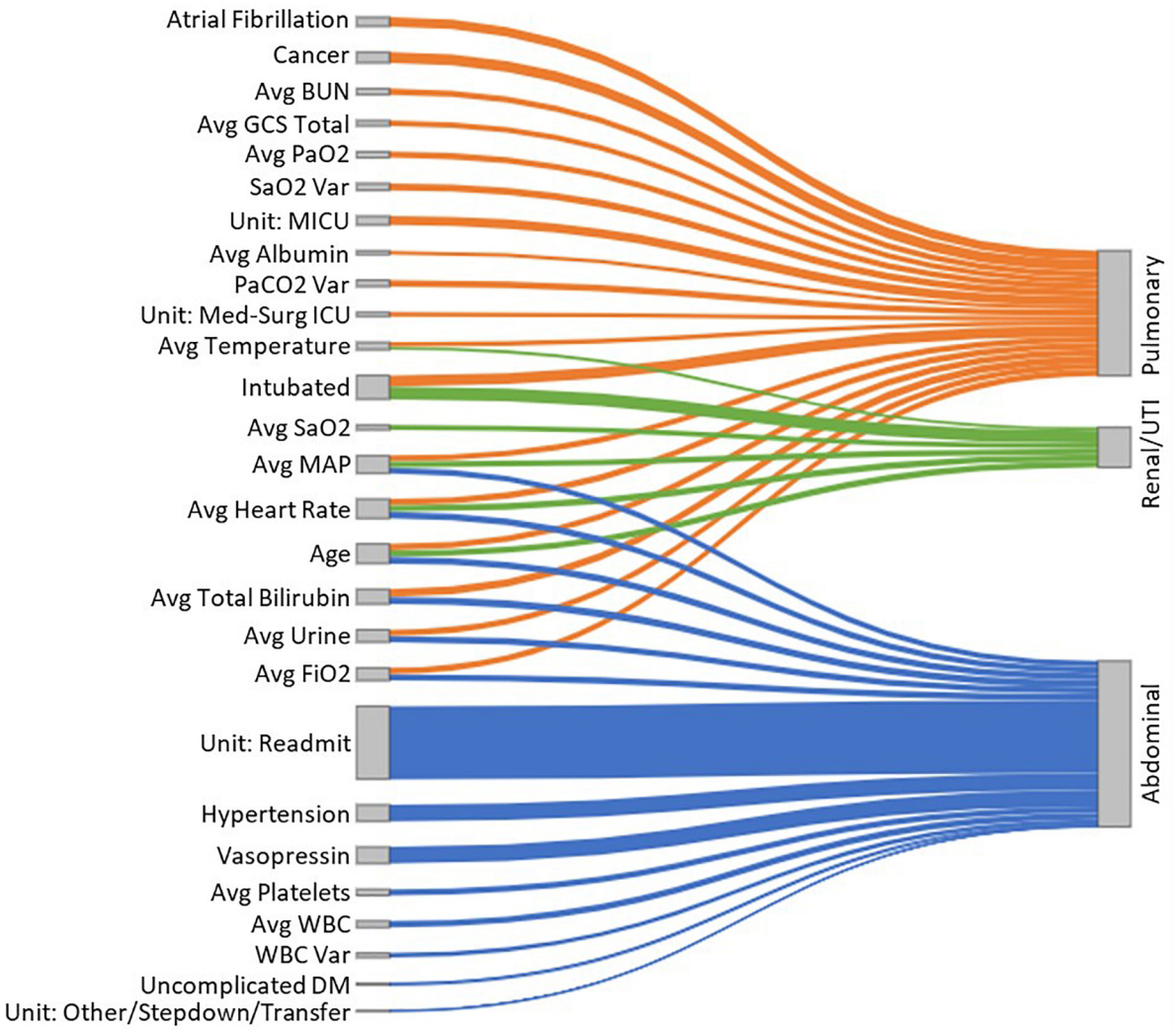


FIGURE 5 | A Sankey diagram representing the relationship between several clinical features (nodes on the left-hand side) and the sepsis groups (nodes on the right-hand side), with the link widths representing the absolute ORs proportional to the risk of in-hospital mortality for each of the sepsis groups.

not be ideal for routine clinical use as they lack granularity and are designed for use at ICU admission, thus neglecting the change of physiological parameters over time. So far, only a limited number of studies describe prognostication for in-hospital mortality in patients with sepsis comparing different sources of infection as an independent factor (15). In this study, we address this knowledge gap by (a) comparing different risk factors for each sepsis type and (b) highlighting specific factors associated with in-hospital mortality in the distinct sepsis groups, depending on the origin of the underlying infection. This approach may help to address the heterogeneity of the patient population with sepsis, to define discrete patient populations to guide the development of effective therapies and identify cohorts that benefit from certain interventions.

A fundamental difference between our models and existing ones for outcome prediction is that we include data from a longer observation period. For frequently measured variables such as vital signs, up to 72-h' worth of data points were used, with measurements recorded every hour. We extracted the mean and the standard deviation of all data points available to factor in change over time, with the former indicating the average values for each patient, and the latter indicating the range of variation in those values, e.g., a high heart rate variation may be indicative of some form of hemodynamic instability. However, the mean and the standard deviation represent a crude representation of change over time, and further research is required to investigate and define the best mathematical approach to reflect the variation of variables, particularly those with frequent measurement, e.g., heart rate or blood pressure.

We performed outcome prediction at various time points during the early phase of sepsis. Our results demonstrate that the performance of ML models drops over the first 72 h after ICU admission in all the types of sepsis studied. Model performance is

best maintained in pulmonary sepsis, while loss of performance is greatest in urinary sepsis. A possible explanation is that the causes of death from sepsis vary over time. While early deaths occur in about a third of septic patients and are mainly attributable to multiple organ failure caused by the primary infection, late deaths are influenced by end-of-life decisions and often relate to recurrent or late infections (16).

Early deaths in sepsis are typically associated with a hyperinflammatory "cytokine storm" response with fever, refractory shock, acidosis, and hypercatabolism (17). If regulation of the immune response from hyperinflammation to normal activity fails after the acute phase, patients enter a marked immunosuppressive state. Later deaths after the acute phase occur due to an inability to clear primary infections and the development of secondary infections (17). Taken into account the biphasic or even polyphasic course of sepsis, mortality prediction in the acute phase will differ from models predicting later mortality. Hence models that only include admission data are likely to disproportionately focus on early death occurring in the first 24 h of admission. Whilst optimizing data collection periods may improve outcome prediction, the ideal model should reflect dynamic changes and risk profile throughout the Intensive Care admission.

Our results indicate that prediction after the acute phase of sepsis is more complex and not well described in existing prognostication models. In addition, outcome prognostication is often performed early during the ICU stay, and many scores such as APACHE IV, are only validated for use on admission to Critical Care. Generation of a logistic regression model to predict mortality represents the first step in producing a score for wider clinical use; comparison to existing models is required to justify progression to external validation, refinement and eventually development of a new score with different weighting of individual risk factors. The degree of organ failure associated with the type of sepsis and the early progression of disease varies between sepsis groups and may be influenced differently in each group by early deaths and vice versa, early recovery and discharge alive. This assumption is supported by the higher dropout of cases in the urinary sepsis group compared to other sepsis caused by abdominal and chest infections.

Sepsis is not a uniform disease, but a syndrome characterized by the striking variation of biological features (18). Systematic analysis of these features, using data mining, and advanced statistical methods or machine learning, may allow the identification of types of sepsis with different risk profiles and responses to treatment. In an attempt to classify different types of sepsis, several approaches have been chosen (19). More sophisticated definitions of distinct molecular endotypes are based on leukocyte genome-wide expression profiles from samples collected on ICU admission (20–22). However, the implementation of these complex prognostic and predictive strategies at the bedside of patients is limited (23) due to the need for expensive laboratory analysis, which is not routinely available and is often too time-consuming to allow clinical decision making. Different statistical methods, including latent class analysis (24, 25), group-based trajectory modeling (26) and various machine learning algorithms (27) have been applied to large clinical data sets.

Clinicians instantaneously recognize that bacterial sepsis in young otherwise healthy patients carries a better prognosis than fungal sepsis in an elderly hematology patient. Similarly, urinary sepsis is commonly perceived as less fatal than chest or intraabdominal sepsis. A systematic review which addressed the impact of the source of infection on mortality (28), identified several studies in which lower in-hospital mortality was observed for urinary sepsis compared to respiratory sepsis. This observation was independent of the stage of sepsis with lower mortality observed in sepsis, severe sepsis and septic shock. Our results confirm the observation that in-hospital mortality is lower in critically ill patients with urinary sepsis compared to abdominal and respiratory sepsis. Factors influencing mortality differed between sepsis groups in our research, e g., ICU readmission was a significant risk factor in abdominal sepsis, but played no role in pulmonary or urinary sepsis, indicating that the numerous ICU stays required for complex abdominal sepsis are associated with a worsening prognosis. In contrast, for pulmonary and urinary sepsis, the need for invasive ventilation was a significant risk factor for mortality. The origin of infection is often known to treating physicians early in the clinical course and as such, outcome prediction based on the type of causative infection using clinical data only, may be easier to implement than models relying on complex combinations of clinical data and biomarkers, which are often not readily available at the bedside. Modern monitoring devices allow the integration of such prognostic algorithms into their software package and facilitate easy clinical implementation for all patients requiring regular monitoring.

The strength of this study is that we used the eICU database, a public database containing a large number of datasets for critically ill patients to generate our models. Moreover, we included time series for vital signs and laboratory tests for up to 72 h after admission to ICU in patients with different origins of sepsis and demonstrated that the models outperformed existing prediction tools. However, our study also has limitations. External validation and comparison with other machine learning approaches are required to explore the transferability and generalizability of our models in different critical care settings. Furthermore, the combination of molecular diagnostics such as transcriptomics and genomics with the routinely available clinical data used in our model may further improve the performance.

CONCLUSION

We present a logistic regression model for different types of sepsis which are defined by their origin of infection using routinely available clinical data from a large publicly available dataset. We demonstrate that factors of importance show considerable heterogeneity depending on the source of infection.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This study can be found in the eICU Collaborative Research Database repository (https://eicu-crd.mit.edu/).

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

MP extracted the data. MP and IO implemented the code and analyzed the data. IW and MP agreed to be the guarantors of all aspects of the work. All authors made substantial contributions to the design of the study, interpreted the results, drafted and critically revised the manuscript, and approved the final version and were involved in the study design and the selection of relevant variables from the dataset.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.915224/full#supplementary-material

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Heparin-binding protein-enhanced quick SOFA score improves mortality prediction in sepsis patients

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Purpose: The Quick Sequential Organ Failure Assessment (qSOFA) score proposed by Sepsis-3 as a sepsis screening tool has shown suboptimal accuracy. Heparin-binding protein (HBP) has been shown to identify early sepsis with high accuracy. Herein, we aim to investigate whether or not HBP improves the model performance of qSOFA.

Methods: We conducted a multicenter prospective observational study of 794 adult patients who presented to the emergency department (ED) with presumed sepsis between 2018 and 2019. For each participant, serum HBP levels were measured and the hospital course was followed. The qSOFA score was used as the comparator. The data was split into a training dataset (n = 556) and a validation dataset (n = 238). The primary endpoint was 30-day all-cause mortality.

Results: Compared with survivors, non-survivors had significantly higher serum HBP levels (median: 71.5 ng/mL vs 209.5 ng/mL, $p < 0.001$). Serum level of HBP weakly correlated with qSOFA class ($r^2 = 0.240$, $p < 0.001$). Compared with the qSOFA model alone, the addition of admission HBP level to the qSOFA model significantly improved 30-day mortality discrimination (AUC, 0.70 vs. 0.80; $P < 0.001$), net reclassification improvement [26% (CI, 17–35%); $P < 0.001$], and integrated discrimination improvement [12% (CI, 9–14%); P < 0.001]. Addition of C-reactive protein (CRP) level or neutrophil-to-lymphocyte ratio (NLR) to qSOFA did not improve its performance. A web-based mortality risk prediction calculator was created to facilitate clinical implementation.

Conclusion: This study confirms the value of combining qSOFA and HBP in predicting sepsis mortality. The web calculator provides a user-friendly tool for clinical implementation. Further validation in different patient populations is needed before widespread application of this prediction model.

KEYWORDS

sepsis, qSOFA score, heparin-binding protein, mortality, risk stratification, web calculator conceptualization, clinical data collection, data curation

Introduction

Sepsis continues to be a major global health concern with the possibility of serious short and long-term complications (1). Despite increased clinical awareness, expedited administration of antibiotics and intravenous fluids, and advances in technology for organ function support, the mortality rate remains as high as 35% in severe sepsis. The Emergency Department (ED) plays an important role in sepsis care as the majority of sepsis patients are admitted to the hospital through the ED. Approximately 25% of ED sepsis patients' progress to severe sepsis or septic shock within 72 h of presentation, highlighting the importance of early identification of high risk patients who would benefit from early intervention (2, 3). Early initiation of evidence-based sepsis bundle care has been associated with improved outcomes (4).

According to Sepsis-3 definition, sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection. Life-threatening organ dysfunctions are quantified by a change in the Sequential Organ Failure Assessment (SOFA) score by 2 or more points. Because SOFA score is not routinely calculated outside the ICU, a simplified version called the quick SOFA (qSOFA) score was developed for non-ICU settings, including the ED (5). qSOFA is used as a bedside assessment tool where patients with 2 or more should be further evaluated for sepsis. Since the introduction of qSOFA, more than 40 validation studies consisting of more than 400,000 patients have been conducted. A recent meta-analysis, however, showed that the accuracy of qSOFA was suboptimal with a pooled sensitivity of only 0.48 (95% CI: 0.41–0.55) (6–8).

Laboratory markers such as C-reactive protein (CRP), neutrophil to lymphocyte ratio (NLR), and lactate have been widely used to aid in the diagnosis of sepsis in clinical settings. However, none of them adequately predict the outcome (9). Recently, heparin-binding protein (HBP), a 37-kDa protein in the polymorphonuclear leukocyte, has been shown to outperform other infectious biomarkers in predicting the risk of progression to sepsis in a large meta-analysis (10). HBP is rapidly released upon adhesion of leukocytes to endothelial cells and induces capillary leakage with microcirculatory dysfunction (11). The unique feature that distinguishes HBP from other inflammatory biomarkers is its ability to predict shock as early as 72 h before its onset (12), and its high correlation with organ dysfunction (13). Neither CRP nor lactate have demonstrated these features.

Despite the suboptimal accuracy of qSOFA, its simplicity and clinical utility justifies its use in the management of sepsis (5). One plausible explanation for the suboptimal accuracy of qSOFA may be that it lacks variables that could detect early pathophysiological changes in sepsis before vital signs deteriorate (14). Therefore, the aim of this study was to evaluate whether or not adding HBP to the qSOFA score improves its ability to predict in-hospital mortality. We conducted a prospective multicenter cohort study and compared the relative performance of qSOFA modified by HBP to qSOFA modified by either CRP or NLR.

Materials and methods

Study design and population

We performed a multicenter prospective cohort study at three tertiary-care urban medical centers in China and Taiwan. Shenzhen PoAn Hunan People's Hospital, Hunan Provincial People's Hospital, and National Taiwan University Hospital. Patients were enrolled prospectively from June 1, 2018 to December 31, 2019. Adult patients (≥20 years old) who presented to the ED with suspected systemic infection were eligible for inclusion. Systemic infection was defined as the presence of at least two signs of systemic inflammation and laboratory or radiologic evidence of infection. In addition, included patients must have had at least one blood culture drawn. Signs of systemic inflammation include fever (>38.3°C) or hypothermia

Abbreviations: SOFA, Sequential Organ Failure Assessment; qSOFA, Quick Sequential Organ Failure Assessment; ED, Emergency department; HBP, Heparin-binding protein; CRP, C-reactive protein; NLR, Neutrophil-to-lymphocyte ratio; ICU, Intensive care unit; WBC, White blood cell; ANC, Absolute neutrophil count, IQR, Interquartile range; AUC, Area under curve; NRI, Net reclassification improvement; IDI, Integrated discrimination improvement; SAPS, Simplified acute physiology score; CRRT, Continuous renal replacement therapy.

(<36°C), tachycardia (heart rate >90 beats/min), tachypnea (respiratory rate >20 breaths/min or $PaCO_2$ <32 mmHg), and leukocytosis (WBC >12,000 cells/mm^3) or leukopenia (WBC <4,000 cells/mm^3). Laboratory evidence of infection included signs of inflammation [e.g., CRP levels lower than 10 mg/L are considered normal. CRP greater than 10 mg/L indicates clinically significant inflammatory processes (15)], the presence of pathogenic microorganisms cultured from bodily fluid (e.g., urine), or the presence of a local abscess. Radiologic evidence of infection includes infection-related findings on plain X ray, ultrasound, computed tomography, or magnetic resonance imaging. Those excluded were those with known pregnancy, do-not-resuscitate orders, immunocompromised patients, neutropenic patients (ANC count < 500/mm^3), or those who received heparin treatment within 72 h (as this may affect serum levels of HBP). Hematological malignancies, terminal cancers, cancers under chemotherapy or radiation, HIV infections, patients taking steroids or immunosuppressants are considered immunocompromised. Patients transferred from an outside hospital were also excluded. They were excluded from the study since they had already been treated and stabilized, thus not comparable to individuals who presented to the emergency department for the first time. This study was approved by the Institutional Review Boards of all institutions.

Measurement of heparin-binding protein

Blood samples of eligible participants were collected in the ED and centrifuged at 2,200 g for 10 min. Serum levels of HBP were measured in a blinded manner with regard to the clinical condition and qSOFA of the patient at the time of blood draw. The concentrations of HBP were assayed in a single batch at three major sites using an enzyme immunoassay from JoinStar (Hangzhou, China), according to manufacturer's instructions. Upon collection, samples were centrifuged and stored at −20°C refrigerator until measurement. Limit of detection is reported to be 5.9 ng/mL. Inter-assay coefficients of variation were measured in 11 replicates and were 11% at 21 ng/mL and 7% at 81 ng/mL. Serum levels of CRP at ED admission were determined by Aeroset 2.0 analyzer (Abbott Diagnostics, Santa Clara, CA, United States). The neutrophil to lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count.

Data collection

Physicians involved in the study collected patient data using a standardized instrument. Physiological and laboratory variables at time of ED admission were recorded. SIRS criteria variables included abnormal body temperature, tachycardia, tachypnea, and abnormal white blood cell count. Criteria for qSOFA included altered mental status (Glasgow coma scale ≤14), hypotension (systolic blood pressure ≤100 mmHg), and tachypnea (respiratory rate >22/min). For organ dysfunction, we adopted the CDC adult sepsis event criteria definition (16). In brief, we defined septic shock as Initiation of a new vasopressor infusion (norepinephrine, dopamine, epinephrine, phenylephrine, or vasopressin), respiratory failure as the need for invasive mechanical ventilation, acute kidney injury as doubling of serum creatinine or decrease by ≥ 50% of estimated glomerular filtration rate (eGFR) relative to baseline levels in 7 days or ≥ 0.3 mg/dL within 48 h, excluding patients with ICD-10 code for end-stage renal disease, acute hepatic dysfunction as total bilirubin ≥ 2.0 mg/dL and increase by 100% from baseline, acute hematological function as platelet count < 100 cells/μL and ≥ 50% decline from baseline (baseline must be ≥ 100 cells/μL), acute mental status change as Glasgow Coma Scale score of < 15 or a decrease in the score by at least 1 in those with pre-existing central nervous system disease. The source of infection was classified by the final discharge diagnosis of pneumonia, urinary tract infection, biliary tract infection, intra-abdominal infection, skin and soft tissue infection, bloodstream infection, and miscellaneous source of infection.

Statistical analysis

Categorical variables were expressed as frequencies and compared using Fisher's exact test or a Chi-squared test, as appropriate. Continuous variables were reported as median with interquartile range (IQR) and compared using Mann–Whitney *U*-test. We calculated the Spearman's rank correlation coefficient and drew qSOFA score-stratified box plots to assess the correlations between three laboratory markers and clinical severity. We randomly split the data into a derivation cohort (70%) and a validation cohort (30%). We created three laboratory marker-modified models (qSOFA_NLR score, qSOFA_CRP score and qSOFA_HBP score) in the derivation cohort and validated the accuracy in the validation cohort. The serum levels of HBP were classified into tertile ordinal classes (0 for HBP under 41 ng/mL, 1 for HBP between 41 and 151 ng/mL, and 2 for HBP above 151 ng/mL), bringing qSOFA to a five-point scale. The new model still considers 2 qSOFA points positive. The cutoff level was determined empirically based on previous literature review and a restricted cubic spline analysis (10, 17). Following the best practice of presenting a clinical prediction model (18), we reported the discrimination and calibration of the three models. Discrimination was calculated by area under the receiver operating characteristic curve (AUC) and compared with a de Long test. Calibration was evaluated by a calibration plot and Brier score. Brier score checks the goodness of a predicted probability score.

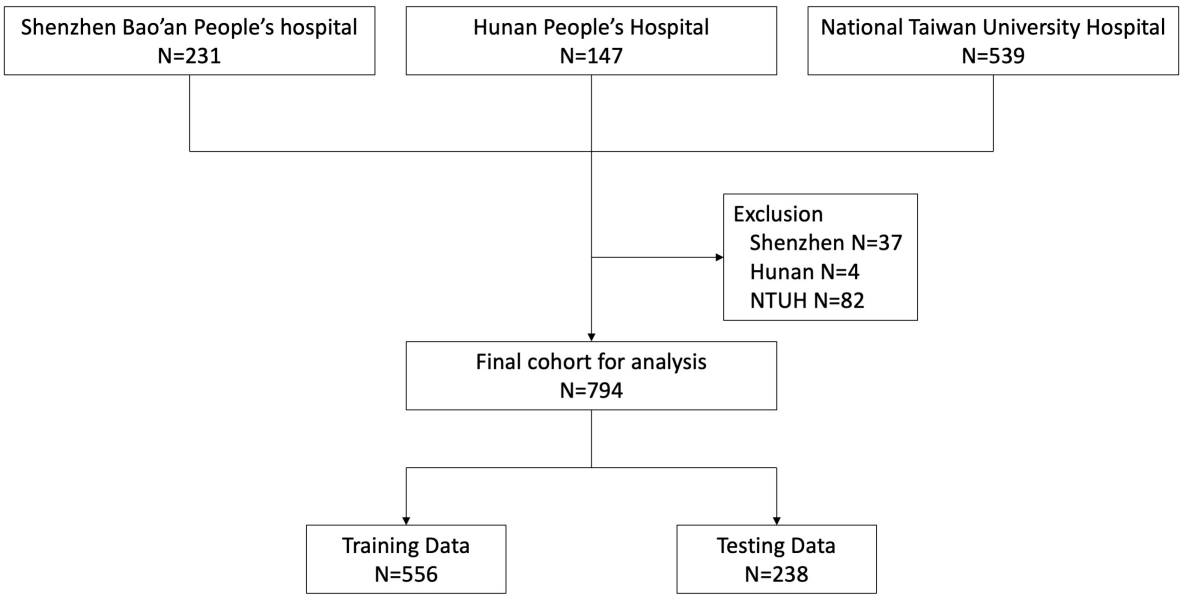

FIGURE 1
Flowchart of patient inclusion and exclusion.

Next, we conducted reclassification analysis to assess whether or not the biomarker-modified qSOFA models significantly reclassified patients into more appropriate risk categories. We divided all patients into three predicted mortality risk groups empirically: low risk (0% to less than 15%), moderate risk (15% to less than 35%), and high risk (35% or greater) and calculated the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI). The NRI was calculated by summing the proportion of participants across risk categories whose estimated risk shifts in the correct direction minus the proportion of participants whose risk shifts in the incorrect direction. The IDI calculates the difference in discrimination slopes between the two models, thereby demonstrating the improvement in both discrimination and reclassification. Continuous NRI is a non-parametric analog of the IDI and equals twice the difference in probabilities of upward reclassification for events minus for non-events. The NRI estimated overall improvement in reclassification with the new model. The IDI estimated improvement in both discrimination and reclassification. We performed two sensitivity analyses to verify the robustness of the analysis. We calculated the categorical NRI using different risk categories (20%, 40%) and continuous NRI. The detailed methods for calculating NRI and IDI are presented in the **Supplementary Material**. Lastly, we developed a risk calculator using the Shiny package of R (Foundation for Statistical Computing, Vienna, Austria). We adhered to the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement for reporting (18). All analyses were performed with SAS Version 9.4 (Cary, NC, United States) except for the NRI and IDI statistics which were performed with R. A 2-sided p-value < 0.05 was considered significant.

Results

Study design and patient characteristics

During the study period, 231, 147, and 539 patients were enrolled from Shenzhen Bao'an People's Hospital, Hunan People's Hospital and National Taiwan University Hospital, respectively. We excluded 37 patients from Shenzhen, 4 from Hunan and 82 from NTUH according to our exclusion criteria. Ultimately, 794 patients were eligible for analysis (**Figure 1**). We classified the patient cohort into three severity groups: survivors (patients hospitalized without events), critically-ill (patients admitted to the ICU but survived for more than 30 days), and non-survivors (patients who died within 30 days of hospital admission). Compared to survivors, critically-ill and non-survivors were older and more likely to have developed acute organ dysfunction or shock. In addition, critically-ill or non-surviving patients more frequently had infections of the lower respiratory tract, abdomen, and bloodstream. In contrast, surviving patients more frequently had infections of the urinary tract, biliary tract, and skin and soft tissue. Vital signs and laboratory data were also correlated with the severity groups. Comparison of patient characteristics across three groups is summarized in **Table 1**.

Association between laboratory markers and organ dysfunction or qSOFA

Table 2 details the discrimination of three different markers on six sepsis-associated six acute organ dysfunctions. HBP had high discrimination for all six organ dysfunctions. CRP had moderate discrimination and NLR had the least discrimination for acute organ dysfunctions. Figure 2 shows the boxplots of three laboratory markers stratified by qSOFA score class (0, 1, $\geq$ 2). CRP has the highest correlation with qSOFA class (r^2 = 0.30, $p < 0.001$), followed by HBP (r^2 = 0.240, $p < 0.001$). NLR did not significantly correlate with the qSOFA class (r^2 = 0.063, p = 0.076). Both CRP and HBP were weakly correlated with qSOFA.

Biomarker-enhanced qSOFA models: Discrimination and calibration

We built three biomarker-enhanced qSOFA models: qSOFA_NLR, qSOFA_CRP and qSOFA_HBP. In the validation cohort, the qSOFA_HBP score had the highest AUC (0.80, 95% CI, 0.73–0.87), followed by qSOFA (0.70, 95% CI, 0.62–0.77), qSOFA_CRP (0.66, 95% CI, 0.58–0.74) and qSOFA_NLR (0.61, 95%CI: 0.53–0.69) (Table 3 and Supplementary Figure 1). Compared to qSOFA alone, the addition of HBP to qSOFA significantly improved sepsis mortality discrimination (de Long test $P < 0.001$). Visual examination of observed versus model-predicted 30-day mortality suggested improved agreement with the qSOFA_HBP model (Brier score: 0.134), followed by qSOFA (Brier score: 0.155), qSOFA_CRP: (Brier score:

TABLE 1 Characteristics of the study patients, stratified by three different severity groups.

	Surviving patients (N = 350)	Critically-ill patients (N = 265)	Non-surviving patients (N = 179)	P-value
Age (years)	62 (52, 77)	67 (52, 77)	67 (53, 80)	0.4206
Male gender	214 (61.1%)	171 (64.5%)	128 (71.5%)	0.0618
Severe sepsis	226 (66.7%)	239 (91.2%)	153 (91.6%)	< 0.0001***
Septic shock	31 (8.9%)	57 (21.7%)	83 (46.9%)	< 0.0001***
Source of infection				
Pneumonia	114 (32.6%)	176 (66.4%)	107 (59.8%)	< 0.0001***
Urinary tract infection	64 (18.3%)	28 (10.6%)	13 (7.3%)	0.0006***
Biliary tract infection	51 (14.6%)	9 (3.4%)	11 (6.2%)	< 0.0001***
Intra-abdominal infection	89 (25.4%)	42 (15.1%)	27 (15.9%)	0.0024**
Skin and soft tissue infection	34 (9.7%)	5 (1.9%)	8 (4.5%)	0.0002**
Bloodstream infection	7 (2.0%)	26 (9.8%)	22 (12.3%)	< 0.0001***
Miscellaneous	12 (3.4%)	33 (12.5%)	21 (11.7%)	< 0.0001***
Organ dysfunction				
Acute respiratory failure	95 (27.1%)	196 (74.0%)	130 (72.6%)	< 0.0001***
Cardiovascular dysfunction	82 (23.4%)	123 (46.4%)	119 (66.5%)	< 0.0001***
Acute renal dysfunction	61 (17.4%)	111 (41.9%)	91 (50.8%)	< 0.0001***
Acute hepatic dysfunction	52 (14.9%)	78 (29.4%)	53 (29.6%)	< 0.0001***
Acute hematologic dysfunction	37 (10.6%)	62 (23.4%)	47 (26.3%)	< 0.0001***
Altered mental status	62 (17.7%)	120 (45.3%)	127 (71.0%)	< 0.0001***
qSOFA variables				
GCS	15 (15, 15)	15 (11, 15)	11 (5, 15)	< 0.0001***
SBP (mmHg)	130 (110, 148)	123 (105,145)	114 (94,135)	< 0.0001***
Respiratory rate (min^{-1})	20 (18, 20)	22 (20, 27)	22 (20, 26)	< 0.0001***
Laboratory markers				
WBC count ($10^3/mm^3$)	10.20 (6.90, 14.06)	10.95 (7.11, 14.73)	12.36 (8.75, 17.31)	0.0003***
Platelet count ($10^3/mm^3$)	217 (147, 282.)	174 (114, 261)	194 (110, 267)	0.0008*
HBP (ng/mL)	71.5 (28.7, 156.6)	73.8 (36.2, 139.5)	209.5 (116.0, 286.2)	< 0.0001***
CRP (mg/L)	10.3 (6.6, 16.4)	48.4 (17.8, 108.4)	22.0 (11.3, 101.2)	< 0.0001***
NLR ratio	8.0 (4.5, 13.6)	11.2 (5.8, 21.2)	7.8 (4.5, 15.2)	0.0002***

***Means p-value < 0.001, ** means p-value < 0.01, * means p-value < 0.05.

TABLE 2 Discrimination of HBP, CRP, and NLR on acute organ dysfunction.

AUC with 95% Confidence Intervals	HBP	CRP	NLR
Acute respiratory failure	0.79 (0.76–0.83)	0.65 (0.62–0.70)	0.65 (0.60–0.69)
Cardiovascular dysfunction	0.80 (0.77–0.84)	0.70 (0.66–0.74)	0.68 (0.63–0.73)
Acute renal dysfunction	0.79 (0.76–0.83)	0.65 (0.61–0.70)	0.63 (0.58–0.68)
Acute hepatic dysfunction	0.78 (0.74–0.81)	0.61 (0.56–0.66)	0.55 (0.50–0.60)
Acute hematologic dysfunction	0.78 (0.74–0.81)	0.60 (0.55–0.65)	0.57 (0.52–0.62)
Altered mental status	0.82 (0.78–0.85)	0.73 (0.69–0.77)	0.73 (0.69–0.77)

0.160), and qSOFA-NLR: (Brier score: 0.169) (**Supplementary Figure 2**). **Figure 3** demonstrates the calibration plot of qSOFA alone, qSOFA_NLR, qSOFA_CRP and qSOFA_HBP. Hosmer–Lemeshow Chi−square for qSOFA score only, qSOFA_HBP, qSOFA_NLR and qSOFA_CRP is 0.90 ($P = 0.34$), 3.64 ($P = 0.30$), 2.52 ($P = 0.47$), and 7.70 ($P = 0.05$) respectively.

Mortality risk reclassification

With the addition of HBP to the qSOFA model, the difference between the proportion of non-survivors who moved up a risk category and the proportion who moved down, plus the difference between the proportion of survivors who moved down a risk category and the proportion who moved up (net reclassification improvement), was 26% (CI, 17–35%; $P < 0.0001$). This improvement in risk reclassification was largely driven by enhanced prediction among surviving patients (24%) and to a lesser extent by reclassification of non-surviving patients (2%) (**Supplementary Table 1**). The difference in average predicted probability of mortality between surviving and non-surviving patients (integrated discrimination improvement) significantly increased after adding HBP to the qSOFA model (12%, 95%CI, 9–14%, $P < 0.0001$). Sensitivity analysis using a different cutoff (20%/40%) to define the risk category or using a category-free continuous NRI also showed a significant improvement in mortality risk reclassification (**Table 4**).

Web-based calculator

The online mortality risk calculator developed based on our study is available at: (https://stacysu.shinyapps.io/Mortality_Prediction_Probability/) (**Supplementary Figure 3**). It illustrates how qSOFA and HBP affect mortality estimates. Clinical users can input data for Glasgow coma scale, systolic blood pressure, respiratory rate, and serum HBP level to calculate predicted 30-day mortality.

Discussion

As the list of biomarkers and validated clinical scores for sepsis continues to grow the potential value of combining these diagnostic tools is of particular interest. In this prospective multicenter study of sepsis patients, we demonstrate that incorporating serum HBP levels with qSOFA score at time of ED admission significantly improves classification. We found that HBP predicts sepsis-related acute organ dysfunction and may improve the accuracy of qSOFA scores. In our study, both CRP and NLR failed to improve predictive accuracy of qSOFA.

Few studies have investigated the value of combining clinical scoring systems and infection biomarkers in predicting sepsis mortality. Yu et al. showed that combining qSOFA

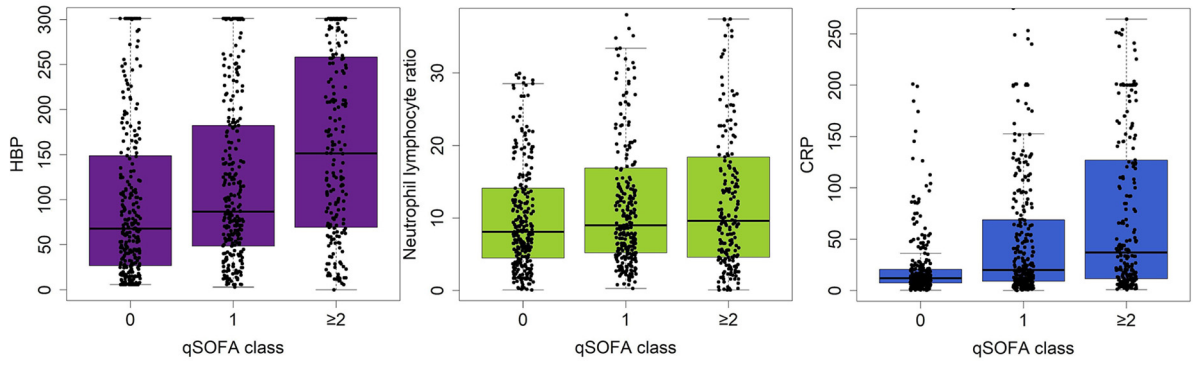

FIGURE 2
Boxplot showing the correlation between serum levels of HBP, CRP and NLR and the qSOFA class (0, 1, ≥ 2). HBP has the highest correlation with qSOFA class, followed by CRP or NLR.

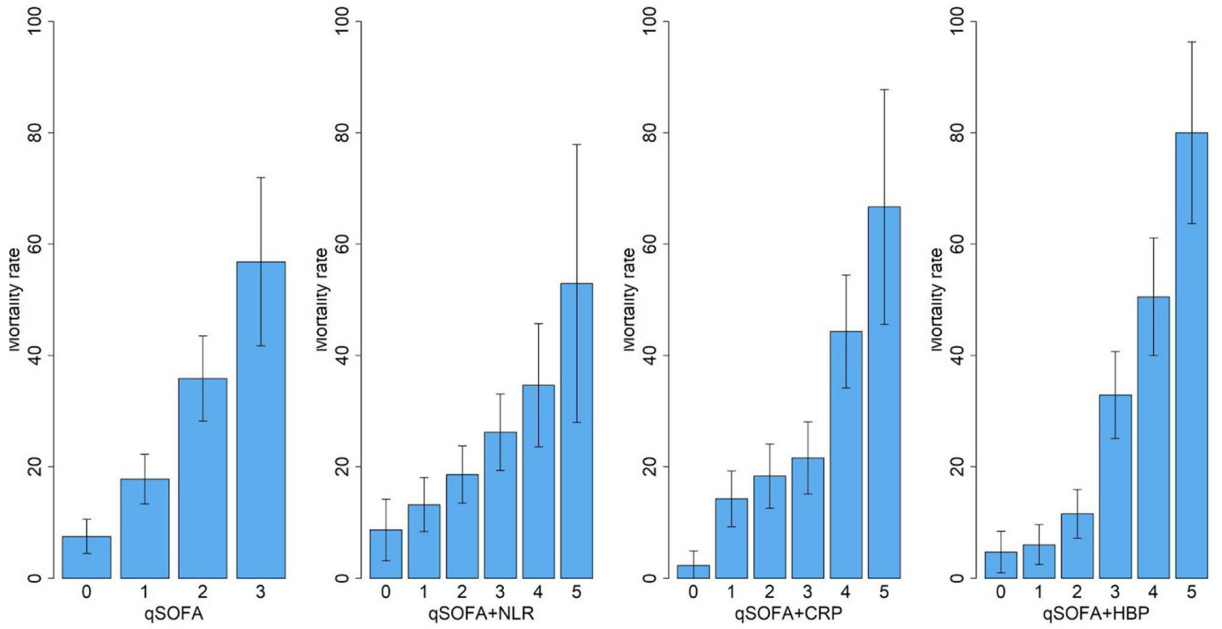

FIGURE 3
Calibration of qSOFA, qSOFA-NLR, qSOFA-CRP and qSOFA-HBP. Hosmer-Lemeshow Chi-square is 0.90 for qSOFA score only (P = 0.34),3.64 for qSOFA_HBP (P = 0.30), 2.52 for qSOFA_NLR score (P = 0.47), and 7.70 for qSOFA_CRP score (P = 0.05).

and procalcitonin may significantly improve the performance of qSOFA score (19). Viallon et al. showed that combining SAPS-2, procalcitonin, lactate, and IL-6, could predict sepsis mortality with high accuracy (AUC 0.94) (20). However, this was a single center study without an independent sample validation. Furthermore, the SAPS-2 and SAPS-3 scores, which include 17 and 20 variables respectively, are complicated and not routinely available outside of the ICU (21). Mellhammar J et al. found that including HBP into qSOFA (additional 1 point for HBP > 30 ng/mL) significantly improved prediction of mortality in patients with suspected infection (20); the AUC improved from 0.70 (95%CI: 0.66–0.75) for qSOFA alone to 0.78 (95%CI: 0.74–0.82) for HBP modified qSOFA. Nevertheless, independent sample validation was not performed in their study, and prognostic information was lost because HBP was dichotomized. Per Sepsis-3, qSOFA is a standard tool for sepsis diagnosis and prognosis in settings outside the ICU. Although calculating qSOFA is simple and straightforward, its suboptimal predictive accuracy limits its use. Our work demonstrates how to quantitatively combine a clinically useful biomarker with a widely validated prediction rule. Our approach has the advantage of easy clinical implementation without needing to develop a more complicated new scoring system.

The physiological mechanism of HBP release in sepsis may offer insight into why HBP can provide incremental prognostic value to the qSOFA score. Heparin-binding protein (HBP), also known as azurocidin or CAP37, is a chemoattractant that activates neutrophils, T lymphocytes and monocytes, enhances cytokine release and phagocytosis, and induces vascular leakage (22). HBP is an inflammatory mediator released immediately upon neutrophil stimulation (23). Although most inflammatory processes involving neutrophil activation can induce HBP release, several bacteria, including *Streptococcus pyogenes, Staphylococcus aureus, and E. coli* were found to be potent inducers (24–26). Therefore, serum level of HBP is particularly elevated in bacterial infections that result in sepsis (27). It has been shown that HBP levels are significantly elevated in sepsis, urinary tract infections, bacterial skin and soft tissue infections, and bacterial meningitis (28, 29). Compared to common inflammatory biomarkers such as CRP, procalcitonin or IL-6, HBP is unique in that it induces vascular leakage (22), and therefore microcirculatory dysfunction, the hallmark of sepsis-induced organ dysfunction (30). Accordingly, our study, as well as previous ones, observed a correlation between serum level of HBP and acute kidney injury, respiratory failure, and circulatory failure (31, 32). In a recent systematic review and

TABLE 3 Discrimination of qSOFA and modified qSOFA prediction models in derivation and validation datasets.

AUC	Derivation dataset (n = 556)	Validation (n = 238)
qSOFA only	0.71 (0.67–0.76)	0.70 (0.62–0.77)
qSOFA + NLR	0.63 (0.58–0.68)	0.61 (0.53–0.69)
qSOFA + CRP	0.70 (0.65–0.75)	0.66 (0.58–0.74)
qSOFA + HBP	0.80 (0.75–0.84)	0.80 (0.73–0.87)

TABLE 4 Net reclassification improvement (NRI) with HBP-modified qSOFA score using 15 and 35% or 20% and 40% as cutoffs to define patient subgroups at low, intermediate, or high risk.

	NRI (95% CI)	*P*-value	IDI (95% CI)	*P*-value
qSOFA_HBP vs. qSOFA (endpoint: 30-day mortality)				
NRI (15%/35%)	25.7% (16.7%–34.6%)	< 0.0001***	0.12 (0.09–0.14)	< 0.0001***
NRI (20%/40%)	15.7% (8.1%–23.3%)	< 0.0001***	0.12 (0.09–0.14)	< 0.0001***
NRI (continuous)	82.4% (66.9%–97.9%)	< 0.0001***	0.12 (0.09–0.14)	< 0.0001***

Category-free NRI was also calculated.
The analysis is based on all patients.
CI, confidence interval; NRI, net reclassification index, IDI, integrated discrimination improvement.

meta-analysis consisting of 3,868 patients, HBP demonstrated high specificity and sensitivity in predicting progression to sepsis in critically ill patients with a pooled sensitivity of 0.85 (95% CI, 0.79–0.90) and a pooled specificity of 0.91 (95% CI 0.82–0.96). In addition, HBP has been shown to be an important predictor of sepsis mortality with a sensitivity of 0.87 and specificity of 0.71 (33). Moreover, it has been shown that patients have elevated serum HBP levels up to 72 h before sepsis shock or organ dysfunction develop (34), which makes HBP a promising tool for the early detection of patients at risk of developing severe sepsis in the ED.

Results of this study should be interpreted in light of its strengths and limitations. To begin, strengths include the prospective multicenter cohort design and independent sample validation, as this may minimize risk of selection bias while maximizing generalizability. The rigorous statistical analysis ensures the robustness of the model. The web calculator increases the feasibility of clinical implementation. This study also has limitations. First, due to the observational nature, this study does not address whether or not the use of qSOFA_HBP as a risk prediction tool improves patient outcome in clinical practice. Second, due to the high cost for the central laboratory ELISA-based HBP measurement, HBP may be difficult to apply in rural areas. The recent development of point-of-care (POC) tests for HBP makes the wide application of HBP-modified qSOFA possible. Third, we used SIRS as the inclusion criteria to enroll study patients. Studies have shown SIRS has suboptimal sensitivity in identifying critical sepsis patients, especially elderly or immunosuppressed patients with fewer signs of inflammation. The benefit of combining HBP and qSOFA in this underrepresented patient population may need to be verified in future studies. Fourth, we did not exclude patients with renal function impairment, and it is plausible that sepsis-related acute kidney injury and subsequent continuous renal replacement therapy (CRRT) may confound HBP measurements and mortality outcome. However, it is notable that a recent study by Samuelsson showed that CRRT does not influence serum levels of HBP (35). Finally, evaluation of the relationship between the level of heparin binding protein and specific pathogens, was beyond the scope of the study. Further studies are required to determine the reliability of HBP as a marker for all sepsis-inducing microbes.

In conclusion, this study confirms the value of combining qSOFA and HBP in sepsis mortality prediction. The web calculator provides a user-friendly tool for convenient and accessible clinical implementation. Further validation in different patient populations is needed before widespread application of this tool.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Shenzhen Baoan Hunan People's Hospital (BYL 20190801), Hunan Provincial People's Hospital (HNSRMYY REC2018-40), National Taiwan University Hospital (NTUH 201712161RINA). The patients/participants provided their written informed consent to participate in this study.

Author contributions

XH and QD: clinical data collection, methodology, data curation, and writing—reviewing and editing. YiZ and PL: clinical data collection and writing—reviewing and editing. Y-HS: writing—original draft, project administration, and writing—reviewing and editing. JL and ZZ: clinical data collection, data curation, project administration, and writing—reviewing and editing. YuZ, MF, and S-SH: clinical data collection and writing—reviewing and editing. C-CL: conceptualization, methodology, clinical data collection, data curation, statistical

analysis, writing—original draft, reviewing and editing, supervision, full access to all of the data in the study, responsibility for the integrity of the data, and the accuracy of the data analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.926798/full#supplementary-material

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Association between glucose-to-lymphocyte ratio and in-hospital mortality in intensive care patients with sepsis: A retrospective observational study based on Medical Information Mart for Intensive Care IV

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Background: This study aimed to evaluate the association between the glucose-to-lymphocyte ratio (GLR) and in-hospital mortality in intensive care unit (ICUs) patients with sepsis.

Methods: This is a retrospective cohort study. Patients with sepsis from the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database had their baseline data and in-hospital prognosis retrieved. Multivariable Cox regression analyses were applied to calculate adjusted hazard ratios (HR) with 95% confidence intervals (CI). Survival curves were plotted, and subgroup analyses were stratified by relevant covariates. To address the non-linearity relationship, curve fitting and a threshold effect analysis were performed.

Results: Of the 23,901 patients, 10,118 patients with sepsis were included. The overall in-hospital mortality rate was 17.1% (1,726/10,118). Adjusted for confounding factors in the multivariable Cox regression analysis models, when GLR was used as a categorical variable, patients in the highest GLR quartile had increased in-hospital mortality compared to patients in the lowest GLR quartile (HR = 1.26, 95% CI: 1.15–1.38). When GLR was used as a continuous variable, each unit increase in GLR was associated with a 2% increase in the prevalence of in-hospital mortality (adjusted HR = 1.02, 95% CI: 1.01–1.03, p = 0.001). Stratified analyses indicated that the correlation between the GLR and in-hospital mortality was stable. The non-linear relationship between GLR and in-hospital mortality was explored in a dose-dependent manner. In-hospital mortality increased by 67% (aHR = 1.67, 95%

CI: 1.45–1.92) for every unit GLR increase. When GLR was beyond 1.68, in-hospital mortality did not significantly change (aHR: 1.04, 95% CI: 0.92–1.18).

Conclusion: There is a non-linear relationship between GLR and in-hospital mortality in intensive care patients with sepsis. A higher GLR in ICU patients is associated with in-hospital mortality in the United States. However, further research is needed to confirm the findings.

KEYWORDS

glucose-to-lymphocyte ratio, sepsis, MIMIC-IV, in-hospital mortality, non-linearity, intensive care unit

Background

Sepsis is a serious public health concern worldwide. Sepsis is a life-threatening organ dysfunction caused by dysregulated host systemic inflammation and immune response to infection (1, 2). Despite advances in the recognition and management of clinical sepsis (3), morbidity and mortality remain high (4, 5), with sepsis-related deaths accounting for 19.7% of global deaths (6). To date, the exact mechanism of sepsis remains unclear but is widely hypothesized.

Many clinical studies consider sepsis to be a host-mediated systemic inflammatory response to infection, and evidence of dysregulated immune cell activation and host response has been observed in patients with severe sepsis (7, 8). In addition, some systemic inflammatory biomarkers have been reported to be associated with sepsis and poor prognosis, including neutrophil-lymphocyte ratio (NLR) (9–11), platelet–lymphocyte ratio (PLR) (12), lymphocyte–monocyte ratio (LMR) (13), and red cell distribution width (RDW) (14–16). The loss and dysfunction of immune cells are considered the main factors for secondary infections and poor outcomes in patients with sepsis. Therefore, alterations in immune cell number and function may be related to mortality in patients with sepsis (17). Lymphocytes are one of the primary effector cells involved in the systemic inflammatory response of sepsis. Extensive lymphocyte apoptosis is a key contributor to the development of the immunosuppressive phase of sepsis (18). Their profound role in immunosurveillance, which may protect the host from sepsis development and impaired immune system, has been reported to be associated with poor prognosis in patients with sepsis (9). Consequently, lymphocyte count indicating the state of the immune system appears to predict the outcomes of patients with sepsis (18).

In addition, numerous studies have demonstrated an association between failure to control hyperglycemia and adverse outcomes in patients in the intensive care unit (ICU), including death, nosocomial infection, wound complications, prolonged ICU stay, and an increased incidence of critical illness neuropathy (19). Acute hyperglycemia is an independent risk factor for in-hospital mortality in critically ill patients with sepsis (20).

The imbalance between these two indicators is reflected in the changes in the glucose-to-lymphocyte ratio (GLR). In this case, increased GLR indicates an imbalance in glucose regulation and immune responses (21). This imbalance leads to organ failure, metabolic problems, immune deficiencies, and oxygen supply and demand mismatch, all leading to death (22). There is growing evidence that elevated glucose levels and decreased lymphocyte counts are strongly associated with sepsis severity (11, 23). GLR may reflect the synergistic effect of hyperglycemia and immune dysfunction in critically ill patients (24). In addition, an increased GLR has been associated with poor prognosis in a range of disease cases, such as gallbladder cancer (25), pancreatic cancer (26), acute pancreatitis (27), and acute kidney injury (24). However, previous studies have not evaluated the prognostic relationship between biomarkers combined with glucose and lymphocyte counts in patients with sepsis. This study sought to assess the relationship between the GLR and hospital outcomes in patients with sepsis, an index that includes both glucose levels and systemic inflammation and may provide a new basis and reference for the clinical management of sepsis.

Materials and methods

Data source

We enrolled patients with sepsis from the MIMIC-IV (Medical Information Mart for Intensive Care IV, version 1.0) (28) database of the Massachusetts Institute of Technology (MIT). More than 70,000 adult patients were admitted to the intensive care unit (ICU) of Beth Israel Deaconess Medical Center in Boston between 2008 and 2019. Informed consent was waived because the data were obtained from publicly available sources. One author, Shaoyan Cai, obtained full

access to the database and completed the data extraction (certification number 46658933). Strengthening the Reporting of Observational Studies in Epidemiology guidelines (29) was used to conduct this study.

Participants

Patients aged >18 years who fulfilled the Sepsis-3 criteria (1) were eligible for our study. Sepsis was defined as an increase of ≥2 points in the sequential organ failure assessment (SOFA) score, plus documented or suspected infection (1, 30).

Septic shock was defined as (ICD) code 78552 (9th revision) and ICD code R6521 (10th revision). The diagnosis of diabetes was based on ICD-9. If patients were admitted to the ICU more than once, we only adopted the date of their first ICU admission (31).

Variates

Variables considered confounders of sepsis outcomes based on existing literature and clinical judgment were included (23, 32), except glucose and lymphocytes count because of their collinearity with GLR.

Demographic and admission information: age, sex, ethnicity, insurance, weight, Charlson comorbidity index (CCI), and severity at admission, as measured by the Acute Physiology Score (APS) III score and SOFA score.

Vital signs: Heart rate, mean arterial pressure (MAP), and SPO2 at ICU admission.

Interventions: Mechanical ventilation, renal replacement treatment (RRT), and vasopressor agent use during the first 24 h of ICU admission.

Laboratory results: Glucose, lymphocyte count, hemoglobin, white blood cell (WBC) count, platelet count, neutrophil count, lactate, and pH.

GLR was calculated using the serum blood glucose (mmol/L)/lymphocyte count (× 109/L).

If the above data were tested multiple times within 24 h, we chose the first set of parameters.

Outcome

The outcome was in-hospital mortality, which is defined as survival status at hospital discharge. Patients without any outcome information were excluded from the final cohort.

Statistical analysis

Descriptive analysis was performed for categorical variables to assess the significance of differences between groups stratified by GLR quartiles (<0.43; 0.43–0.78; 0.78–1.56; ≥1.56) using the Kruskal–Wallis test or one-way analysis of variance. Baseline characteristic data are presented as proportions (%) and were compared using chi-square tests for categorical variables. Normally distributed continuous data are presented as mean ± standard deviation (SD) and compared using Student's *t*-test between groups, while skewed distribution data are presented as the median and interquartile range (IQR) and compared using the Wilcoxon rank-sum test.

A multivariate Cox proportional hazard model was used to assess the independent association between the GLR and in-hospital mortality. We constructed three models: Model 1, adjusted only for age and sex. Model 2 was additionally adjusted for ethnicity, weight, MAP, hazard ratio (HR), SPO2,

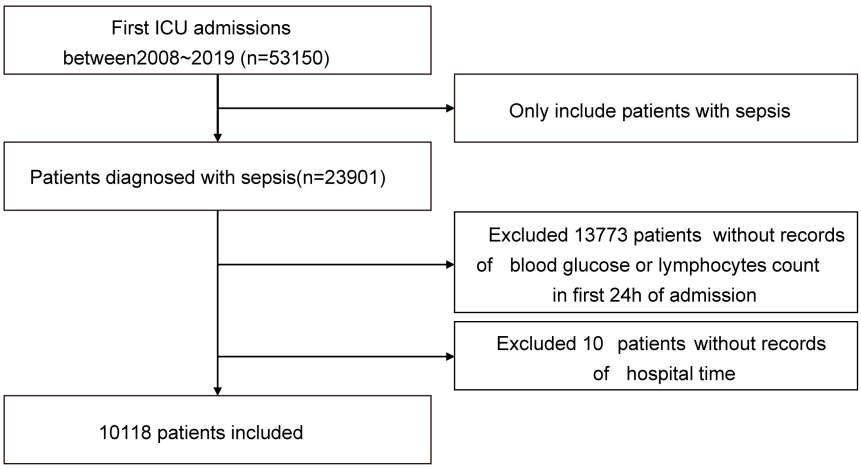

FIGURE 1
Flowchart of study patients.

TABLE 1 Baseline characteristics of participants and outcome parameters.

Variables	All patients	Q1	Q2	Q3	Q4	*P*-value
		(GLR < 0.43)	(0.43 ≤ GLR < 0.78)	(0.78 ≤ GLR < 1.56)	(GLR ≥ 1.56)	
N	10118	2447	2576	2546	2549	
Age(year)	65.8 ± 16.3	64.7 ± 16.0	65.1 ± 16.3	66.1 ± 17.0	67.3 ± 15.8	< 0.001
Female, n (%)	4262 (42.1)	1004 (41)	991 (38.5)	1139 (44.7)	1128 (44.3)	< 0.001
Ethnicity, white, n (%)	6643 (65.7)	1630 (66.6)	1724 (66.9)	1640 (64.4)	1649 (64.7)	0.188
Insurance, Medicaid, n (%)	5602 (55.4)	1429 (58.4)	1476 (57.3)	1378 (54.1)	1319 (51.7)	< 0.001
weight(kg)	83.7 ± 23.7	83.0 ± 21.7	84.2 ± 23.4	83.9 ± 24.3	83.8 ± 25.2	0.295
Vital Signs						
Heart rate (bpm)	87.8 ± 16.3	85.1 ± 15.3	86.7 ± 15.3	89.1 ± 16.8	90.2 ± 17.3	< 0.001
MAP (mmHg)	75.8 ± 9.9	75.6 ± 9.2	75.8 ± 9.8	76.1 ± 10.1	75.9 ± 10.5	0.246
SPO2 (%)	96.8 ± 2.6	97.2 ± 2.4	96.9 ± 2.6	96.7 ± 2.3	96.4 ± 2.9	< 0.001
Laboratory results						
Hemoglobin (g/L)	10.4 ± 1.9	10.1 ± 1.7	10.4 ± 1.8	10.5 ± 2.0	10.6 ± 2.1	< 0.001
Platelet (× 1012)	171.0 (121.5, 239.0)	145.5 (109.5, 197.5)	167.0 (124.5, 231.1)	186.5 (128.5, 256.6)	195.0 (132.5, 272.5)	< 0.001
WBC(× 109/L)	12.5 (8.9, 16.9)	9.7 (6.6, 13.1)	11.9 (8.7, 15.3)	13.3 (9.7, 17.7)	15.7 (11.7, 21.5)	< 0.001
Neutrophil (× 109/L)	9.9 (6.6, 14.1)	6.7 (4.3, 9.4)	9.6 (6.8, 12.5)	10.8 (7.8, 14.7)	13.8 (9.8, 18.6)	< 0.001
Lactate (mmol/L)	2.6 ± 2.2	2.3 ± 1.8	2.4 ± 1.9	2.7 ± 2.4	3.1 ± 2.4	< 0.001
pH	7.4 ± 0.1	7.4 ± 0.1	7.4 ± 0.1	7.3 ± 0.1	7.3 ± 0.1	< 0.001
Glucose (mmol/L)	7.2 (6.1, 9.1)	6.2 (5.4, 7.1)	6.8 (5.9, 7.9)	7.7 (6.5, 9.6)	9.3 (7.3, 12.2)	< 0.001
Lymphocytes(× 109/L)	9.7 (5.3, 16.0)	21.4 (17.4, 27.7)	12.0 (10.0, 14.5)	7.3 (5.9, 9.2)	3.4 (2.1, 5.0)	< 0.001
GLR	0.8 (0.4, 1.6)	0.3 (0.2, 0.4)	0.6 (0.5, 0.7)	1.1 (0.9, 1.3)	2.6 (2.0, 3.9)	< 0.001
Score system, points						
CCI	5.8 ± 2.9	5.3 ± 2.8	5.5 ± 2.9	5.9 ± 3.0	6.3 ± 3.0	< 0.001
APS III score	58.0 ± 27.6	49.2 ± 25.5	53.3 ± 25.8	61.0 ± 27.2	68.3 ± 27.9	< 0.001
SOFA score	3.9 ± 2.2	3.8 ± 2.0	3.7 ± 2.0	3.9 ± 2.3	4.1 ± 2.4	< 0.001
Interventions						
Ventilator use, n (%)	5202 (51.4)	1259 (51.5)	1363 (52.9)	1284 (50.4)	1296 (50.8)	0.304
Diabetes, n (%)	3058 (30.2)	617 (25.2)	675 (26.2)	793 (31.1)	973 (38.2)	< 0.001
RRT, n (%)	565 (5.6)	85 (3.5)	95 (3.7)	166 (6.5)	219 (8.6)	< 0.002
Vasopressin use, n (%)	996 (9.8)	148 (6)	204 (7.9)	263 (10.3)	381 (14.9)	< 0.001
death, n (%)	1726 (17.1)	227 (9.3)	326 (12.7)	479 (18.8)	694 (27.2)	< 0.001

Data are presented as the mean ± standard deviation (SD), median (IQR) for skewed variables, and numbers (proportions) for categorical variables.
bpm, beats per minute; MAP, mean arterial pressure; WBC, white blood count; GLR, glucose-to-lymphocyte ratio; CCI, Charlson comorbidity index; APS III, Acute Physiology Score III; SOFA, Sequential Organ Failure Assessment; RRT, renal replacement treatment.

hemoglobin, platelet (PLT), WBC, lactate, and pH. Model 3 was additionally adjusted for SOFA score, APS III score, ventilator use, diabetes, CCI, vasopressin usage, and neutrophil count. In all models, linear trends were tested using GLR quartiles as categorical variables by assigning the median values of the quartiles to the variable.

A Cox proportional hazards regression model was used to assess the non-linear relationship between GLR and the outcome of sepsis. Based on the curve fitting (restricted cubic spline), we conducted a two-piecewise linear regression model to identify threshold effects, if a non-linear correlation was observed. Threshold levels of GLR were determined using a recursive method, and a maximum likelihood model was yielded.

A sensitivity analysis was performed to ensure the robustness of the data analysis. GLR was transformed into a categorical variable and a *p*-value for the trend was calculated. The purpose of this test was to validate the results of treating the GLR as a continuous variable and to determine the possibility of non-linearity.

Hospital survival was assessed using Kaplan–Meier survival curves according to GLR quartiles and evaluated using the log-rank test.

Stratified and interaction analyses were applied based on sex (male or female), age (<65 or ≥65 years), diabetes (yes or no), ventilator use (yes or no), and RRT use (yes or no). Subgroup analyses were adjusted for relevant covariates (age, sex, ethnicity, weight, MAP, HR, SPO2, hemoglobin, PLT, WBC,

TABLE 2 Multivariable Cox regression to assess the association of GLR with in-hospital mortality.

Variable	Unadjusted		Model 1		Model 2		Model 3	
	HR_95CI%	*P*-value	HR_95CI%	*P*-value	HR_95CI%	*P*-value	HR_95CI%	*P*-value
GLR	1.11 (1.1∼1.12)	< 0.001	1.11 (1.1∼1.12)	< 0.001	1.06 (1.05∼1.07)	< 0.001	1.02 (1.01∼1.03)	0.004
GLR4								
Q1(GLR < 0.43)	1(Ref)		1(Ref)		1(Ref)		1(Ref)	
Q2(0.43 ≤ GLR < 0.78)	1.23 (1.12∼1.36)	< 0.001	1.23 (1.12∼1.36)	< 0.001	1.18 (1.07∼1.3)	0.001	1.2 (1.08∼1.32)	0.001
Q3(0.78 ≤ GLR < 1.56)	1.6 (1.46∼1.76)	< 0.001	1.57 (1.43∼1.72)	< 0.001	1.34 (1.22∼1.47)	< 0.001	1.23 (1.12∼1.35)	< 0.001
Q4(GLR ≥ 1.56)	2.33 (2.14∼2.55)	< 0.001	2.25 (2.06∼2.46)	< 0.001	1.6(1.46∼1.75)	< 0.001	1.3(1.185∼1.43)	< 0.001
P for trend.test		< 0.001		<0.001		< 0.001		<0.001

GLR, glucose-to-lymphocyte ratio.
Model 1 = Adjust for (Age + sex).
Model 2 = Model 1 + (ethnicity + weight + MAP + HR + SPO2 + hemoglobin + PLT + WBC + lactate + pH).
Model 3 = Model 2 + (SOFA score + APS III + ventilator use + diabetes + CCI + vasopressin use + neutrophil).

lactate, pH, SOFA score, APS III, ventilator use, diabetes, CCI, and vasopressin use).

The percentages of covariates with missing data were less than 30% for all analyses. The missing values of the covariates were imputed *via* multiple imputations. We created and analyzed three datasets together. To assess the robustness of the findings, we applied sensitivity analysis of patients after excluding missing data from the study (**Supplementary Table 1**).

Data analyses were performed using packages R 4.1.2 (The R Foundation)[1] software and Free Statistics software versions 1.5. *P*-values < 0.05 were considered significant.

Results

Population

In total, 23,901 patients were identified according to the sepsis-3 criterion. Of these, 13,343 patients without GLR values and in-hospital time were excluded, and 10,118 with sepsis were included in the final cohort (**Figure 1** shows a flow chart).

Baseline characteristics

The basic demographic characteristics of all selected patients are summarized in **Table 1**, stratified by GLR quartile. In general, the age of all participants was 65.8 ± 16.3 years old, and approximately 42.1% were female. The in-hospital mortality rate was 20.1% (480/2,383). Participants in the highest group of GLR (Q4) had higher values for age, heart rate, hemoglobin, platelet, WBC, neutrophil, lactate, glucose, APS III score, CCI, SOFA score, and were more likely to have diabetes, RRT, vasopressin use, and death than those in the other groups. The opposite patterns were observed for SPO2, pH, lymphocytes, and insurance for medical aid.

Multivariable Cox regression analysis

In this study, we constructed three models to analyze the independent effects of the GLR on in-hospital mortality (multivariate Cox regression model; **Table 2**). The effect sizes (HRs) and 95% confidence intervals were listed. We observed that the HRs were robust between the unadjusted and adjusted models in all three models ($p < 0.05$). In the unadjusted model, the effect size of GLR for in-hospital mortality means that a difference of one unit of GLR is associated with an in-hospital mortality difference increased by 11% (HR = 1.11, 95% CI: 1.10–1.12). In the minimum-adjusted model (Model 1), with an increase in the GLR of one unit, the in-hospital mortality difference increased by 11% (HR = 1.11, 95% CI 1.1–1.12). In the fully adjusted model (Model 3) (adjusted covariates of age, sex, ethnicity, weight, MAP, HR, SPO2, hemoglobin, PLT, WBC, lactate, pH, SOFA score, APS III, ventilator use, diabetes, CCI, vasopressin usage, and neutrophil count) for each additional unit of GLR, in-hospital mortality difference increased by 2% (HR = 1.02, 95% CI 1.01–1.03). For further sensitivity analysis, the continuous variable GLR was converted into a categorical variable (quartile of GLR), of which the first category GLR (Q1) was used as a baseline reference. Patients in the highest GLR quartile had increased in-hospital mortality compared to patients in the lowest GLR quartile (HR = 1.26, 95% CI 1.15–1.38). The *P* for the trend in the fully adjusted model for GLR as a categorical variable was the result when GLR was a continuous variable. Moreover, the trend for effect size in the different GLR groups was equidistant.

1 http://www.R-project.org

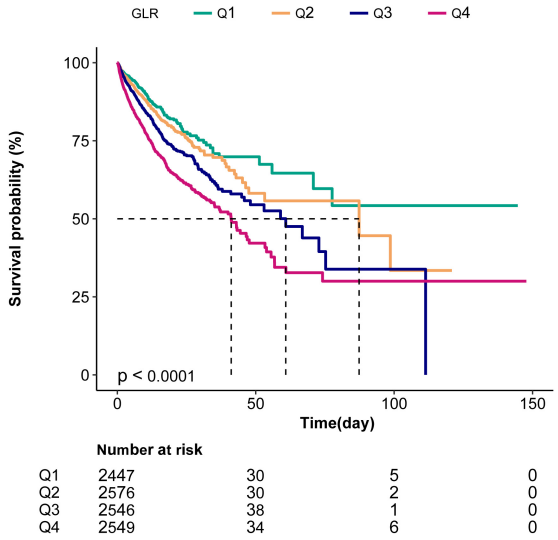

FIGURE 2
Kaplan–Meier curves indicating the association between the GLR and in-hospital mortality of sepsis patients. Q1, GLR < 0.43; Q2,0.43 ≤ GLR < 0-78; Q3,0.78 ≤ GLR < 1.56; Q4, GLR ≥ 1.56.

Kaplan–Meier curves

The Kaplan–Meier curve demonstrated that the in-hospital survival of the highest GLR quantile (Q4) patients was the lowest of all groups, which declined with declining baseline GLR (log-rank test: $p < 0.0001$; Figure 2).

Subgroup analysis

Subgroup analyses indicated no significant interaction in the subgroup analysis (all p-values for interaction were >0.05; Figure 3).

The analyses of the non-linear relationship

Restricted cubic spline (Figure 4) showed that the relationship between GLR and in-hospital mortality was non-linear after adjusting for related confounding factors. Because the P for the log-likelihood ratio test was <0.05, we chose the two-piecewise Cox proportional hazard model for fitting the association between GLR and in-hospital mortality. By the two-piecewise Cox proportional hazard model and recursive algorithm, we calculated the inflection point was 1.68. It was shown that stronger positive association between GLR and in-hospital mortality within the inflection point of 1.68. In-hospital mortality increased by 67% (aHR = 1.67, 95% CI: 1.45–1.92) for every unit GLR increase. When GLR was beyond 1.68, in-hospital mortality did not significantly change (aHR: 1.04, 95% CI: 0.92–1.18; Table 3).

Discussion

This study evaluated the association of GLR, a combination of blood glucose levels and lymphocyte count, with in-hospital mortality after adjusting for the variables in a population-based analysis. Our findings indicate that an elevated GLR is associated with higher in-hospital mortality. Furthermore, as a continuous or categorical variable, GLR was positively associated with in-hospital mortality in intensive care patients with sepsis in the United States. Besides, the inflection point of GLR was 1.68, and we found the trend of HR on the two sides of the inflection point was not consistent. The result suggested a turning point effect on the independent association between GLR and in-hospital mortality.

Sepsis is characterized by systemic and organ-specific metabolic changes. Altered oxygen consumption, elevated circulating substrate levels, impaired glucose and lipid oxidation, and mitochondrial dysfunction are associated with organ dysfunction and adverse outcomes in animal models and patients (33). Sepsis can lead to a loss of glucose homeostasis, and the resulting hyperglycemia adversely affects immune function and metabolism, leading to poor outcomes (34, 35). The mechanisms that lead to glucose dysregulation are complex. Elevated blood glucose levels tend to reduce membrane fluidity, which impedes polymorphonuclear leukocyte (PMN) function, leading to reduced phagocytosis, intracellular killing, suboptimal migration, and chemotaxis (20, 36, 37). In addition, the neuroendocrine stress response can increase adrenal cortex secretion by 10 times, including excessive glycogenolysis, gluconeogenesis, and insulin resistance (38).

A low lymphocyte count may also be associated with a shortened survival time in sepsis (22). Clinical studies have shown that lymphocyte counts in the blood decrease during sepsis and remain low for up to 28 days (39, 40). Although the absolute lymphocyte counts of sepsis survivors and non-survivors were severely decreased at the onset of sepsis, lymphocyte counts recovered in survivors, while absolute lymphocyte counts remained persistently low in non-survivors (41). Various anti-inflammatory cytokines released into the bloodstream can induce immunosuppression and lead to massive lymphocyte apoptosis (42). Lymphopenia is a common marker of sepsis-induced immunosuppression, as it prevents microbial clearance and induces severe infections, which are the leading causes of sepsis-related death (39). Apoptosis-induced lymphocytopenia often occurs in sepsis and severe injuries, including major surgery, burns, and trauma. As active lymphocytes migrate to inflammatory areas, lymphocyte apoptosis increases (43). This process begins immediately after

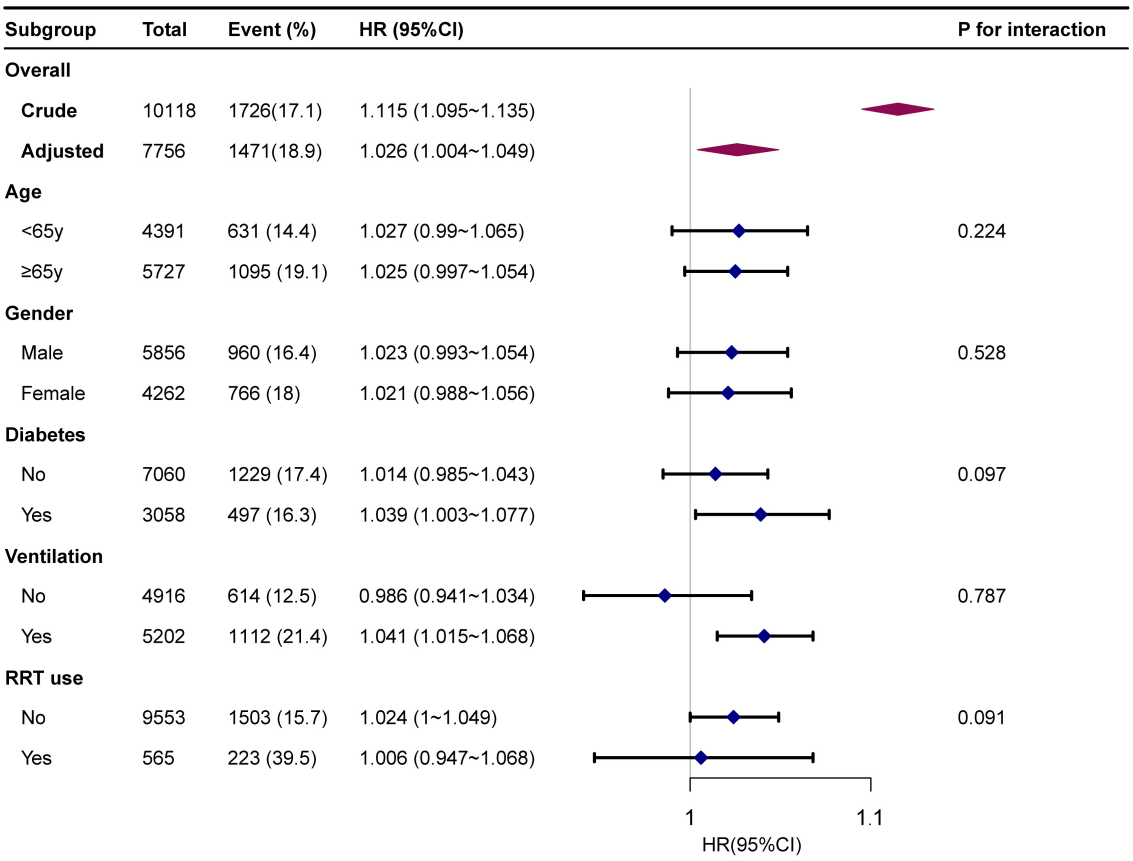

FIGURE 3
Forest plot for subgroup analysis for the association between GLR and in-hospital mortality. Each stratification adjusted for all the factors of model 3 in the Multivariable cox regression, except for the stratification factor itself.

the potential damage occurs. The severity and duration of lymphocytopenia are associated with poor clinical outcomes. The severity and duration of lymphopenia are associated with poor clinical outcomes. Extensive apoptosis of lymphocytes occurs in lymphoid (lymph nodes, thymus, and spleen) and other organs (44) leading to impaired immune cell activity, which is a key contributor to the development of the immunosuppressive phase of sepsis and plays a direct or indirect role in injury-induced immune paralysis (45).

The exact mechanism underlying the association between elevated GLR levels and poor prognosis in patients with sepsis is unclear. Recently, several researchers have been interested in biomarkers that combine blood glucose levels and inflammatory indicator lymphocytes to predict the prognosis of certain diseases. Navarro suggested that the preoperative GLR was an independent predictor of overall survival (OS) and disease-free survival (DFS) after surgery for T2 gallbladder cancer. This is the first report of the predictive value of GLR (25). As an easily available biomarker, Chen et al. reported that GLR was an independent predictor of in-hospital mortality in critically ill patients with acute pancreatitis. They combined

TABLE 3 Threshold effect analysis of the relationship between GLR and in-hospital mortality of patients with sepsis.

Threshold of GLR	HR 95CI%	*P*-value
< 1.68	1.67 (1.45,1.92)	< 0.001
≥ 1.68	1.04 (0.92,1.18)	0.5223
Likelihood Ratio test	-	< 0.001

Data were adjusted for all the factors of Model 3 of Table 2.

GLR with other clinical characteristics of acute pancreatitis to construct nomograms with favorable predictive performance for in-hospital mortality (27). Two other studies showed that GLR is an independent predictor of prognosis in patients with pancreatic cancer (26, 46). Preoperative GLR was also a promising predictor of acute kidney injury after cardiac surgery in ICU patients (24). Therefore, it is worth considering that GLR may reflect a synergistic effect of immunocompromise and hyperglycemia in sepsis.

To the best of our knowledge, this is the first report of an independent association between GLR and in-hospital mortality in ICU patients with sepsis. This study could help establish

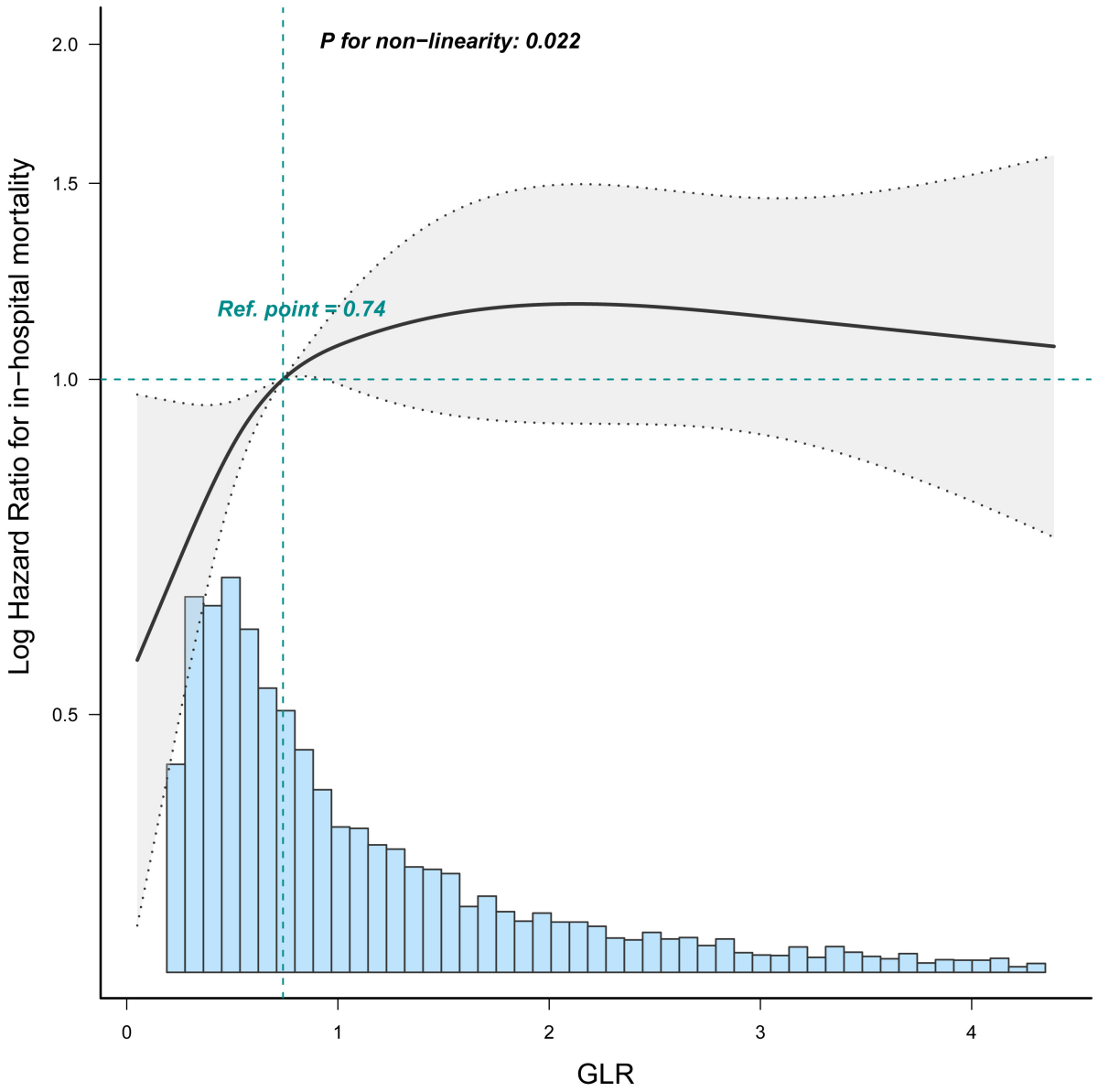

FIGURE 4
Restricted cubic spline shows the association between GLR and in-hospital mortality of sepsis patients. Data were fit by a Cos proportional hazard regression model based on restricted cubic splines. GLR was entered as continuous variable. Data were adjusted for all the factors of model 3 of **Table 3**. The curves line and shaded areas around depict the estimated values and their corresponding 95% confidence intervals. Only 95% of the data is displayed.

diagnostic or predictive models of in-hospital sepsis mortality in future research.

Our study has several strengths. First, the study used real-world data for a large and diverse population. Second, strict statistical adjustment was used to minimize susceptibility to potential residual confounders in this retrospective observational study. Third, we considered the target independent variables as both continuous and categorical variables. With this approach, contingency in the data analysis was reduced, and the robustness of the results was enhanced. Fourth, the non-linear processing of the study is a major improvement compared to former studies. Finally, the effect modifier factor analysis improved data usage and yielded more robust results in different subgroups.

There are some noteworthy limitations to this study. First, in the MIMIC-IV database, we could not obtain data on procalcitonin and organ functions, and other residual confounders potentially exist, as in all retrospective analyses. Some patients with sepsis were excluded from our study because of the lack of necessary data, which may have led to bias in

the study results. Second, the influence of antibiotic use on results was not considered. We believe that this is an important subject and will be the objective of our future research. Third, our research subjects were intensive care patients with sepsis. Therefore, the universality and extrapolation of research are lacking. Moreover, GLR values changed dynamically during hospitalization. However, the GLR value used in the present study was not calculated based on the date of the onset of sepsis but on the first day of admission to the ICU or hospital. Therefore, this may have caused bias in the results. Finally, it was a retrospective study based on the MIMIC-IV database; therefore, our study was a *post hoc* analysis of the MIMIC-IV database, the level of evidence was not strong enough, and further high-quality prospective studies are needed to validate the relationship between GLR and sepsis prognosis.

Conclusion

There was a non-linear relationship between GLR and in-hospital mortality in intensive care patients with sepsis. A higher GLR in ICU patients is associated with in-hospital mortality.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://mimic.physionet.org/.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SC: study design and manuscript writing. CM: modified the manuscript. LeZ and YW: data collection. JC: data interpretation. ZF: statistical analysis. LiZ and CG: project administration. All authors have approved the manuscript and agreed to the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.922280/full#supplementary-material

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A bibliometric analysis of publications on burn sepsis using VOSviewer

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Background: Sepsis is one of the most common complications in burn patients and causes high morbidity, especially in those with severe burns. Nevertheless, there are no formal criteria for diagnosing and treating burn sepsis. Therefore, this bibliometric analysis is applied to reveal research trends in this field and predicts its possible hot spots.

Methods: We screened relevant literature on burn sepsis that met the inclusion criteria of the Web of Sciences (WOS) database and analyzed publication trends and research hot spots in related fields using VOSviewer software.

Results: From 1981 to 2022, we screened 2,486 documents that met the requirements and analyzed them bibliometrically. The American scholar Herndon DN had a much higher h-index [47] than other authors. Most published, cited, and h-indexed publications are from the USA (Np: 1193, Nc: 42154, H: 98). The second most publishing country is China, but the second most cited and h-indexed country is Germany. Burns also outperforms other journals in this field (Np: 376, Nc: 8019, H: 46). "Biomarkers" is a newly emerging keyword (cluster "clinical research," APY was 2018.16), and clinically relevant research in burn sepsis maybe a future research trend.

Conclusions: Sepsis in burn patients has unique pathophysiological characteristics and the general diagnostic criteria for sepsis lack specificity. Consequently, we must establish a database and construct an intelligent predictive model to help achieve a more individualized and precise early diagnosis and treatment of burn sepsis. This may also be an important development direction for future research in this field.

KEYWORDS

burn sepsis, bibliometric analysis, VOSviewer, direction, Web of Science

Introduction

Burns are one of the most common and devastating forms of trauma, and 75% of deaths in patients with severe burns exceeding 40% of the total body surface area (TBSA) are associated with sepsis from burn wound infections and other infectious complications or inhalation injury (1). Initially, we believed that the main cause of death in burn patients who passed through the shock phase was multiple organ dysfunction

syndromes (MODS), which directly respond to sepsis after burn injury. Burn patients lose the skin, which is the major barrier against external bacterial infectious attack, resulting in infection vulnerability that can induce sepsis. In addition, this potentially life-threatening infection leads to inadequate tissue perfusion, inflammatory and stress reactions, a prolonged hypermetabolic response, and even sequential multiorgan failure. They are at risk of sepsis and MODS, at least as long as the wound remains open (2). However, the survival rate of patients with post-burn sepsis has not improved significantly over the past decades. Due to these frightening statistics, there have been efforts to improve the salvage rate of post-burn sepsis. Even though more studies have been conducted to investigate this phenomenon, no standardized criteria remain for diagnosing and treating burn sepsis. Therefore, this research aims to comprehensively analyze the current state of sepsis and burn research using the Web of Science (WOS). We applied bibliometric analysis to reveal research trends in this field and provide new directions for burn sepsis.

WOS search platform is an important scientific citation index database, recognized as the most authoritative indexing tool for scientific and technical literature worldwide (3), and the system of SCI citation search is unique, which can evaluate the educational value of articles from the perspective of literature citation and quickly and easily set up a reference network of research topics (4).

Bibliometrics is the cross-cutting science that quantitatively analyzes all knowledge carriers using mathematical and statistical methods. It is a comprehensive knowledge system that integrates mathematics, statistics, and bibliography while emphasizing quantification. Bibliometrics is a convenient method to estimate trends in scientific archives and reveal key research directions by analyzing the characteristics of databases and literature (5, 6). The findings of bibliometric analysis have been applied to various medical fields, including gynecology, orthopedics, ophthalmology, and basic medicine (7–9). However, there remains a lack of bibliometric studies on burn sepsis. Therefore, this study aimed to systematically analyze the research on burn sepsis to identify research trends and hotspots in this field.

Methods

The search database was WOS database, the search time was March 27, 2022, and the search formula used was as follows: TS = [sepsis OR (septic shock)] AND TS = (burn) AND DOP = (1981-01-01/2022-03-27) AND LA = (English). Articles and review articles written in English only were screened among various publication types. The number of articles that met the criteria was 2,486. The search results were exported as plain text files. The exported information was a complete record, including year of publication, language, journal, title, author, affiliation, keywords, document type, abstract, citation count, etc. The metric package was imported, and VOSviewer analyzed the data. v.1.6.18 (Center for Science and Technology Studies, CWTS, Leiden University, based on JAVA).

Bibliometric analysis

Bibliometric indicators included the volume of literature, the authors (individual, organization, or country), keywords, the number of citations, and so on. In general, productivity was represented by the number of publications (Np), and the number of citations without self-citations (Nc) was used to measure influence. In addition, citations reflected a general trend. The h-index unified productivity and impact by finding the threshold that connected Np and Nc (10). In other words, A researcher's H-index is defined as having at most H papers that have been cited at least H times each. It also can be extended to describe the impact of publication output of a country, region, institution, or journal (11).

VOSviewer can map and visualize keyword networks related to sepsis and burns. For example, an average year of publication (APY) was used to quantify the relative novelty of a keyword, and link strength can represent the relevance of these items in these networks (12). WOS search platform provides representative citation reports generated by built-in analysis tools, which include Np, Nc, and citations (3).

Results

Analysis of thesis on burn sepsis

We searched for articles matching the search formula through WOS website. From January 1, 1981 to March 27, 2022, 2,669 English-language articles were searched, including 2,175 (81.5%) research articles and 311 (11.7%) review articles. As depicted in Figure 1, the number of publications grew fastest in the last decade compared to 40 years, accounting for nearly half (46.4%) of the total literature searched. The number of citations in the last decade is also the fastest growing. More interestingly, the citation number was growing faster than the publication number. For the 2,486 documents that met the requirements, citations were 83,119 times, with an average of 33.21 citations per document and an overall h-index of 120.

Analysis of authors

Table 1 lists the top 10 fruitful authors. They published 535 papers, accounting for 21.52% of all papers. Herndon DN from the US was ranked first in the field of burn sepsis research, followed by Jeschke MG from Canada and Gamelli RL from

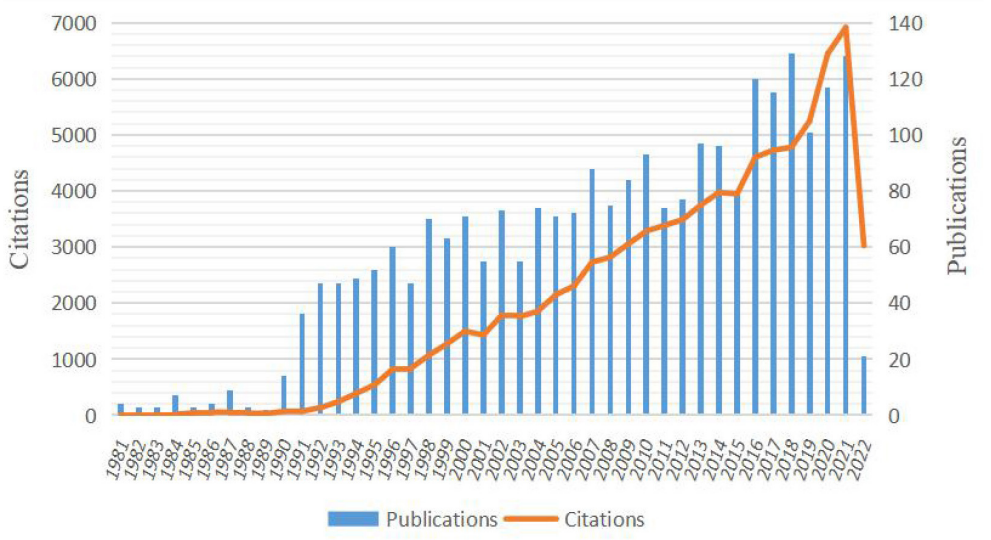

FIGURE 1
Times cited and publications over time from total documents.

TABLE 1 Top 10 active authors.

Authors	Countries	Np	Nc	h-index
Herndon DN	USA	137	6752	47
Jeschke MG	Canada	87	3521	34
Gamelli RL	USA	61	1994	32
Horton JW	USA	45	1997	24
Wolf SE	USA	37	2083	23
Sheng ZY	China	35	702	16
Traber DL	USA	35	1164	18
Finnerty CC	USA	34	2200	24
Tompkins RG	USA	33	1968	23
Yao YM	China	31	746	16

the US. As revealed in Table 1, Herndon DN had a significantly higher Nc and h-index. In addition, most of the top 10 authors are from the US (7) or China (2). We can also identify from the density visualization map in Figure 2 that Herndon DN and Jeschke MG contributed the most in this field.

Analysis of the top 10 most influential countries/institutions/journals

We ranked the ten highest-output countries/institutions/journals among all authors according to Np (Table 2). The US published the most articles (1193/H:98), followed by China (243/H:31) and Germany (168/H:41). US papers were cited 42,154 times, accounting for 56.45% of the total. This was followed by Germany (5,364) and Canada (4,857). In addition, the US had the highest h-index (98), which was more than twice as high as Germany (41). The relatively low Np but significantly higher h-index and Nc in the UK and Canada compared to China.

Nonetheless, the proportion of Chinese publications and citations in this field has increased rapidly (Figure 3). Meanwhile, we identify from the overlay visualization map (Figure 4) that the US (Total link strength: 224) was the most closely linked country to others in burn sepsis research, reflecting its leadership role in this field. Furthermore, China (Np: 240, APY: 2013. 77) was the most recent major producer of literature in this field, with greater potential for the future.

Table 2 lists the top 10 organizations with the highest number of publications related to burn sepsis. The University of Texas System had the highest Np (286), followed by The University of Texas Medical Branch, Galveston (188), and Shriners Hospitals for Children (138). The University of Texas System was ranked first in Nc (10787) and h-index (60), followed by The University of Texas Medical Branch, Galveston (Nc:7368, H:48). Interestingly, all above organizations belonged to a branch of the University of Texas. The University of Texas was far ahead of the other organizations in all areas. Most of these institutions were located in the US.

Table 2 lists the top 10 journals with the highest number of publications in this field. "Burns" (Np: 376, h-index: 46) published the most papers on burn sepsis, as well as "Journal of Burn Care and Research" (Np: 139, h-index: 23) and "Shock" (Np: 126, h-index: 35), ranked second and third, respectively. Of 2486 documents, about 41% were published in the top 10 academic journals (1014/40.8%). "Critical Care Medicine,"

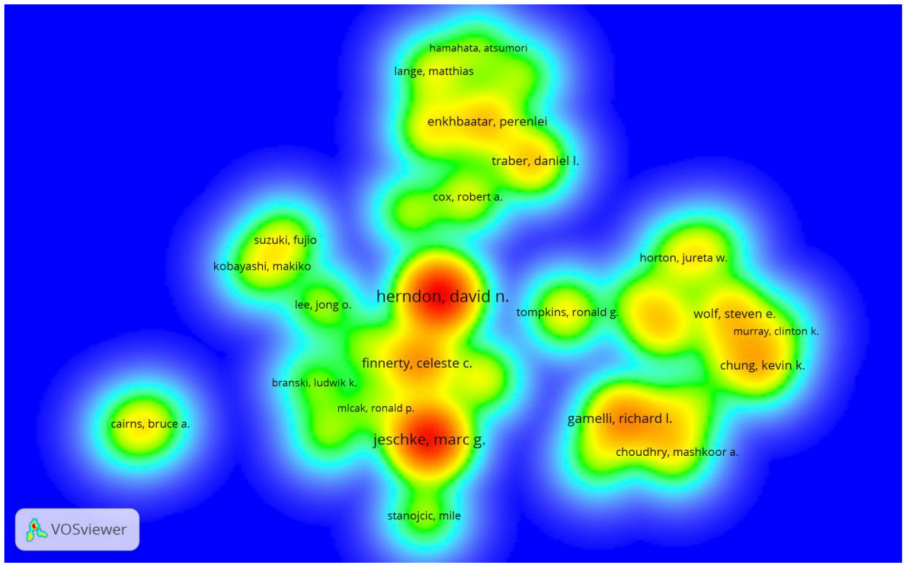

FIGURE 2
Authors density visualization map according to co-authorship affiliations. Seventy-four authors were included in the map who have at least ten papers. The color represents the number of co-authored documents. Red indicates a higher frequency of occurrence, while green indicates a lower frequency of occurrence.

ranked fifth, and "Annals of Surgery," ranked seventh among the top 10 journals, had higher citation rates and h-indexes.

Bibliometric analysis of co-citation

The co-citation graph of cited references is displayed in Figure 5A (the references cited 50 times and more were chosen). "The American Burn Association consensus conference defines sepsis and infection in burns" (Greenhalgh dg, 2007) as the most cited literature (192 times). As indicated in the density visualization map (Figure 5B), the highest citation of this article was probably because it provides the diagnostic standard for burn sepsis (ABA criteria) (13). The next most cited paper is "Burn wound infections" (Church d, 2006), with 137 citations.

Bibliometric analysis of keywords

Excluding the search terms, synonyms, and duplicate terms (sepsis, burn, burns, septic shock, thermal injury, thermal-injury, severe sepsis, burn injury, and trauma), the keywords extracted from the titles and abstracts of 2,486 papers were analyzed using VOSviewer, and the 133 keywords that appeared more than 25 times were divided into three clusters (Figure 6).

Cluster 1 refers to "studies related to inflammation." The most frequent keywords were inflammation (178 times), expression (162 times), tumor-necrosis-factor (138 times), cytokines (107 times), and mice (104 times).

Cluster 2 refers to "clinical research." The most frequent keywords were mortality (349 times), infection (255 times), children (105 times), management (113 times), and critically ill patients (100 times).

Cluster 3 refers to "injury-related studies." The keywords that appeared more frequently were injury (273 times), bacterial translocation (116 times), shock (90 times), hemorrhagic shock (64 times), and multiple organ failure (64 times).

As illustrated in Figure 7, VOSviewer colored all keywords based on the average time of word occurrence. The blue indicates the words that appeared relatively early in the time course, while the yellow indicates recent occurrences. The trend indicates that "clinical research" was the most recent research direction. Among these, "biomarkers" (cluster 2, APY was 2018.16) may be the most recent direction for research in burn sepsis. The most recent keywords in the first cluster ("inflammation-related research") were "inflammation" (cluster 1, APY was 2012.67), "pseudomonas aeruginosa" (cluster 1, APY was 2012.89), and "dendritic cell" (cluster 1, APY was 2012.42), appearing 178, 37, and 26 times, respectively. As for the third cluster ("injury-related research "): "oxidative stress" (cluster 3, APY was 2013.48) appeared 50 times. In the second cluster ("clinical research"), "acute kidney injury" (cluster 2, APY was 2016.71) appeared 49 times, and it was the most recent keyword besides "biomarkers."

TABLE 2 Top ten countries/institutions/journals.

	Subject	Np	Nc	h-index
Countries				
	USA	1193	42154	98
	China	243	3228	31
	Germany	168	5364	41
	Canada	123	4857	36
	England	112	4822	35
	Japan	106	2803	27
	Australia	79	2530	31
	Turkey	64	892	20
	Italy	62	2458	27
	France	61	4712	29
Organizations				
	University of Texas System (USA)	286	10787	60
	University of Texas Medical Branch Galveston (USA)	188	7368	48
	Shriners Hosp Children (USA)	138	5197	41
	Harvard University (USA)	125	6226	44
	Loyola University Chicago (USA)	110	2899	31
	University of Cincinnati(USA)	88	3294	33
Journals				
	Burns	376	8019	46
	Journal of Burn Care Research	139	1929	23
	Shock	126	4048	35
	Journal of Trauma Injury Infection and Critical Care	83	3098	32
	Critical Care Medicine	75	4757	38
	Journal of Surgical Research	49	988	20
	Annals of Surgery	48	4345	34
	PLOS ONE	43	1203	20
	Archives of Surgery	39	1710	26
	Journal of Burn Care Rehabilitation	36	1255	20

Furthermore, as shown in the visual map of keyword density in Figure 8, the three most hot words were mortality (349 times), injury (273 times), and infection (255 times).

Discussion

Trends in the study of burn sepsis

The increase in the overall number of publications indicated that scholars paid increasing attention to burn sepsis research over the last decade. Also, the understanding of burn sepsis was grown. Similarly, the quality of published papers improves, as evidenced by comparing publication growth and citation growth. It is clear from the current study that the US and Germany ranked first and second in the total number of references and h-index values in the burn sepsis research area, respectively. The US has made the most significant contribution to the study of burn sepsis, with the highest number of publications, citation frequency, and h-index.

American clinicians were the first to present the criteria for defining burn sepsis, representing that the US was interested in this research field before the rest of the world. The US has the strongest ties with other countries in this area of research. In addition, conditions for basic medical research and clinical trial study appeared superior in the US. Nine of the top ten influential institutions are located in the US. Moreover, seven of the top ten active authors belong to the US. These characteristics also suggest that the US is leading in this area.

Notably, China ranked second in the total number of published papers but fifth in citation frequency and h-index. The contradiction between the quantity and quality of publications in China may have several causes. The two most important reasons: sepsis diagnosis remains far from standardized in China. In most hospitals in China, even in tertiary hospitals, medical and nursing staff do not regularly perform sepsis-related organ failure assessment (SOFA) scores for critically ill patients, resulting in a high rate of missed sepsis diagnoses. Secondly, China lacks high-quality multicenter randomized clinical trials (RCT) and has a relatively large number of observational studies, which may be insufficient to provide solid evidence in clinical practice. Similarly, Germany, Canada, and the UK have a serious discrepancy between the number of articles and their quality. However, these countries have a high potential for development in this area (Figures 3, 4).

As indicated in Table 2, although Germany, Canada, and England published fewer papers than China from 1981 to 2022, they were more frequently cited and had a higher h-index than China. The US has nine institutions from the top 10 ranking in burn sepsis research, indicating its dominance in this field. The institution with the most publications in this field is the University of Texas. However, it is worth noting that The University of Texas Medical Branch, Galveston, and Shriners Hospitals for Children are all branches of the University of Texas. Although they could also be considered independent organizations because the institutions labeled in the relevant literature are Galveston Hospital and Schreiner Children's Hospital rather than the University of Texas, the key is whether this affiliation affects the results of Np and Nc. We believe it is possible, which may be a shortcoming of the bibliometric analysis. The US has some of the most elite institutions and authors, which partly explains why it has remained a leader in burn sepsis research. In addition, the list includes one Canadian institution. other countries do

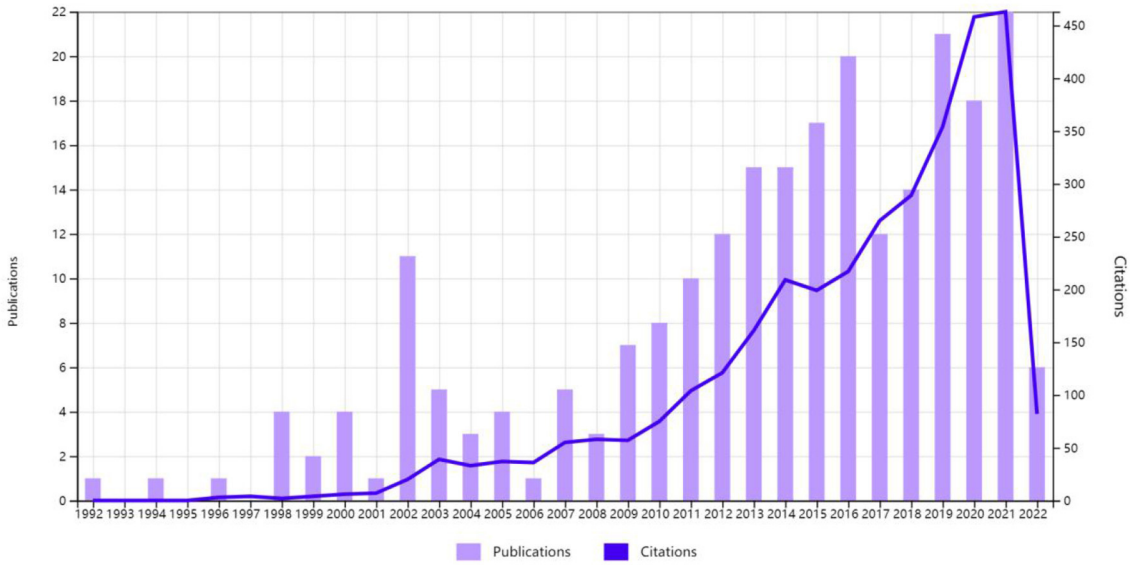

FIGURE 3
Times cited and publications over time from China.

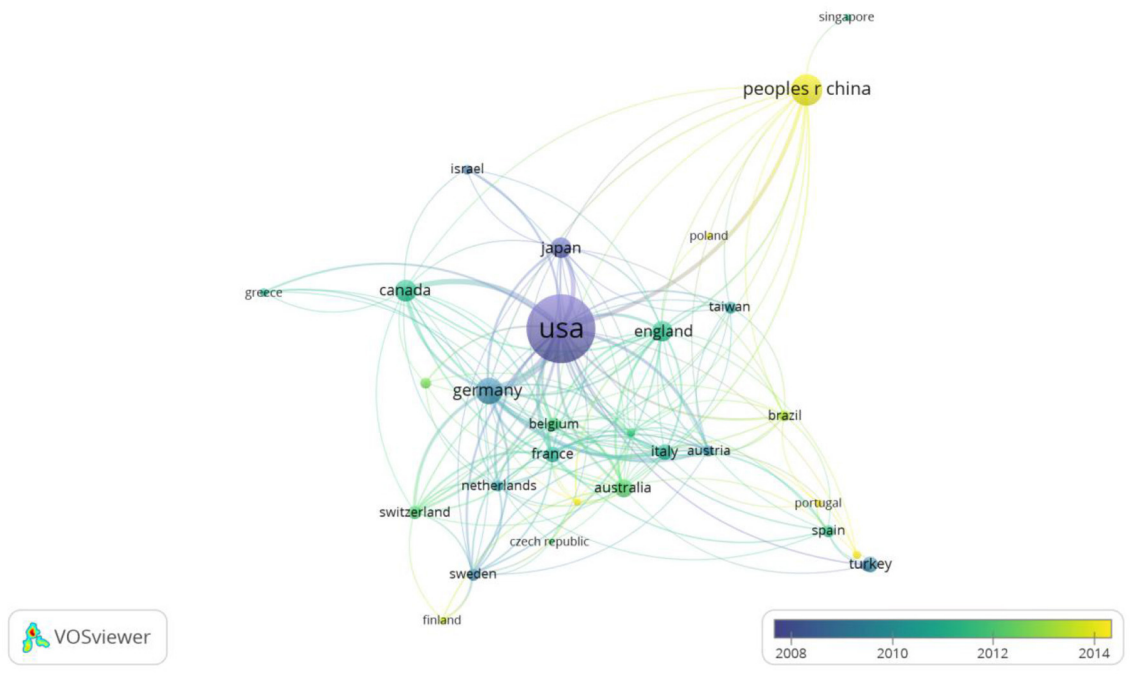

FIGURE 4
Bibliographic analysis and development of countries with respect to time from more than ten records. Node size represents the number of publications; color represents the average publication year; distance only represents the link strength between two nodes.

not have an institution in the top 10 for now. Consequently, more elite other countries' institutions must improve their international position in important research directions related to burn sepsis.

The journal "Burns" has published 376 papers in the field, far ahead of other journals. The remaining journals, including "Journal of Burn Care and Research," "Shock," and "Trauma-Injury Infection and Critical Care," are the leading journals

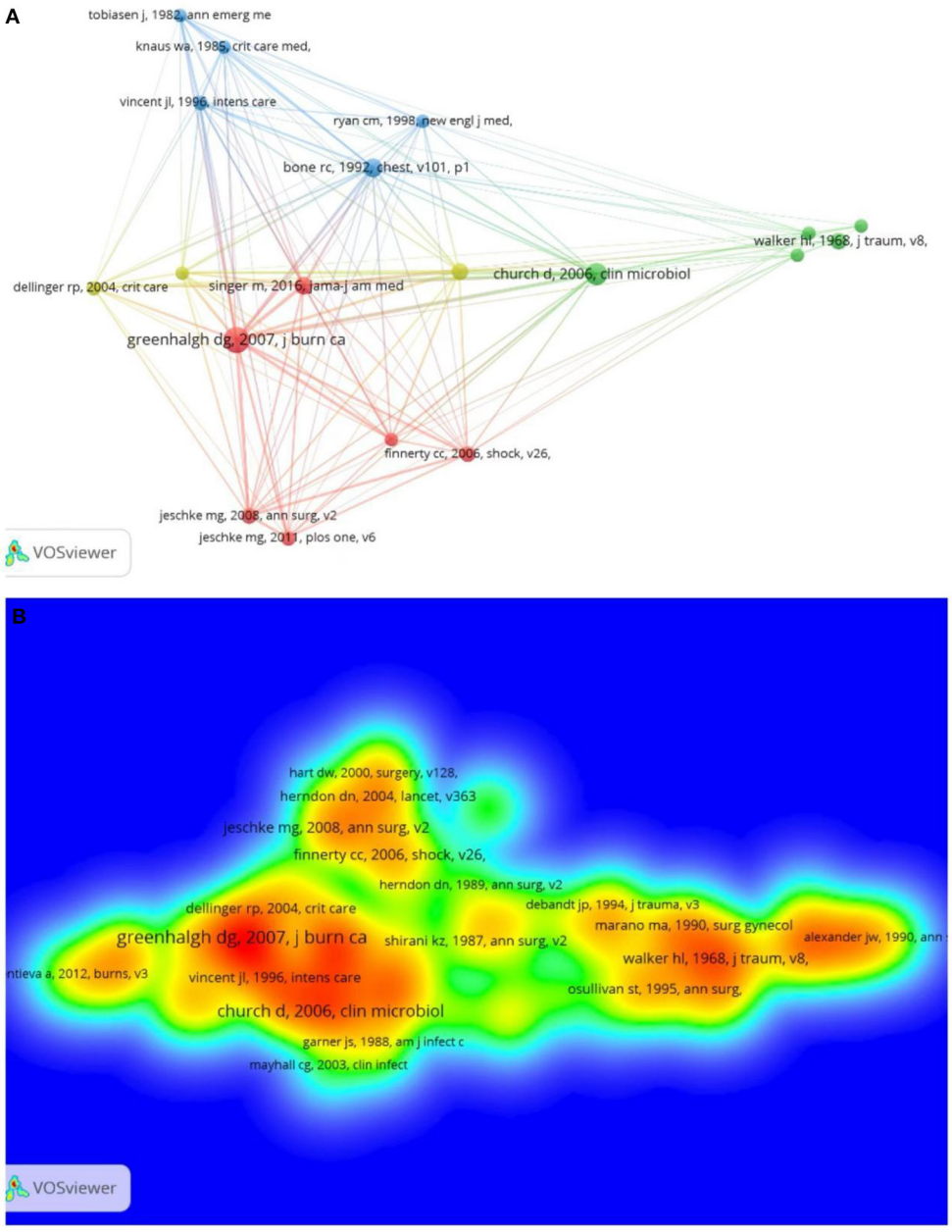

FIGURE 5
(A) Analysis of the co-citation network of cited references: the node's size indicates the frequency of occurrence; the larger the node, the higher the number of references cited. **(B)** Visual analysis of the density of the cited references: the color represents the density of the cited literature. Red indicates a higher frequency of occurrence, while green indicates a lower frequency of occurrence.

published in the field involving burn sepsis. Therefore, it suggests that future developments in this field may be presented in the journals mentioned above.

As for the authors, Herndon DN from the US and Jeschke MG from Canada published the top two articles on burn sepsis. Herndon DN focuses on clinical research on burn sepsis, including diagnostic criteria and treatment, and his papers have the highest total citation frequency in the list (14). In contrast, Jeschke MG evaluates the potential role of inflammation-related factors in burn sepsis and attempts to understand the pathophysiological response to burn sepsis (15). Herndon DN is a leader in exploring the field of burn sepsis research, and his impressive articles on burn sepsis have been cited extensively. They have made a remarkable contribution to the development of the field (16). In addition, a collaboration between different authors has been significant in studying sepsis

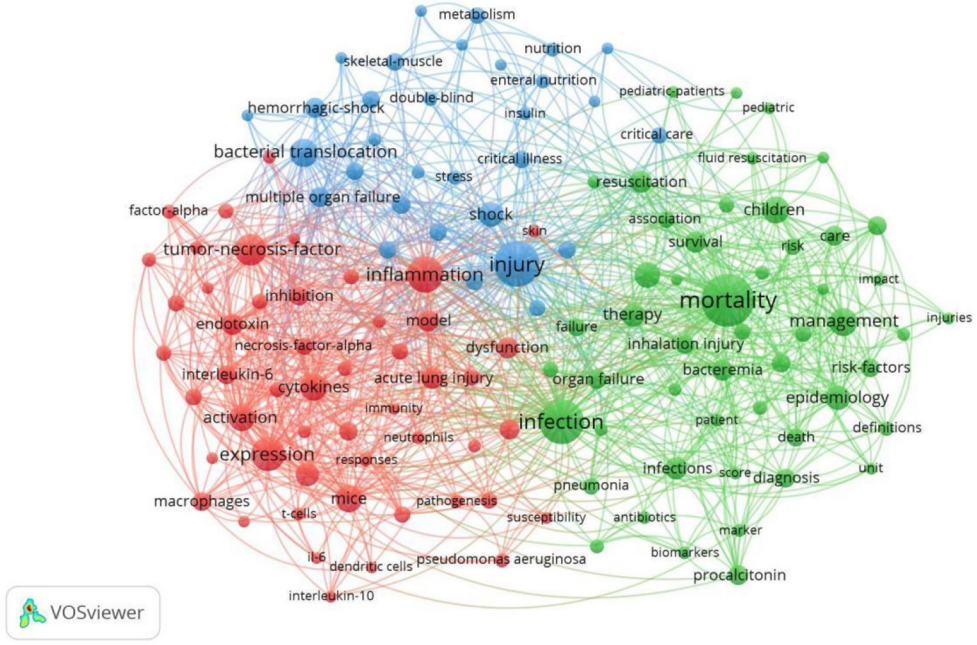

FIGURE 6
Bibliographic analysis of all keywords in co-occurrence references network map. Based on the relevance of keywords, it can be divided into three different color clusters: cluster one is red, cluster two is green, and cluster three is blue. The size of circles indicates the frequency of occurrence. The larger the nodes, the more frequently the keyword appeared.

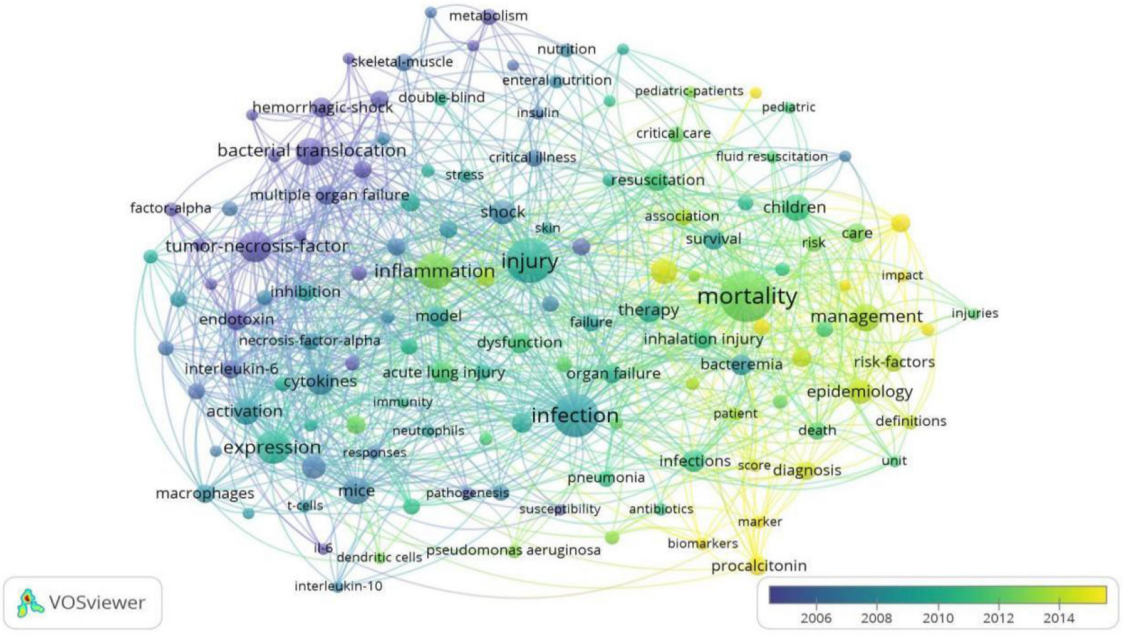

FIGURE 7
Overlay visualization. Keywords are distributed according to the average time of occurrence. Blue represents the early keywords, and yellow represents the most recent ones. The smaller the distance between two keywords, the more frequently the keywords appear in the same literature simultaneously.

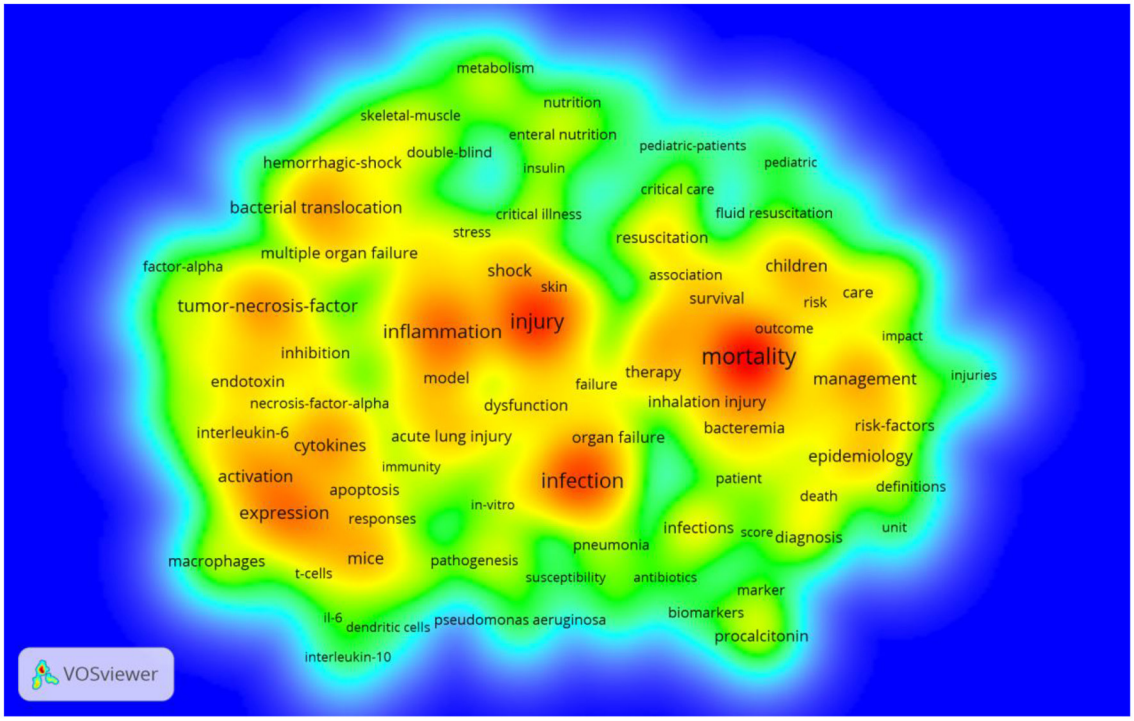

FIGURE 8
Bibliographic analysis of all keywords in density visualization map. The color represents the density of the keyword. Red represents a more frequent appearance, and green represents a less frequent appearance.

and burns. For example, Herndon DN and Jeschke MG, Wolf SE, and Herndon DN have collaborated on research, showing close cooperation between authors and institutions. We believe that these investigators may play a unique and integral role in burn sepsis research, broadly influencing future developments and predicted hot spots in the field.

Research focuses on burn sepsis

The keyword analysis revealed that most studies in this area were clinical studies, closely followed by basic research on inflammation-related factors. Also, as revealed in the analysis of the cited literature, research has focused on the diagnostic criteria for burn sepsis and its pathophysiological mechanisms. In addition, it began with a consensus conference held by the American College of Chest Physicians and the Society of Critical Care Medicine in 1992 (17) to define sepsis, then progressed to the American Burn Association sepsis criteria (13) and finally to the third international consensus definition of sepsis and septic shock in 2016 (sepsis-3) (18). It is quite clear from these mainstream criteria that the gold standard for diagnosing burn sepsis is yet unclear.

The presence of infection in burn patients is one of the leading causes of sepsis, which in turn is the main cause of death in these patients. In fact, burns are associated with a cascade of events leading to sepsis and multiorgan dysfunction syndromes, such as hypovolemic states, immune and inflammatory reactions, and metabolic changes (19). The incidence of sepsis in burn patients may range from 3 to 30% if the burn area represents more than 20% of the total surface area (TBSA) (20). A more significant concern is that approximately 54% of burn-related deaths result from septic shock and MODS rather than osmotic shock and hypovolemia (21). Recent medical literature has reported that more than 60% of fatalities in burn patients were due to infectious complications and MODS, a direct consequence of sepsis and poor prognosis (22). As a result, early diagnosis and effective treatment of sepsis would benefit burn patients. Besides, mortality was our most frequently used keyword (Figures 7, 8). The most frequent and most popular cited literature is the American burn association consensus conference to define sepsis and infection in burns (Figures 5, 6).

As demonstrated in the mean year of publication analysis of keywords (Figure 8), the most recent research is directed toward clinical studies on "biomarkers" (cluster 2, APY was 2018.16). For promising biomarkers, the potential of some cytokines in the early diagnosis of sepsis after burns has recently been investigated (23). Second, Procalcitonin has been widely studied and clinically applied as a popular biomarker

in bacterial infections and sepsis (24). There is growing evidence that presepsin (sCD14-ST) is a promising biomarker for diagnosing sepsis in burn patients. However, it cannot be used alone to confirm or exclude the presence of sepsis in burn patients (25). Mid-regional pro-atrial natriuretic peptide is another promising biomarker (26). In addition, Hampson et al. found that neutrophil function, immature granulocyte counts, and plasma cell-free DNA levels have significant potential in the early diagnosis of sepsis in burn patients (27). It is particularly interesting to observe that miRNA can also be used as a diagnostic biomarker (28). However, no single biomarker can diagnose post-burn sepsis alone, and its values must be interpreted cautiously to ensure an accurate diagnosis.

The heterogeneity of burn patients should be fully considered in the clinical management of sepsis in burn patients (13). Much is known about the pathophysiology of sepsis, which is generally considered an extreme response to inflammation (29). However, burn sepsis has its unique pathogenesis (30), mainly including the following aspects: 1. post-burn infection (trauma infection, inhalation injury, etc.) (31), 2. intestinal flora/endotoxin translocation (32), 3. hypermetabolic state (33), 4. immune dysfunction (34), 5. Other factors include stress response to the neuroendocrine system, coagulation dysfunction, and damage to vital tissues and organs (35). These pathophysiological reactions synergistically induce the development and progression of sepsis and MODS. Accordingly, sepsis treatment in burn patients (36) is broadly divided into the following aspects: 1. fluid resuscitation (37), 2. anti-infection treatment surgical removal of traumatic necrotic tissue, etc. (31, 36), 3. renal replacement therapy (38), 4. immune conditioning strategies (39), 5. adjuvant support and symptomatic treatment, which includes correction of hyperglycemia and electrolyte disorders according to the patient's status; early enteral or parenteral nutrition and reasonable nutritional support; cautious application of glucocorticoids to avoid infection aggravation; and strengthening of adjuvant support therapy for vital organ functions to prevent the occurrence and development of MODS, etc. (40). The diversity of pathogenesis and the lack of recognized diagnostic criteria have prevented the timely and effective treatment of burn sepsis patients. Therefore, based on the massive collection of sepsis patient data, the optimal diagnosis and prognosis prediction model based on different algorithms analyzing patient genetic characteristics, disease history, life history, clinical manifestations, biochemical indicators, treatment response, and so on is the foundation for achieving proper treatment of sepsis in the future (41). The current diagnosis and treatment process for burn sepsis varies between hospitals worldwide, so it is critical to establish a database. Based on establishing a standardized database, bioinformatics professionals with clinical work experience and scientific research ability are required to continuously analyze and revise big data to propose more accurate diagnostic criteria and assessment systems for burn sepsis to truly realize an accurate and intelligent diagnosis and treatment. Therefore, clear diagnostic criteria and predictive biomarkers are essential in preventing and treating burn sepsis. In this regard, establishing a predictive model for early diagnosis, prognosis, and precise treatment of burn sepsis using some reliable indicators (burn area, biomarkers, etc.) may be a hot spot for future research in this field.

Advantages and limitations

The publications on burn sepsis evaluated in this study were extracted from the Science Citation Index Extended Journals Web of Science database. The data analysis is relatively comprehensive and objective. Nevertheless, some limitations are unavoidable. Due to our inclusion criteria, we only registered publications in English in this survey. Therefore, important studies on burn sepsis research in non-English languages may have been omitted and excluded from the database and analysis. Furthermore, more detailed areas on burn sepsis were not analyzed.

Conclusion

This study summarized the global research trends regarding burn sepsis over time. The US had made the most significant contribution. Although there are many publications from China, the quality of these papers requires further improvement. The latest research and new developments can be found in Burns and Burn Care Research. Herndon DN, Jeschke MG, Gamelli RL, Horton JW, Wolf SE, and Sheng ZY are good candidates for academic collaboration in this field. Clinically relevant research in burn sepsis has become a hot topic recently, especially in using biomarkers for early diagnosis and prognosis and providing a precise treatment plan.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary material.

Author contributions

ZC and YZ co-designed this study, conducted the data collection, and wrote the manuscript. J-HL and W-QL participated in the analysis and generated the graphs. XC and J-HZ critically reviewed the original manuscript. All authors have read and approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.971393/full#supplementary-material

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Incidence, risk factors and clinical outcomes of septic acute renal injury in cancer patients with sepsis admitted to the ICU: A retrospective study

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Background: The purpose of this study was to clarify the incidence, risk factors, and clinical outcomes of septic acute kidney injury (AKI) in cancer patients with sepsis admitted to the intensive care unit (ICU).

Methods: A total of 356 cancer patients admitted to the ICU due to sepsis from January 2016 to October 2021 were analyzed retrospectively. According to the incidence of septic AKI, all patients were divided into the non-AKI group (n = 279) and the AKI group (n = 77). The clinical data after ICU admission were compared between the above two groups, and the risk factors and the clinical outcomes of septic AKI in the ICU were identified.

Results: The incidence of septic AKI in all patients was 21.6% (77/356). LASSO regression and logistic regression all showed that lactate, sequential organ failure assessment (SOFA) score and septic shock were closely related to the occurrence of septic AKI. In terms of clinical outcomes after ICU admission, the rate of mechanical ventilation (MV) and continuous renal replacement therapy (CRRT), MV time, hospitalization time and 28-day mortality in the ICU were significantly higher in the septic AKI group than in the non-septic AKI group. Among the three subgroups of septic AKI (AKI combined with septic shock, septic cardiac dysfunction or acute respiratory failure), the mortality of patients in the subgroup of AKI combined with septic shock was significantly higher than others. CRRT has no significant effect on the short-term outcome of these patients.

Conclusion: Lactate level, SOFA score and septic shock were closely related to the occurrence of septic AKI in the ICU. The clinical outcomes within 28 days

after ICU admission of cancer patients with septic AKI were worse than those without septic AKI. The short-term outcome was worse in patients with septic AKI complicated with septic shock. CRRT does not have any significant effect on the short-term prognosis of cancer patients with septic AKI in the ICU.

KEYWORDS

cancer, sepsis, acute kidney injury, risk factor, outcome

Introduction

Acute kidney injury is considered as one of the serious comorbidities in critically ill patients. AKI may have higher short-term and long-term mortality, and the use of medical resources is considerably increased. AKI is characterized by a sudden decrease in glomerular filtration rate (GFR), resulting in the accumulation of nitrogenous waste and the inability to maintain the homeostasis of body fluids and electrolytes (1). Although there is not any clear causal relationship between AKI and chronic kidney disease (CKD), the AKI non-intervention group may increase the risk of CKD (2). Patients with AKI are the most likely to suffer from accelerated loss of renal function and progress to CKD than patients without AKI with all else being equal (3). CRRT is an effective treatment for AKI, but it does not reduce long-term mortality of AKI or the risk of CKD (4). Even if AKI patients return to normal kidney function after discharge from the hospital, there is still a risk of adverse kidney events for up to 10 years (5). In addition, a meta-analysis suggests that the duration of AKI is independently related to long-term mortality, cardiovascular events and the development incident CKD of stage 3 (6). Considering the above situation, AKI should be given full attention and early disposal.

The most common cause of AKI in critically ill patients is sepsis. Cohort studies indicate that the incidence of septic AKI ranges from 19 to 48%, while the mortality of patients with septic AKI fluctuates from 22 to 70% (7, 8). The pathophysiology of septic AKI is still not fully appreciated. Traditionally, it is believed that septic AKI is mainly caused by global renal ischemia and hypoperfusion, septic endotoxin-mediated cell damage, and renal tubular necrosis (9). However, other studies suggest that septic AKI is a bioenergy adaptive response of the body to microcirculation dysfunction and inflammation caused by sepsis, which has no significant correlation with the existence of systemic hypoperfusion or the severity of sepsis (10–12).

Abbreviations: ICU, intensive care unit; AKI, acute kidney injury; SOFA, sequential organ failure assessment; MV, mechanical ventilation; CRRT, continuous renal replacement therapy; CKD, chronic kidney disease; GFR, glomerular filtration rate; KIDGO, kidney disease improving global outcomes; SCD, septic cardiac dysfunction; ARF, acute respiratory failure; PCT, procalcitonin; cTnI, cardiac troponin I; BNP, brain natriuretic peptide.

Because the immune system of cancer patients with sepsis cannot cope with the initial injury, pathogen invasion emerged on the basis of malignant cell transformation. Compared with non-cancer patients, cancer patients with sepsis had a 2.5-fold higher in-hospital mortality rate due to sepsis. Cancer patients with sepsis have a worse prognosis (13, 14). Therefore, there may be a great proportion of septic AKI in cancer patients with sepsis. This retrospective study aimed at the precise population of cancer patients with sepsis to clarify the incidence, risk factors and short-term clinical outcomes of septic AKI after ICU admission to guide clinical intervention and judge prognosis.

Materials and methods

Participants

The study complies with the Declaration of Helsinki and was approved by the Ethics Committee of Peking University Cancer Hospital(ethics approval number 2020KT33), and all patients provided written informed consent for the treatment of sepsis and related scientific research purposes A total of 356 cancer patients with sepsis were retrospectively screened out of 3,362 patients admitted to the ICU in Peking University Cancer Hospital from January 2016 to October 2021, according to the inclusion criteria. Inclusion criteria: (1). Patients with sepsis aged >18 years; (2). Diagnosis satisfying the definition of sepsis 3.0. Exclusion criteria: (1). CKD stage 3 and above; (2). After kidney transplantation; (3). Incomplete clinical data. All the included patients were divided into the non-AKI group ($n = 279$) and the AKI group ($n = 77$) in terms of the occurrence of septic AKI (**Figure 1**).

The diagnosis of septic AKI: (1). Clinical judgment of AKI has a positive correlation with sepsis; (2). AKI refers to the definition and diagnostic criteria from kidney disease improving global outcomes (KIDGO) in 2012.

Data collection

Demographic characteristics and baseline data [including sex, age, body mass index (BMI), cancer types, cancer treatment,

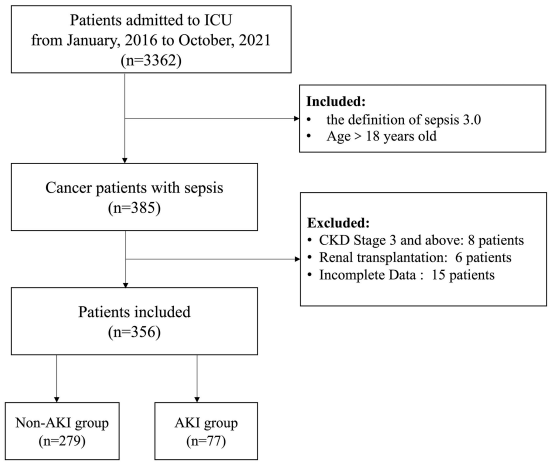

FIGURE 1
Flow chart of the research scheme.

TABLE 1 Demographic data and characteristics of the two groups.

	Non-AKI group (n = 279)	AKI group (n = 77)	P-value
Sex, male	205 (73.4%)	57 (74.0%)	0.832
Age (year)	63.9 ± 9.8	61.9 ± 12.3	0.206
BMI (kg/m^2)	22.8 ± 5.1	23.7 ± 7.0	0.195
Cancer types			0.002
Lung	29 (10.4%)	7 (9.1%)	
Digestive system	202 (72.4%)	42 (54.5%)	
Retroperitoneum	18 (6.5%)	13 (16.9%)	
Uria	4 (1.4%)	7 (9.1%)	
Bone and soft tissue	2 (0.7%)	1 (1.3%)	
Gynecology	9 (3.2%)	3 (3.9%)	
Breast	4 (1.4%)	1 (1.3%)	
Lymphoma	4 (1.4%)	1 (1.1%)	
Melanoma	3 (1.0%)	1 (1.3%)	
Others	4 (1.4%)	1 (1.1%)	
Cancer treatment			
Surgery	186 (66.7%)	47 (61.0%)	0.358
Chemotherapy	106 (38.0%)	34 (44.2%)	0.327
Radiotherapy	37 (13.3%)	11 (14.3%)	0.816
Targeted therapy	53 (19.0%)	16 (20.8%)	0.726
Immunotherapy	34 (12.2%)	12 (15.6%)	0.431
Chronic diseases			
Hypertension	63 (22.6%)	20 (26.0%)	0.533
Diabetes	49 (17.6%)	13 (16.9%)	0.889
Coronary heart disease	43 (15.4%)	7 (9.1%)	0.158
COPD	32 (11.5%)	7 (9.1%)	0.489
Cerebrovascular disease	25 (9.0%)	6 (7.8%)	0.748

AKI, acute kidney injury; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

TABLE 2 Infectious data and laboratory data of the two groups after ICU admission.

	Non-AKI group (n = 279)	AKI group (n = 77)	P-value
Infection category			0.620
Respiratory	92 (32.9%)	21 (27.2%)	
Gastrointestinal	20 (7.1%)	8 (10.3%)	
Abdominal cavity	129 (46.2%)	39 (50.6%)	
Thoracic cavity	27 (9.7%)	6 (7.8%)	
CLABSI	3 (1.1%)	1 (1.2%)	
Genitourinary	5 (1.8%)	1 (1.3%)	
Others	3 (1.1%)	1 (1.3%)	
Organism			0.712
Gram negative	89 (31.9%)	23 (29.9%)	
Gram positive	41 (14.7%)	13 (16.8%)	
Fungi	27 (9.7%)	8 (10.4%)	
Two or more	56 (20.1%)	16 (20.8%)	
Laboratory examination			
Leukocyte (10^9/L)	9.6 ± 5.5	8.9 ± 7.0	0.691
Neutrophil (10^9/L)	7.6 (4.9–10.7)	6.8 (3.5–11.0)	0.442
Lymphocyte (10^9/L)	0.5 (0.3–1.0)	0.5 (0.2–0.8)	0.420
NLR	14.9 (7.9–20.5)	13.0 (6.8–22.0)	0.918
Creatine (μmol/L)	66.3 ± 15.5	147.8 ± 73.9	0.032
Albumin (g/L)	31.9 ± 4.8	31.3 ± 3.6	0.280
Lactate (mmol/L)	2.4 ± 1.5	4.3 ± 3.5	0.002
PCT (ng/mL)	10.3 ± 23.9	39.6 ± 74.4	0.001
BNP (pg/mL)	550.7 ± 704.2	913.5 ± 1046.1	0.005
cTnI (ng/mL)	0.03 (0.01–0.14)	0.08 (0.03–0.31)	0.106
Severity of illness			
SOFA score	6.0 (5.0–9.0)	10.0 (7.0–14.0)	0.001

CLABSI, central line associated blood stream infection; NLR, neutrophil-to-lymphocyte ratio; PCT, procalcitonin; BNP, brain natriuretic peptide; cTnI, cardiac troponin I.

TABLE 3 Other complications between the two groups.

Other complications	Non-AKI group (n = 279)	AKI group (n = 77)	P-value
Septic shock	99 (35.5%)	57 (74.0%)	0.001
SCD[#]	40/166 (24.1%)	29/61 (47.5%)	0.001
ARF	126 (45.2%)	45 (58.4%)	0.041

SCD, septic cardiac dysfunction; ARF, acute respiratory failure. [#]227 patients (166 patients in the non-AKI group and 61 patients in the AKI group) underwent bedside echocardiography.

chronic diseases], infection site and etiological data, some laboratory test results within 24 h after ICU admission, the first SOFA scores, and other complications related to sepsis, including septic shock, septic cardiac dysfunction (SCD), and acute respiratory failure (ARF), were collected from all the included patients. The short-term clinical outcomes of all patients in the ICU were recorded, including mechanical ventilation (MV), continuous renal replacement therapy

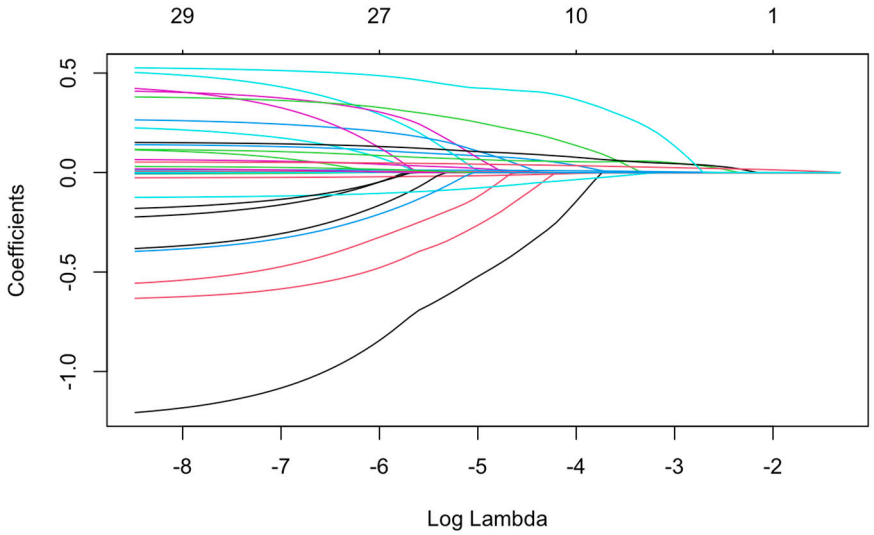

FIGURE 2
All variables were screened with LASSO regression.

(CRRT), MV time, length of stay in the ICU and 28-day mortality in the ICU.

Statistics

SPSS 26.0 (Armonk, NY: IBM) and R language (version 4.1.2, involving software packages such as *"survival," "surviviner," "glmnet," "pROC"*) were used for statistical analysis. Continuous variables with normal distributions were expressed as means ± SD; otherwise, they were expressed as medians (IRQ). Categorical data were expressed as numbers (proportions). categorical variables were reported as frequency or percentage (%). Continuous variables with a normal distribution were compared by unpaired independent t test, continuous variables with a skewed distribution were compared by the Mann–Whitney U test, and the classified data were compared using the $\chi 2$ test or Fisher's exact probability method. Logistic regression and LASSO regression were utilized to compare and screen out the significant risk factors of septic AKI. The number of septic AKI related variables of non-zero parameters was controlled by adjusting the Lambda(λ) value in the LASSO regression. 1se (the dashed line on the right side) was taken as a reference, the method of ten-fold cross-validation was utilized to obtain the minimum number of variables for the optimal model. The Kaplan–Meier method was used to analyze the short-term clinical prognosis of patients with septic AKI. The ROC curve was used to determine the predictive value of relevant risk factors for septic acute renal injury. Bivariate correlation analysis is applied to the comparison of critical variables. For all the above tests, a two-tailed $P < 0.05$ was regarded as statistically significant.

Results

1. Occurrence of sepsis-related AKI among different cancer types: After being regrouped, septic patients with retroperitoneal cancers and urinary cancers were more likely to suffer from septic AKI ($P = 0.002$) (Table 1).
2. Comparison of variables with statistical differences between the two groups of patients: There were significant

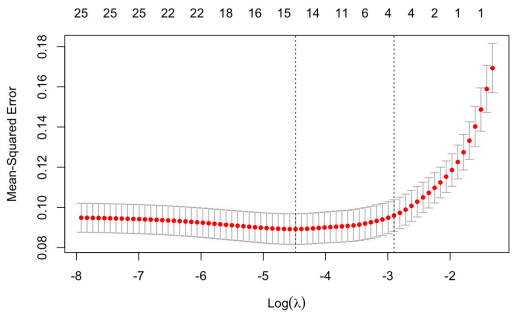

FIGURE 3
Important variables identified with ten-fold cross-validation.

TABLE 4 Multivariate analysis with logistic regression in the two groups.

Variables	*B*	Wald	*P*-value	OR	95% CI
Lactate	0.228	10.095	0.001	1.256	1.091–1.446
SOFA score	0.164	18.781	0.001	1.179	1.094–1.270
Septic shock	0.849	6.778	0.009	2.338	1.234–4.430

SOFA, sequential organ failure assessment.

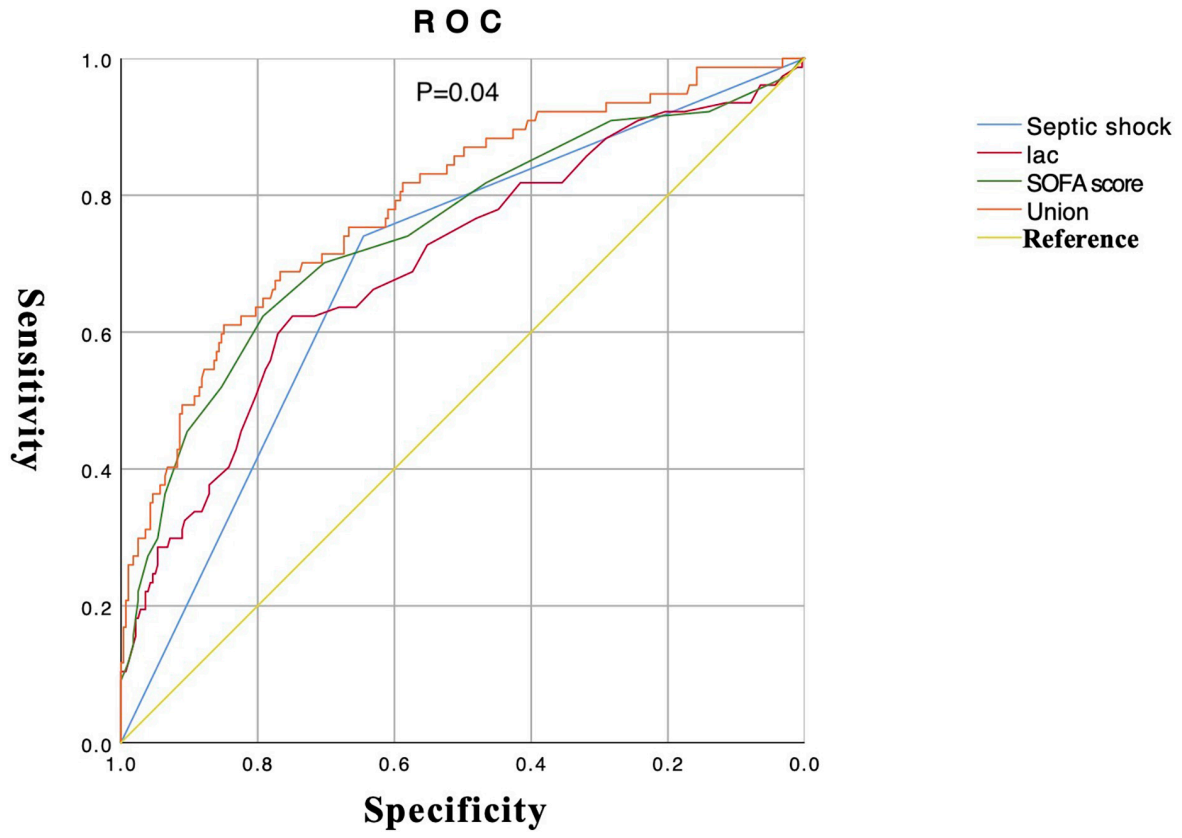

FIGURE 4
Drawing of multivariable ROC curve.

differences in creatinine, lactate, procalcitonin (PCT), brain natriuretic peptide (BNP), and SOFA scores after ICU admission between the septic AKI group and the non-septic AKI group (P = 0.032, P = 0.002, P = 0.001, P = 0.005, P = 0.001) (Table 2).

3. Comparison of sepsis-related complications between the two groups: Sepsis-related complications (septic shock, SCD and ARF) were more likely to occur in the septic AKI group than in the non-septic AKI group (P = 0.001, P = 0.001, P = 0.041) (Table 3).

TABLE 5 Clinical outcomes with the two groups.

	Non-AKI group (n = 279)	AKI group (n = 77)	P-value
MV	119 (42.7%)	47 (61.0%)	0.004
CRRT	1 (0.3%)	24 (31.2%)	0.001
ICU MV-time(day)	3.0 ± 5.4	5.4 ± 6.9	0.006
ICU stay-time(day)	7.3 ± 5.1	11.7 ± 12.9	0.004
The 28-day mortality	23 (8.2%)	37 (48.1%)	0.001

MV, mechanical ventilation; CRRT, continuous renal replacement therapy; ICU, intensive care unit.

4. LASSO regression was used to screen the important risk factors of septic AKI: All the variables in Tables 1–3 were screened with LASSO regression for avoiding overfitting the data in order to improve accuracy (Figures 2, 3). These important variables including lactate, SOFA score, septic shock, and PCT were strongly associated with septic AKI.
5. Independent risk factors of septic AKI were screened out by multivariate analysis of Logistic regression: Lactate, SOFA score and septic shock (variables from Tables 1, 3) were closely related to septic AKI, and these three variables were independent risk factors for septic AKI (P = 0.001, P = 0.001, P = 0.009) (Table 4).
6. The drawing of ROC about important variables that affect the occurrence of septic AKI: Lactate, SOFA score, and septic shock were screened out with the intersection of Wayne diagram adopted from the combination of Lasso regression and logistic regression. The union ROC (lactate combined with SOFA score and septic shock) showed that the performance in predicting septic AKI (AUC 0.79, 95% CI 0.73–0.85) is better than the predictive performance of each variable (septic shock, AUC 0.69, 95% CI 0.63–0.76; lactate, AUC 0.70, 95% CI 0.63–0.77; SOFA sore, AUC 0.74, 95% CI 0.67–0.81)

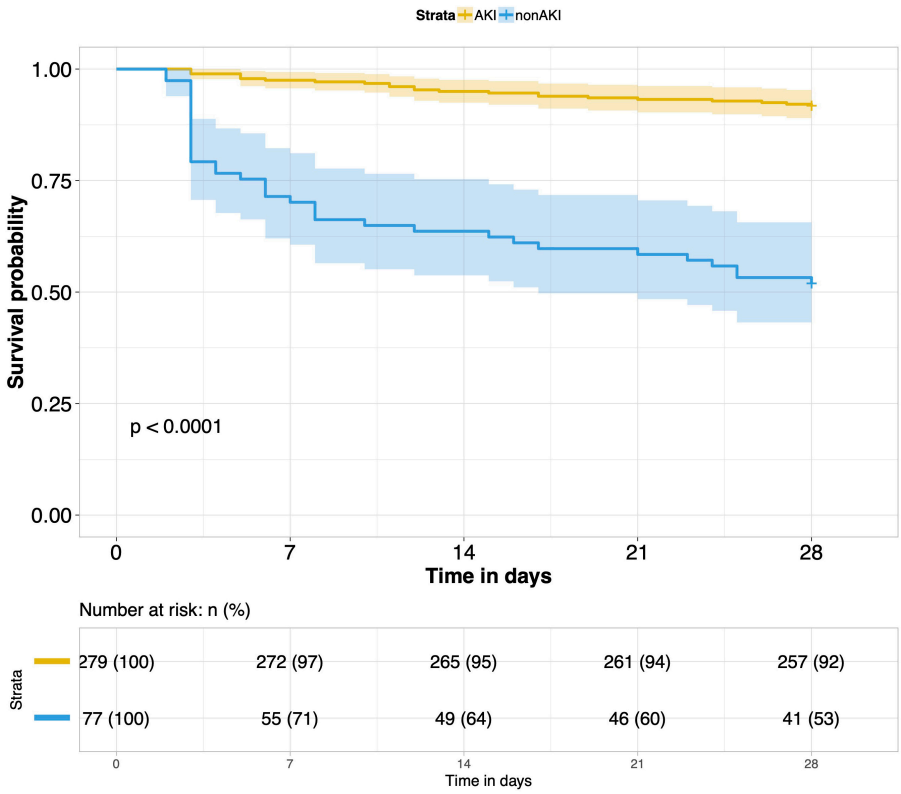

FIGURE 5
Survival analysis of septic acute kidney injury (AKI) group and non-septic AKI group.

(P = 0.04) (Figure 4). Bivariate correlation analysis of these three variables showed that there was a positive correlation between septic shock and lactate ($P < 0.001$, r = 0.330), a positive correlation between septic shock and SOFA score ($P < 0.001$, r = 0.413), and a positive correlation between lactate and SOFA score ($P < 0.001$, r = 0.378).

7. Comparison of the difference on the short-term clinical outcome between two groups: In terms of short-term clinical outcomes, patients with septic AKI had higher rates of MV and CRRT, longer durations of MV-time and ICU stay-time, and higher 28-day mortality in the ICU (P = 0.004, P = 0.001, P = 0.006, P = 0.004, P = 0.001) (Table 5).
8. Comparison of 28-day survival rates in the two groups and in multiple subgroups of sepsis AKI: The 28-day survival rate of patients with septic AKI was significantly lower than that of patients with non-septic AKI within 28 days after ICU admission ($P < 0.001$) (Figure 5). In the three subgroups of septic AKI (septic AKI combined with septic shock, septic cardiac dysfunction or acute respiratory failure), the 28-day survival rate of septic AKI combined with septic shock decreased significantly (P = 0.005) (Figure 6); However, there was no significant difference in the other two subgroups of patients (P = 0.07, P = 0.34) (Figures 7, 8).
9. Effects of CRRT treatment on the short-term prognosis of septic AKI patients: According to whether CRRT was performed in the ICU, patients with septic AKI were divided into the CRRT group and the non-CRRT group. There was not any significant difference in the 28-day outcome of the two groups. CRRT had no meaningful effect on the short-term prognosis of septic AKI patients (P = 0.19) (Figure 9).

Discussion

Septic AKI is a life-threatening complication characterized by an abrupt deterioration in renal function, manifested as elevated serum creatinine levels, oliguria, or both. It closely relates to infection or sepsis. Septic AKI is one of the earliest focal manifestations in patients with sepsis. Current estimates suggest that septic AKI affects 10–67% of patients with sepsis (8, 15). However, more than two-thirds of patients with septic shock

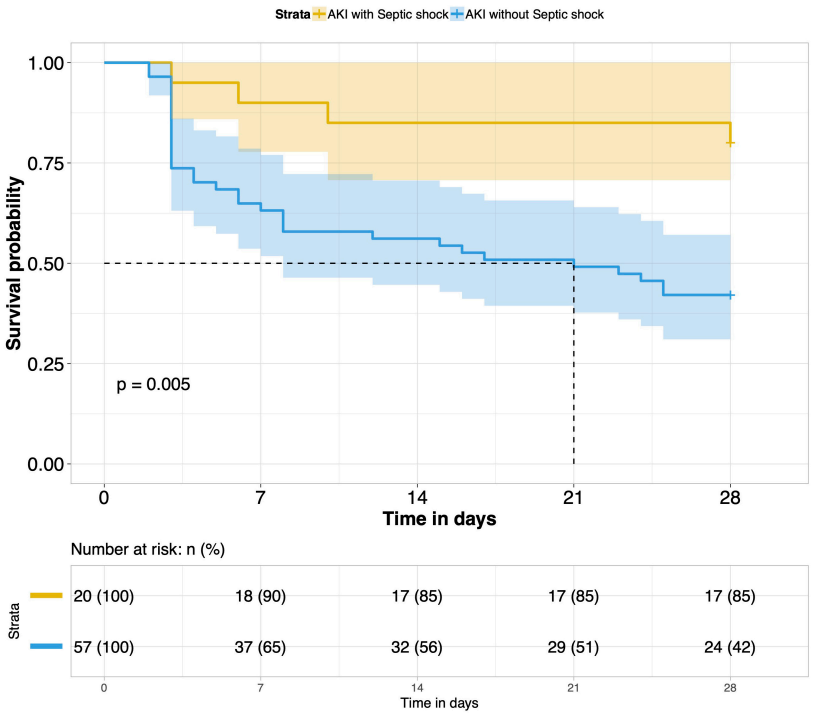

FIGURE 6
Survival analysis of AKI with septic shock group and AKI without septic shock group.

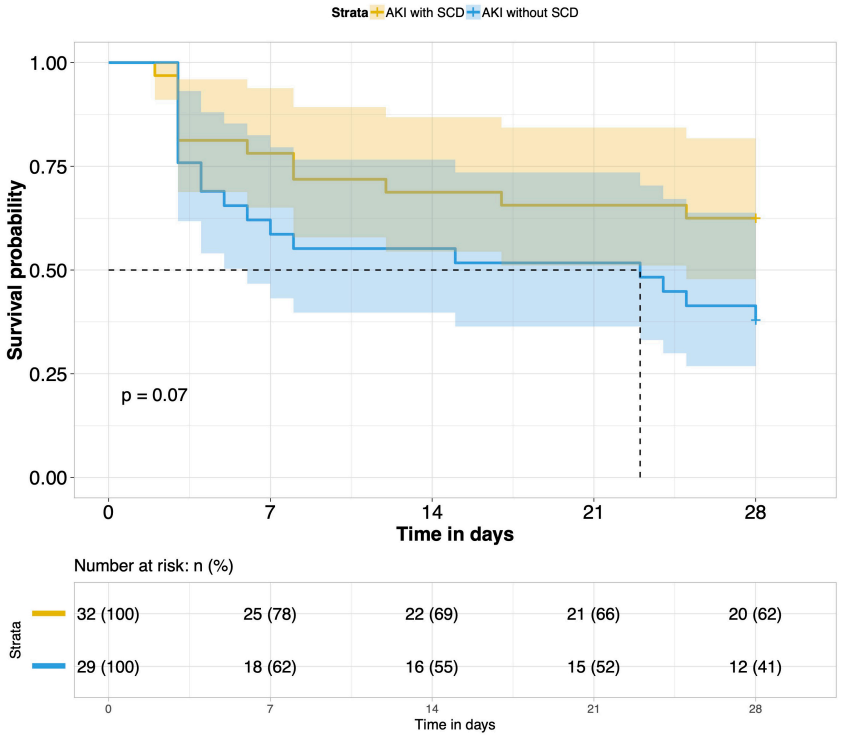

FIGURE 7
Survival analysis of AKI with SCD group and AKI without SCD group (61 of 77 patients underwent bedside echocardiography).

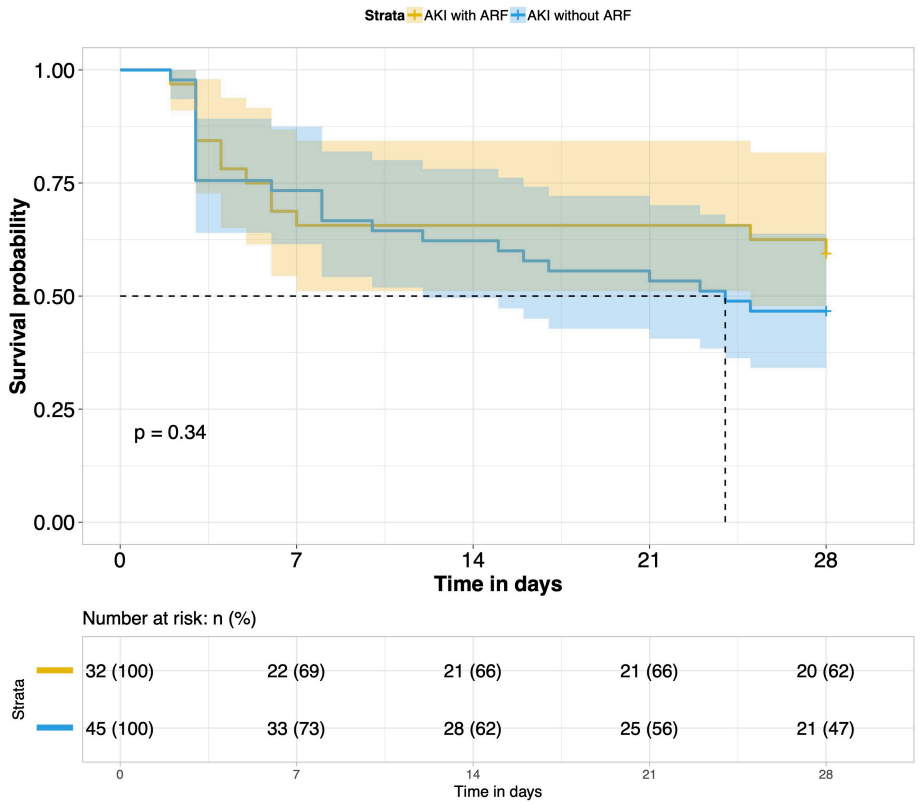

FIGURE 8
Survival analysis of AKI with ARF group and AKI without ARF group.

may be complicated with septic AKI (16). For unexplained AKI, the possibility of sepsis should be examined first. Cancer patients are more likely to suffer from sepsis and have a significantly higher mortality rate due to sepsis than non-cancer patients (14). Our study aimed to understand the related factors of septic AKI in cancer patients with sepsis and is used as a basis for the prevention, treatment and renal function recovery of septic AKI for this population.

We found that there may be a definite relationship between septic AKI and cancer type. Regroup analysis showed that sepsis patients with retroperitoneal and urinary tumors were more vulnerable to septic AKI. For the two types of cancer patients, we analyzed the reasons. The mechanism of retroperitoneal and urinary tumors with septic acute kidney injury may include the following: Firstly, the tumor has oppressed or invaded the urinary system, causing local obstruction or postrenal obstruction, resulting in impaired renal function. Secondly, most patients with retroperitoneal and urinary tumors have undergone surgery, and there is a risk of low organ perfusion during the operation. Some patients may undergo single nephrectomy, and patients may be complicated with abdominal infection, paralytic intestinal obstruction, intra-abdominal hypertension after surgery (17). In addition, tumor-related thrombotic microvascular disease and septic coagulation dysfunction may affect the kidneys, resulting in acute kidney damage caused by renal microvascular thrombosis with endothelial swelling and microvascular obstruction (18). All of the above related factors may significantly increase the probability of septic AKI in these cancer patients. However, it was not found that the two types of cancers were closely related to the occurrence of septic AKI in the septic patients with the two types of cancers were included in the multivariate analysis.

Our study also concluded that lactate, SOFA score and septic shock were closely related to the occurrence of septic AKI with LASSO regression and Logistic regression. Serum lactate levels in the septic AKI group were significantly higher than those in the non-septic AKI group. The serum lactate level is a sensitive but non-specific indicator of metabolic stress (19). As a product of anaerobic glycolysis, lactate is markedly elevated in settings of hypoxia, stress, and critical illness (20). Most studies have demonstrated that high levels of lactate are significantly positively correlated with sepsis mortality, and the higher the lactate level is, the worse the prognosis of sepsis (21, 22). Hyperlactatemia is a significant manifestation of increasing tissue anaerobic metabolism in patients with sepsis. It is regarded as a sensitive marker of systemic or local organ tissue hypoperfusion (23). Based on the above studies, it is reasonable to believe that elevated lactate levels can predict

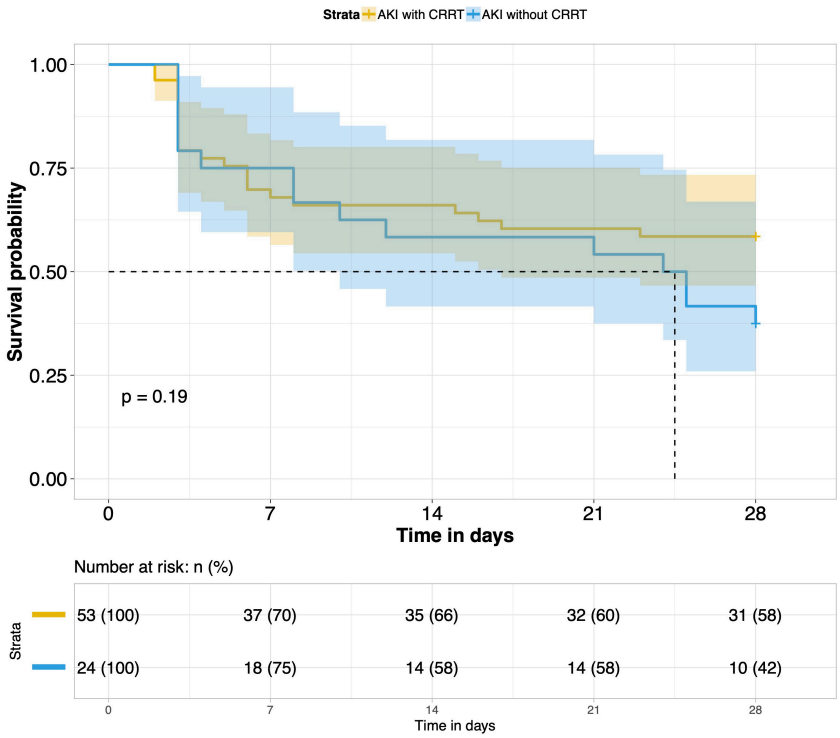

FIGURE 9
Survival analysis of AKI with CRRT and AKI without CRRT.

renal hypoperfusion, which may eventually progress to AKI. SOFA score in the septic AKI group was also significantly higher than that in the non-septic AKI group. The SOFA score is a key component of the third edition of the definition of sepsis. Clinical diagnosis of infection and SOFA $\geq$ 2 points can be considered as the definition of sepsis (24). The higher the SOFA score, the more severe organ dysfunction due to sepsis. In our study, the differences in SOFA score between the two groups were consistent with the short-term prognosis, which suggested that the higher the SOFA score, the more severe the illness and the worse the prognosis. Studies have demonstrated that there is a good correlation between the SOFA score and lactate level. The higher the SOFA score is, the higher the lactate level in serum, both of which are signals of increased organ dysfunction and suggest the need for urgent medical intervention (25). We also found that the proportion of patients with septic shock in the septic AKI group was considerably higher than that in the non-septic AKI group. This indicated that septic shock was closely related to the occurrence of septic AKI, which was an independent risk factor for septic AKI. Septic shock leads to systemic hypotension and hypoperfusion of multiple organs, including kidney hypoperfusion. In addition, studies have shown that septic shock may lead to dysfunction of the renal vascular bed, leading to a dramatic decrease in GFR and the development of septic AKI (26). Finally, we carried out a bivariate correlation analysis of these three variables, which showed a significant positive correlation among these variables ($P < 0.001$). This result shows that septic shock may have higher levels of blood lactate, and both of which are positively correlated with the severity of the disease, that is, SOFA score.

In our study, rates of MV and CRRT for the septic AKI group were significantly higher than those of the non-septic AKI group, and the MV time and the ICU stay time were also significantly prolonged. There was a major difference in the 28-day mortality between the above two groups. The 28-day mortality was also significantly increased when septic AKI was combined with septic shock. We compared the effect of CRRT on the prognosis of patients with septic AKI. CRRT cannot prolong the short-term survival time of patients with septic AKI, so CRRT did not improve the short-term prognosis of septic AKI. These conclusions are in agreement with most studies (27, 28).

Our study on septic AKI is of definite clinical significance. Firstly, the group of this study focused on cancer patients with sepsis, and we found that septic cancer patients of retroperitoneal and urinary tumors were more likely to have septic AKI. The group studied and this conclusion are not common in previous studies. Secondly, we screened out three variables with the intersection of Wayne diagram adopted from the combination of Lasso regression and logistic regression. The prediction of the combined ROC based on the three variables

for the occurrence of septic AKI has good performance. Later, it can be modeled and verified after increasing the sample size. If the predictive ability of the model is reliable, it can be adopted in clinical application to judge the prognosis of septic AKI at an early stage. Finally, we understand that if cancer patients with sepsis have septic AKI at the same time, the short-term outcome will be poor, and CRRT cannot effectively improve the prognosis. The above aspects are helpful for us to understand the risk factors of septic AKI in cancer patients with sepsis, which play a good reference role in the diagnosis, treatment, and prognosis of septic AKI in cancer patients.

However, our study has its limitations. Firstly, this study was a retrospective study, and our data were taken from single-center studies, so the incidence and severity of septic AKI may be biased. Secondly, for all patients with septic AKI, we focused on the short-term outcomes within 28 days after ICU admission and lacked 90-day or longer follow-up data on cancer patients with sepsis. The lack of awareness of the long-term survival and physical and mental health of patients with sepsis is also something that needs to be improved in future research. In addition, in view of the small number of CRRT treatments, a total of 24 cases, we did not conduct a subgroup analysis, but only to explore the overall prognostic differences. If patients with septic AKI were graded to different subgroups according to the KIDGO criteria, and the prognostic value of CRRT in each subgroup is compared, different results may be obtained, which also represents one of the limitations of this study.

Conclusion

Lactate level, SOFA score and septic shock were closely related to the occurrence of septic AKI in the ICU. The clinical outcomes within 28 days after ICU admission of cancer patients with septic AKI were worse than those without septic AKI. The short-term outcome was worse in patients with septic AKI complicated with septic shock. CRRT does not have any significant effect on the short-term prognosis of cancer patients with septic AKI in the ICU. This study was a preliminary exploration of the incidence, influencing factors and clinical outcomes of septic AKI in cancer patients with sepsis, which has certain guiding significance for the diagnosis, treatment and prognosis of septic AKI.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors for a reasonable purpose, without undue reservation.

Ethics statement

The study was approved by the Ethics Committee of Peking University Cancer Hospital and all patients provided written informed consent for the treatment of sepsis and related scientific research purposes.

Author contributions

YY and JD designed, analyzed, and drafted the manuscript. XC and RC collected and interpreted the patients' data. HW administered and revised the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Development and validation of risk-adjusted quality indicators for the long-term outcome of acute sepsis care in German hospitals based on health claims data

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Background: Methods for assessing long-term outcome quality of acute care for sepsis are lacking. We investigated a method for measuring long-term outcome quality based on health claims data in Germany.

Materials and methods: Analyses were based on data of the largest German health insurer, covering 32% of the population. Cases (aged 15 years and older) with ICD-10-codes for severe sepsis or septic shock according to sepsis-1-definitions hospitalized in 2014 were included. Short-term outcome was assessed by 90-day mortality; long-term outcome was assessed by a composite endpoint defined by 1-year mortality or increased dependency on chronic care. Risk factors were identified by logistic regressions with backward selection. Hierarchical generalized linear models were used to correct for clustering of cases in hospitals. Predictive validity of the models was assessed by internal validation using bootstrap-sampling. Risk-standardized mortality rates (RSMR) were calculated with and without reliability adjustment and their univariate and bivariate distributions were described.

Results: Among 35,552 included patients, 53.2% died within 90 days after admission; 39.8% of 90-day survivors died within the first year or had an increased dependency on chronic care. Both risk-models showed a sufficient predictive validity regarding discrimination [*AUC* = 0.748 (95% CI: 0.742; 0.752) for 90-day mortality; *AUC* = 0.675 (95% CI: 0.665; 0.685) for the 1-year composite outcome, respectively], calibration (Brier Score of 0.203 and 0.220;

calibration slope of 1.094 and 0.978), and explained variance (R^2 = 0.242 and R^2 = 0.111). Because of a small case-volume per hospital, applying reliability adjustment to the RSMR led to a great decrease in variability across hospitals [from median (1st quartile, 3rd quartile) 54.2% (44.3%, 65.5%) to 53.2% (50.7%, 55.9%) for 90-day mortality; from 39.2% (27.8%, 51.1%) to 39.9% (39.5%, 40.4%) for the 1-year composite endpoint]. There was no substantial correlation between the two endpoints at hospital level (observed rates: ρ = 0, p = 0.99; RSMR: ρ = 0.017, p = 0.56; reliability-adjusted RSMR: ρ = 0.067; p = 0.026).

Conclusion: Quality assurance and epidemiological surveillance of sepsis care should include indicators of long-term mortality and morbidity. Claims-based risk-adjustment models for quality indicators of acute sepsis care showed satisfactory predictive validity. To increase reliability of measurement, data sources should cover the full population and hospitals need to improve ICD-10-coding of sepsis.

KEYWORDS

sepsis, mortality, risk-adjustment, administrative claims, diagnosis related groups, health care quality assessment

1. Introduction

Sepsis is the final pathway to death from infectious diseases (1) and affects an estimated 49 million patients per year worldwide, of whom 11 million die (2). It is considered as one of the leading causes of preventable deaths in hospitals (3). One-sixth of sepsis survivors experience severe persistent physical disability or cognitive impairment, and one-third die during the following year after the acute disease (4). Acknowledging deficits of care, the World Health Assembly adopted the sepsis resolution WHA70.7 in May 2017, which urges WHO member states to improve prevention, diagnosis and management of sepsis (5).

Measuring and comparing performance of health care providers are a central part of quality improvement (6). For this purpose, administrative health data can be used for performance measurement with the advantage of covering all ICD-coded cases with data readily available, at minimal time and costs (7). Performance measures need to account for differences in the mix of important patient attributes across hospitals by adequate risk-adjustment models (8, 9). Several risk-adjusted quality indicators on sepsis care based on administrative health data have been presented in the literature (10–13). Such indicators have been used to assess and compare hospital performance as well as to evaluate effects of voluntary and mandated quality improvement programs (14, 15). Existing administrative data-based indicators on the quality of sepsis care share two shortcomings. First, they only used in-hospital or 30-day post-discharge mortality as outcomes, although short-term case fatality is increasingly regarded to be inadequate as sole metric for the outcome of sepsis patients (4, 16). Improved quality of care should ideally reduce short-term mortality, but also long-term mortality and morbidity resulting in a higher proportion of patients with full recovery. Second, risk-adjustment models were based on hospital discharge data solely. Therefore, pre-existing conditions were defined only based on ICD-coding during the hospital stay, which may result in bias based on incomplete coding as well as a failure to distinguish conditions present-on-admission from complications (7, 17, 18).

To overcome these shortcomings, we developed risk-adjusted quality indicators based on longitudinal health claims data incorporating long-term outcomes of sepsis care as well as pre-existing conditions coded before hospital admission.

Abbreviations: AOK, "Allgemeine Ortskrankenkasse," German health insurance; AUC, area under the curve; CCI, Charlson Comorbidity Index; ECI, Elixhauser Comorbidity Index; HGLM, hierarchical generalized linear models; ICD, international classification of diseases; ICD-10-GM, international statistical classification of diseases and related health problems–German modification–10th revision; IK, "Institutionskennzeichen," unique institutional identifier for hospitals; OPS, Operationen und Prozedurenschlüssel [German procedure classification]; QSR, "Qualitätssicherung mit Routinedaten," quality assurance using routine data; RSMR, risk standardized mortality rate; SEPFROK, initial study, "Sepsis: Folgeerkrankungen, Risikofaktoren, Versorgung, und Kosten"; USA, United States of America; WIdO, Research Institute of the Local Health Care Funds.

2. Materials and methods

2.1. Data source

This is a secondary analysis of health care claims data provided for the SEPFROK study (19). This cohort study was

based on nationwide anonymous administrative health claims data of the largest German health insurance, the "Allgemeine Ortskrankenkasse" (AOK), which covers approximately 32% of the German population. Data were provided by the Research Institute of the Local Health Care Funds (WIdO). Health insurance is mandatory in Germany; residents can select any insurer and enroll without restriction. Within the AOK data, hospitals were identified by a unique institutional identifier (IK: "Institutionskennzeichen"). More than one hospital site of the same institution might use the same IK, but typically, these sites are organizationally linked and mutually dependent. Based on the AOK health care claims data, the WIdO already provides the quality assurance using health claims data "Qualitätssicherung mit Routinedaten" (QSR, quality assurance using routine data) (20). Indicators are reported to participating hospitals and are part of a web-based information portal to support patients in selecting a hospital. Sepsis is not yet part of the set of quality indicators.

2.2. Study population

The SEPFROK study included patients aged ≥ 15 years with an inpatient hospitalization (discharged January 1, 2013, to December 31, 2014) with an explicit *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, German Modification* (ICD-10-GM) code for sepsis as primary or secondary discharge diagnoses (**Supplementary material 1**–Definition of variables). The first hospitalization with sepsis within this period was defined as the index hospitalization and included in the analyses. Patients with a diagnosis of sepsis in the 2 years preceding the index hospitalization were excluded. Since SEPFROK included a 5-year-look-back period and a 3-year-follow-up, patients who were not continuously insured from January 1, 2009, through their respective 3-year follow-up period after the index hospitalization (or until death) were excluded (**Supplementary Figure 1**).

For this secondary analysis, we included patients with index hospitalization with severe sepsis or septic shock defined by ICD-Codes R65.1 and R57.2 in 2014.

2.3. Outcomes

We included short- and long-term endpoints. 90-day mortality after hospital discharge was chosen as short-term endpoint. As long-term outcome, we defined a composite (binary) outcome of 1-year mortality and increase in the dependency on chronic care during the year after hospital discharge from index hospitalization to address the competing risk they represent (21). The increase in dependency on nursing care was defined by an increase in nursing care level or a new transition to a long-term nursing home, which both are recorded with high reliability in claims data and thus can serve as objective measure of a relevant increase of morbidity and decrease of functioning. In Germany, nursing care levels are defined on graded care needs and entitle patients to long-term care insurance benefits. Care can be provided by informal or formal caregivers or in nursing homes (see **Supplementary material 1**: Definition of variables for details). For the analysis of the composite endpoint only 90-day survivors were included.

2.4. Model derivation

2.4.1. Risk factors

Based on clinical reasoning and existing research, candidate variables were chosen among patient demographics, pre-existing comorbidities, pre-existing conditions and treatments, clinical characteristics of the infection, hospital admission type and specific treatments during the index hospitalization (10–12, 22–24). Detailed definitions of risk factors are given in detail in the **Supplementary material 1**.

2.4.1.1. Patient demographics

Patient demographics included gender and age. To allow for non-linear effects of age, quadratic, and cubic polynomials were included. Age was transformed by mean-centering and standardization to decades [age_t = (age–70)/10].

2.4.1.2. Comorbidities

Comorbidities were assessed in a period of 12 months prior to hospitalization and were defined by the categories of the Charlson Comorbidity Index (CCI) and the Elixhauser Comorbidity Index (ECI) (25, 26) based on a German adaptation of a previously developed ICD-10 coding algorithm (27, 28). If a CCI and an ECI category assessed the same comorbidity, the ECI category was included. An additional indicator variable for presence of leukemia was also included.

2.4.1.3. Pre-existing conditions and treatments

Pre-existing conditions and treatments included the prior dependency on immobility, nursing care, mechanical ventilation, renal replacement therapy, palliative care, which were defined by procedures and general medical measures [OPS: Operationen und Prozedurenschlüssel (German Procedure Classification)] and ICD-10-GM codes, were assessed in a period of 12 months prior to the index hospitalization. The cumulative length of previous hospital stays during the 1-year period before the index hospitalization was categorized as follows: "0 day," "1 day," "> 1 day and < 6 days," "≥ 6 days and ≤ 10 days", and "> 10 days."

2.4.1.4. Clinical characteristics of the infection

Clinical characteristics of the infection included "focus of infection" defined by presence of specific ICD-10-GM codes,

and presence of an explicit sepsis code as a primary diagnosis. "Focus of infection"-codes were derived from the literature (29–31) and clinical knowledge. A primary diagnosis of sepsis was defined if an explicit sepsis code (A40.–A41., R57.2) was present as primary diagnosis. Finally, infection by multi-resistant pathogens was defined by presence of an ICD-10-GM and OPS-code for the presence and treatment of multi-drug resistant pathogens during the index stay.

2.4.1.5. Hospital admission type

Hospital admission type was categorized as "emergency admission," "referral by physician" or "transfer from another hospital."

2.4.1.6. Specific treatments during the index hospitalization

Specific treatments during the index hospitalization not related to sepsis care but associated with increased risk of death were also included and defined by OPS-codes (chemotherapy, stroke treatment).

2.4.2. Model development

Two risk-models were developed–one for each specified endpoint. Risk factors were first selected from the set of candidate variables by a logistic regression model with backward elimination for each endpoint. Because of the large sample size, the criterion to exclude variables from the model was set $p > 0.01$. Since patients with septic shock or sepsis as primary diagnosis are a distinctive subgroup with a special importance for quality measurement, we aimed to make the model suitable also for comparing the endpoints within the subgroups of cases with or without septic shock and with or without sepsis as primary diagnosis. Risk factors might have different effects within these respective subgroups, which can be modeled by statistical interaction effects. Therefore, interaction effects of the selected predictors with the presence of a diagnosis of septic shock or sepsis as primary diagnosis were also included and backward-selected in a second modeling step. Since observed outcomes are expected to be correlated within-hospitals, these models were then refitted by hierarchical generalized linear models (HGLMs) with binomial errors, a logit link and a random intercept for the hospitals (9, 32).

2.4.3. Model validation

We did not conduct a validation in external cohorts, since this model is not intended for use in external cohorts. If such a model is intended to be used in a quality assurance program, like QSR, a recalculation on a yearly base would be necessary. Therefore, we conducted an internal validation with correction for over-fitting using two bootstrap approaches. First, following advice by Harrell et al. (33), two hundred bootstrap replications were done by sampling over the hospitals. In each bootstrap step, the variable selection and the re-fitting by HGLM was repeated within the bootstrap sample. The following validation measures were calculated: the area under the curve (AUC) as a measure of discrimination, the squared Pearson correlation (R^2) as measure of explained variation (34, 35), and the Brier Score and the calibration slope as measures of calibration. These validation measures were calculated in the bootstrap sample on the one hand and in the original sample on the other hand. The difference of these two values is the optimism. The corrected performance is the difference of the validation measure in the original sample and the averaged optimism, respectively. The second approach was similar, but estimated validation measures by prediction on the out-of-bag samples in each bootstrap step and then taking their mean (36). To visualize calibration, the distribution of observed mortality across deciles of predicted mortality was plotted.

2.4.4. Calculation of risk-and reliability-adjusted indicators

Risk-adjusted endpoints per hospital were calculated as risk-standardized mortality rates (RSMR). Note that the expression RSMR will also be used when referring to the composite endpoint. Two methods were used to calculate RSMR. The first method was based on the standard logistic regression approach, in which the RSMR results from the ratio of observed mortality to mortality predicted from the logistic regression model, multiplied with the unadjusted rate in the full sample (37, 38). Low number of cases per hospital cause unreliability in the estimation of the RSMR, which results in higher rates of randomly extreme values among hospitals with small case numbers. Reliability adjustment by shrinkage estimators was repeatedly proposed to achieve more stable estimates (39–41). To implement this, we applied the methodology used for the quality indicators of the Centers for Medicare and Medicaid Service's as a second method (35, 38, 42). Here, reliability-adjusted RSMR are obtained as the ratio of predicted to expected mortality obtained from the HGLM, multiplied by the unadjusted rate of the full sample (38). Confidence limits (95% CI) were calculated by a large sample approximation for the RSMR (37, 38), and by a bootstrap approach, as described by Normand et al. (42), for the reliability-adjusted RSMR. The distribution of the observed rates, RSMR and reliability-adjusted RSMR was analyzed by descriptive statistics and graphics. The bivariate relationships between the 90-day mortality and the composite endpoint of 1-year mortality or increased dependency on nursing care was analyzed by scatterplot and calculation of Pearson's ρ for unadjusted rates, RSMR and reliability-adjusted RSMR, respectively. Hospitals with a CI not overlapping with the unadjusted rate of the full sample are regarded as showing a deviation from the average. We used cross-tabulation to describe the distribution of hospitals with a significant deviation in RSMR or reliability-adjusted RSMR for both endpoints. The data analysis for this paper was generated using SAS software, version 9.4 (Copyright© 2002–2012 SAS Institute Inc., SAS and all other SAS Institute Inc., product or service names are registered trademarks or trademarks of SAS

Institute Inc., Cary, NC, USA) and with R, version 4.1.1 [R Core Team, 2020 (43). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/].

3. Results

Table 1 provides an overview of the study sample (and Supplementary Figure 1 is the corresponding flowchart). Among 35,522 patients who were hospitalized with sepsis or septic shock in 2014, 18,884 (53.2%) died within the first 90 days after admission. Of 16,638 90-day survivors, 3,632 (21.8%) died within the first year. Increase in the dependency on nursing care affected 4,316 (25.9%) of 90-day survivors. Death or increase in the dependency on nursing care (composite endpoint) occurred in 6,639 (39.8%) of 90-day survivors. The mean age of the total sample at hospital cases was 73.96 ± 12.28 years (90-day survivors: 71.58 ± 13.02 years), 45% were males (90-day survivors: 44.7%). Patients of the total sample were treated in 1,174 hospitals. Since part of hospitals had no 90-day survivors, the 1-year composite endpoint was analyzed for 1,105 hospitals only.

3.1. Risk-adjustment models

After backward selection 29 of 58 initial risk factors and 12 of 136 initial interaction effects with septic shock or sepsis as primary diagnosis were identified for the endpoint 90-day mortality. Higher age, emergency admission or transfer from another hospital, and septic shock were associated with increased risk of death. In general, indicators of preexisting morbidity–like pre-sepsis comorbid illness, duration of previous hospital stays, or pre-existing treatments–were associated with an increased risk of death. Exemption were depression, complicated hypertension, obesity, and pre-existing long-term ventilation, which showed protective effects (Table 2). For the 1-year composite endpoint (1-year mortality or increased dependency on nursing care), 27 risk factors and 10 of 112 initial interaction effects with septic shock or sepsis as primary diagnosis were identified. Again, higher age, emergency admission or transfer from another hospital, and septic shock were associated with increased risk. Indicators of pre-sepsis morbidity were all associated with increased risk, with the exemption of pre-existing dependency on chronic care, which showed a protective effect (Table 2).

TABLE 1 Sample of cases with severe sepsis or septic shock.

Cases	N (%)
Hospitalized cases with severe sepsis or septic shock in 2014	35,522 (100%)
90-day deceased	
n (% of cases with severe sepsis or septic shock)	18,884 (53.16%)
90-day survivors	
n (% of cases with severe sepsis or septic shock)	16,638 (46.84%)
1 year mortality	
n (% of cases which survived 90 days)	3,632 (21.83%)
1 year survivors	
n (% of cases which survived 90 days)	13,006 (78.17%)
increased dependency on chronic care	
n (% of cases which survived 90 days)	4,316 (25.94%)
no increased dependency on chronic care	
n (% of cases which survived 90 days)	12,322 (74.06%)
1 year composite endpoint (1 year mortality OR increased dependency on chronic care)	
n (% of cases which survived 90 days)	6,639 (39.8%)
no 1 year composite endpoint (1 year mortality OR increased dependency on chronic care)	
n (% of cases which survived 90 days)	10,029 (60.2%)

3.2. Validation

Uncorrected and corrected estimates of the validity measures are given in Supplementary material 2: Internal validation, Supplementary Tables 1, 2. The approach of Harrel et al. resulted in more conservative estimates and yielded a corrected discrimination of *AUC* = 0.748 [95% CI: 0.742; 0.752], an explained variance of R^2 = 0.242, a Brier Score of 0.203 and a calibration slope of 1.094 for the model for 90-day-mortality. The model for the 1-year composite endpoint showed an estimated discrimination of *AUC* = 0.675 [95% CI: 0.665; 0.685], an explained variance of R^2 = 0.111, a Brier Score of 0.220 and a calibration slope of 0.978. Calibration of both models was good (observed rate in lowest risk-decile and highest decile: 0.17–0.87 and 0.13–0.68, respectively, Figures 1A, B).

3.3. Distribution of indicators across hospitals

There was a large variation in numbers of cases across hospitals. Across 1,174 hospitals, the number of cases with coded sepsis per hospital for 90-day mortality ranged from 1 to 745, 25th, 50th, and 75th percentile of 7, 17, and 36, respectively. Across 1,105 hospitals, the number of 90-day survivors per hospital for the composite 1-year endpoint ranged from 1 to 334, 25th, 50th, and 75th percentile of 3, 8, and 18, respectively.

Figure 2 presents the distribution of the two endpoints–90-day mortality and the 1-year composite endpoint per hospital–with their observed values, their risk-adjusted values (RSMR), and their risk-and reliability adjusted values (reliability-adjusted RSMR). While the variability of the RSMR was comparable to the observed values (panel A vs. C, and panel B vs.

TABLE 2 Coefficients estimates of the risk-adjustment model for 90-days mortality and 1-year composite endpoint of mortality or increased dependency on chronic care.

	90-days mortality			1-year composite endpoint of mortality or increased dependency on chronic care		
Variable	Mean ± SD or%	*P*-value	Odds ratio [95% CI]	Mean ± SD or%	*P*-value	Odds ratio [95% CI]
Patient demographics						
Age[a]	73.96 ± 12.28			71.58 ± 13.02	< 0.001	1.49 [1.44; 1.53]
Effect in non-primary diagnosis of sepsis		< 0.001	1.44 [1.39; 1.50]			
Effect in primary diagnosis of sepsis		< 0.001	1.33 [1.27; 1.39]			
Age^2		< 0.001	1.05 [1.04; 1.07]			
Age^3		< 0.001	1.01 [1.01; 1.02]			
Comorbidities						
Charlson: Dementia	20.09%			16.20%	< 0.001	1.31 [1.18; 1.45]
Effect in non-primary diagnosis of sepsis		0.886	1.01 [0.92; 1.11]			
Effect in primary diagnosis of sepsis		< 0.001	1.26 [1.15; 1.39]			
Charlson: Moderate or severe liver disease	2.44%	< 0.001	1.87 [1.59; 2.20]			
Elix: Alcohol abuse	9.22%	< 0.001	1.29 [1.18; 1.40]	8.87%	< 0.001	1.39 [1.24; 1.57]
Elix: Congestive heart failure	43.03%	< 0.001	1.12 [1.06; 1.19]	38.37%	< 0.001	1.16 [1.08; 1.25]
Elix: Depression	28.26%	0.002	0.92 [0.87; 0.97]			
Elix: Diabetes, uncomplicated				44.32%	< 0.001	1.13 [1.05; 1.21]
Elix: Fluid and electrolyte disorders	34.32%	< 0.001	1.25 [1.18; 1.32]	28.77%		
Effect in non-septic shock					< 0.001	1.27 [1.15; 1.39]
Effect in septic shock					0.978	1.00 [0.85; 1.18]
Elix: Hypertension, complicated	26.34%	< 0.001	0.88 [0.83; 0.93]			
Elix: Leukemia	1.77%	< 0.001	1.66 [1.38; 1.98]	1.33%	0.001	1.64 [1.23; 2.18]
Elix: Metastatic cancer	7.71%			5.57%		
Effect in non-septic shock		< 0.001	2.48 [2.23; 2.76]		< 0.0001	2.12 [1.77; 2.53]
Effect in septic shock		< 0.001	1.46 [1.23; 1.74]		0.048	1.36 [1.00; 1.83]
Elix: Obesity	27.31%					
Effect in non-septic shock		< 0.001	0.83 [0.78; 0.89]			
Effect in septic shock		0.643	0.98 [0.88; 1.08]			
Elix: Other neurological disorders				14.77%		
Effect in non-primary diagnosis of sepsis					< 0.001	1.27 [1.10; 1.46]
Effect in primary diagnosis of sepsis					0.730	0.98 [0.85; 1.13]
Elix: Paralysis				9.57%	< 0.001	1.21 [1.07; 1.37]
Elix: Peripheral vascular disorders	33.03%			30.09%	0.035	1.08 [1.01; 1.17]

(Continued)

TABLE 2 (Continued)

	90-days mortality			1-year composite endpoint of mortality or increased dependency on chronic care		
Variable	Mean ± SD or%	*P*-value	Odds ratio [95% CI]	Mean ± SD or%	*P*-value	Odds ratio [95% CI]
Effect in non-septic shock		0.264	1.04 [0.98; 1.10]			
Effect in septic shock		< 0.001	1.23 [1.12; 1.36]			
Elix: Pulmonary circulation disorders	10.01%	0.007	1.12 [1.03; 1.22]			
Elix: Solid tumor without metastasis				18.99%	0.004	1.14 [1.04; 1.25]
Elix: Valvular disease	21.16%	< 0.001	1.11 [1.04; 1.18]			
Elix: Weight loss	8.62%	< 0.001	1.44 [1.32; 1.57]	6.36%		
Effect in non-primary diagnosis of sepsis					0.140	1.16 [0.95; 1.40]
Effect in primary diagnosis of sepsis					< 0.001	1.66 [1.37; 2.02]
Pre-existing conditions and treatments						
Pre-existing immobility				19.32%	< 0.001	1.14 [1.04; 1.25]
Pre-existing dependency on chronic care	39.51%			32.39%		
Effect in non-primary diagnosis of sepsis		< 0.001	1.29 [1.23; 1.36]		< 0.001	0.52 [0.48; 0.56]
Effect in primary diagnosis of sepsis		< 0.001	1.42 [1.35; 1.49]		< 0.001	0.66 [0.62; 0.70]
Effect in non-primary diagnosis of sepsis/Septic shock		< 0.001	1.31 [1.22; 1.42]			
Effect in primary diagnosis of sepsis/septic shock		< 0.001	1.16 [1.07; 1.27]			
Pre-existing long-term mechanical ventilation	1.64%	0.004	0.76 [0.64; 0.92]	1.72%	< 0.001	1.53 [1.18; 1.97]
Pre-existing renal replacement therapy	4.77%	0.002	1.20 [1.07; 1.34]			
Hospital length of stay (> 10 d) (reference)	0.43%			0.37%		
Hospital length of stay (0 d)	35.69%			40.42%		
Effect in non-primary diagnosis of sepsis		0.455	0.84 [0.53; 1.33]		0.265	0.66 [0.32; 1.37]
Effect in primary diagnosis of sepsis		0.560	0.84 [0.46; 1.52]		< 0.001	0.22 [0.09; 0.55]
Hospital length of stay (1 d)	24.68%			24.48%		
Effect in non-primary diagnosis of sepsis		0.535	0.86 [0.54; 1.37]		0.186	0.61 [0.29; 1.27]
Effect in primary diagnosis of sepsis		0.760	0.91 [0.50; 1.65]		< 0.001	0.26 [0.11; 0.65]
Hospital length of stay (> 1 d and < 6 d)	34.87%			31.26%		
Effect in non-primary diagnosis of sepsis		0.608	0.89 [0.56; 1.40]		0.196	0.62 [0.30; 1.28]
Effect in primary diagnosis of sepsis		0.784	1.09 [0.60; 1.96]		0.013	0.32 [0.13; 0.79]

(Continued)

TABLE 2 (Continued)

	90-days mortality			1-year composite endpoint of mortality or increased dependency on chronic care		
Variable	Mean ± SD or%	*P*-value	Odds ratio [95% CI]	Mean ± SD or%	*P*-value	Odds ratio [95% CI]
Effect in non-primary diagnosis of sepsis		0.969	1.01 [0.63; 1.63]		0.389	0.72 [0.34; 1.53]
Hospital length of stay (≥ 6 d and ≤ 10 d)	4.34%			3.47%		
Effect in primary diagnosis of sepsis		0.606	1.18 [0.64; 2.17]		0.053	0.40 [0.15; 1.01]
Clinical characteristics of the infection						
Primary diagnosis of sepsis	39.15%	0.005	0.34 [0.16; 0.73]	46.99%	0.531	1.45 [0.45; 4.64]
Septic shock	29.70%			20.76%		
Effect in non-primary diagnosis of sepsis		< 0.001	3.33 [2.92; 3.80]		< 0.001	1.22 [1.09; 1.37]
Effect in primary diagnosis of sepsis		< 0.001	4.52 [3.91; 5.22]		< 0.001	1.45 [1.25; 1.67]
Site of infection: Abdominal	21.60%					
Effect in non-septic shock		0.363	0.97 [0.90; 1.04]			
Effect in septic shock		< 0.001	0.80 [0.72; 0.89]			
Site of infection: Respiratory tract	47.65%			45.16%	< 0.001	1.30 [1.22; 1.39]
Effect in non-primary diagnosis of sepsis		< 0.001	1.14 [1.06; 1.22]			
Effect in primary diagnosis of sepsis		< 0.001	1.36 [1.25; 1.47]			
Effect in non-septic shock		< 0.001	1.14 [1.06; 1.22]			
Effect in septic shock		0.038	0.90 [0.82; 0.99]			
Site of infection: Device-related infections	8.90%	< 0.001	0.68 [0.63; 0.74]	10.62%		
Effect in non-primary diagnosis of sepsis					0.646	1.03 [0.91; 1.17]
Effect in primary diagnosis of sepsis					< 0.001	1.44 [1.18; 1.76]
Site of infection: other or unspecified	55.61%			60.81%	< 0.001	1.22 [1.14; 1.31]
Effect in non-septic shock		< 0.001	0.87 [0.82; 0.92]			
Effect in septic shock		< 0.001	0.57 [0.52; 0.63]			
Site of infection: Genitourinary system	29.97%	< 0.001	0.62 [0.59; 0.66]			
Site of infection: Wound/soft tissue infection	6.54%	< 0.001	0.79 [0.72; 0.87]	7.87%		
Effect in non-primary diagnosis of sepsis					< 0.001	1.32 [1.12; 1.55]
Effect in primary diagnosis of sepsis					0.811	1.02 [0.85; 1.24]
Multi-resistant pathogen				6.55%	< 0.001	1.40 [1.22; 1.60]
Hospital admission type						
Reason for admission: Emergency (reference)	60.05%			61.00%		

(Continued)

TABLE 2 (Continued)

Variable	90-days mortality			1-year composite endpoint of mortality or increased dependency on chronic care		
	Mean ± SD or%	*P*-value	Odds ratio [95% CI]	Mean ± SD or%	*P*-value	Odds ratio [95% CI]
Transfer from another hospital	7.09%	< 0.001	1.22 [1.10; 1.34]	5.88%	0.579	1.04 [0.90; 1.21]
Referral by physician or other	32.86%	0.034	0.94 [0.89; 1.00]	33.12%	0.012	0.91 [0.85; 0.98]
Specific treatments during the index hospitalization						
Chemotherapy in index hospitalization				2.53%		
Effect in non-primary diagnosis of sepsis					< 0.001	1.64 [1.29; 2.09]
Effect in primary diagnosis of sepsis					0.685	0.91 [0.57; 1.45]
Stroke treatment in index hospitalization				1.03%	< 0.001	2.57 [1.84; 3.59]

Coefficients estimated by a hierarchical generalized linear model with a logit link and random intercept to adjust for clustering of cases in hospitals. Cases, which were hospitalized with severe sepsis or septic shock in 2014, were included. Italic text presents conditional effects in subgroups of cases estimated based on significant interaction effects with the indicators for presence of septic shock and presence of a primary diagnosis for sepsis. CI, confidence interval. Not all main effects or interaction effects were selected by the backward selection algorithm in both models, which results in some empty cells. [a]Age was standardized by (Age-70)/10.

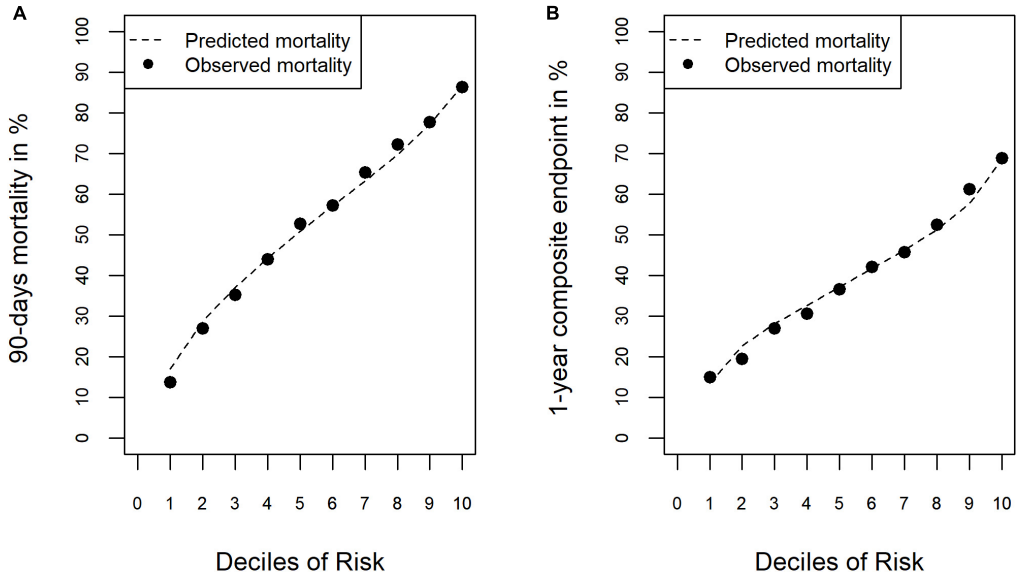

FIGURE 1
Calibration of the risk-adjustment models. **(A)** 90-day mortality. **(B)** 1-year composite endpoint (1-year mortality or increased dependency on chronic care).

D, respectively), the implementation of reliability adjustment let to a strong reduction in variability across hospitals (panels E and F).

Reliability adjustment also had an effect regarding the proportion of hospitals, which showed a deviation of the RSMR from average (Table 3). Without reliability adjustment, 7.6% of hospitals showed a RSMR on 90-day mortality with the lower 95% confidence limit above the average; with reliability adjustment, this was true for only 1.2%. Regarding the 1-year composite endpoint, 3.5% of hospitals showed an RSMR above average without reliability adjustment, while none showed a RSMR above average with reliability adjustment.

The relationships between the different rates for 90-day mortality and the 1-year composite endpoint are depicted in Figure 3. There were no substantial correlations observed between the two endpoints (observed rates: $\rho = 0$, $p = 0.99$; RSMR: $\rho = 0.017$, $p = 0.56$; reliability-adjusted RSMR: $\rho = 0.067$; $p = 0.026$).

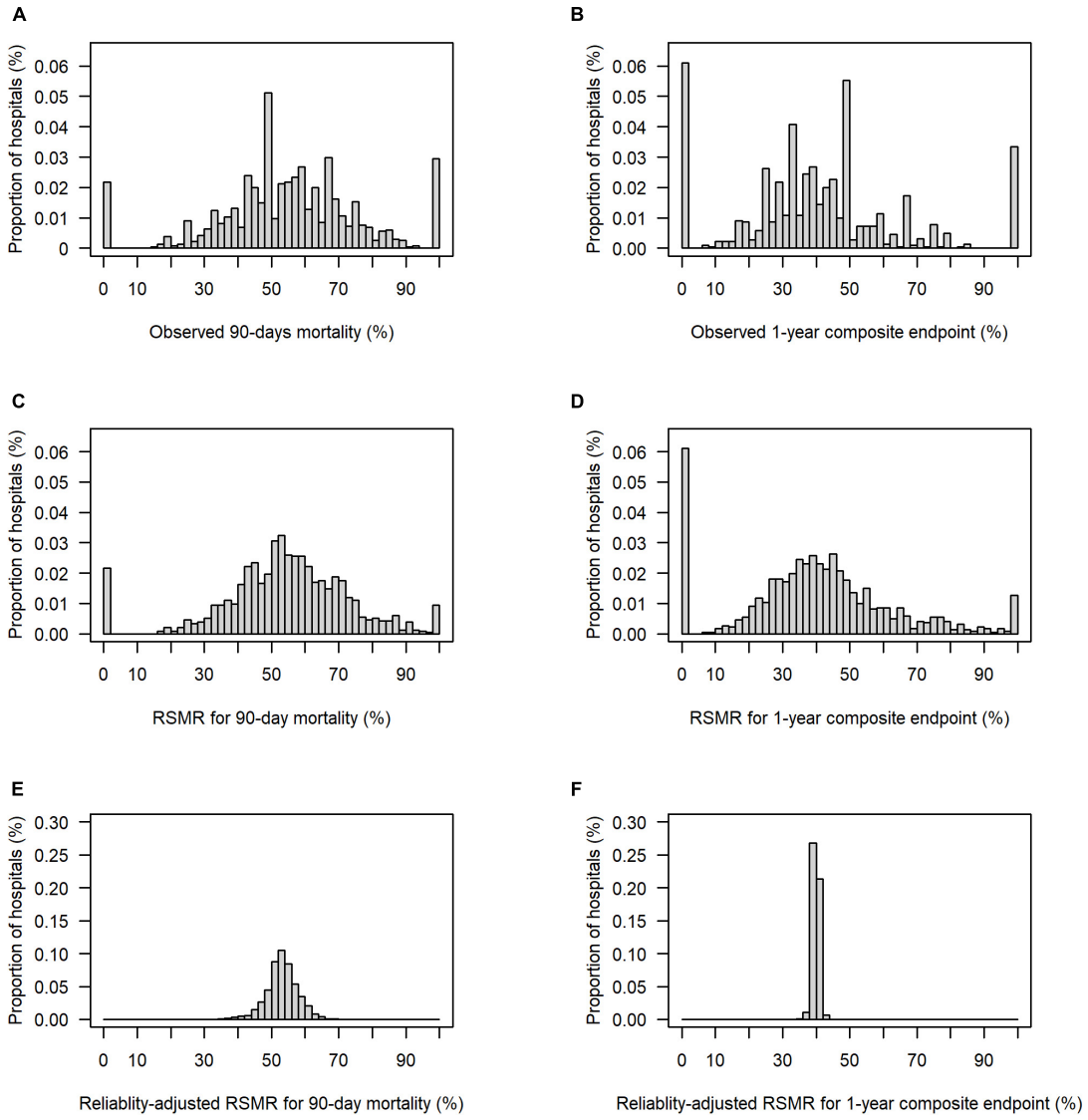

FIGURE 2
Distribution of observed, risk-standardized and risk-and reliability adjusted endpoints per hospital. **(A)** Observed 90-day mortality, range from 0 to 100%, 25th, 50th, and 75th percentile of 44.0, 54.6, and 66.7%, respectively. **(B)** Observed rate for composite outcome of 1-year-mortality or increased dependency on chronic care, range from 0 to 100%, 25th, 50th, and 75th percentile 26.9, 39.3, and 50.0%, respectively. **(C)** Risk-standardized rate (RSMR) for 90-day mortality without reliability adjustment, range from 0 to 100%, 25th, 50th, and 75th percentiles of 44.3, 54.2, and 65.5%, respectively. **(D)** RSMR for the 1-year composite endpoint without reliability adjustment, range from 0 to 100%, 25th, 50th, and 75th percentiles of 27.8, 39.2, and 51.1%, respectively. **(E)** Reliability-adjusted RSMR for 90-day mortality, range from 35.9 to 68.1%, 25th, 50th, and 75th percentiles of 50.7, 53.2, and 55.9%, respectively. **(F)** Reliability-adjusted RSMR for 1-year composite outcome, range from 35.8 to 43.3%, 25th, 50th, and 75th percentile of 39.5, 39.9, and 40.4%, respectively.

4. Discussion

4.1. Summary of results

This is the first study on the development of health claims based risk-adjusted quality indicators for acute sepsis care, which incorporate both 90-day mortality as well as long-term outcomes on mortality and functional dependency. The risk-adjustment models relied on pre-existing conditions actually measured before hospitalization and showed a decent predictive validity. There was no evidence for correlation between short-term and long-term outcomes at the level of hospitals.

4.2. Interpretation

Regarding 90-day mortality, the predictive validity of our model was comparable to previously reported administrative

TABLE 3 Proportion of hospitals showing significant deviation of risk-adjusted outcomes from average.

Indicator	Proportion of hospitals with 95% CI of RSMR below the rate in the population	Proportion of hospitals with 95% CI of RSMR including the rate observed in the population	Proportion of hospitals with 95% CI of RSMR above the rate in the population
RSMR for 90-day mortality			
Without reliability adjustment	66 (5.62%)	1019 (86.80%)	89 (7.58%)
With reliability adjustment	28 (2.39%)	1132 (96.42%)	14 (1.19%)
RSMR for 1-year composite endpoint			
Without reliability adjustment	20 (1.81%)	1046 (94.66%)	39 (3.53%)
With reliability adjustment	0 (0.0%)	1105 (100.0%)	0 (0.0%)

RSMR, risk-standardized mortality rate; CI, confidence interval.

data based models on short-term mortality after acute treatment of sepsis (10–12). Even risk-adjustment models, which were based on clinical data or a mix of clinical and administrative data, did–with AUCs between 0.75 and 0.78–not achieve relevantly higher discrimination (22, 24, 44). The effects of risk factors in the model are similar to previously reported risk-models for sepsis mortality (10–12, 22). Protective effects of some comorbidities on short-term mortality–namely obesity, depression, and hypertension–have also been shown in these studies as well as in studies on the Elixhauser comorbidity index conducted among representative samples of hospital patients (26, 45, 46). It has been argued that these seemingly protective effects reflect a bias in coding, where relatively healthy patients without severe comorbidities have a higher chance of having these milder comorbidities coded compared to more severely ill patients. We found that also pre-existing long-term mechanical ventilation had a protective effect on risk of 90-day mortality. This might be due to the intense ongoing monitoring of these patients, which might have allowed early detection and adequate treatment of sepsis and thereby prevention of acute deterioration and death (47).

To our knowledge, no other risk-adjustment model on long-term outcomes of sepsis care based on administrative data exists. Moreover, prediction scores for long-term outcomes based on clinical data are also lacking (48, 49). Based on an ICU-registry, Shankar-Hari et al. developed a prognostic score for the composite endpoint of 1-year mortality or re-hospitalization, which showed an AUC of 0.68–comparable to the AUC of 0.675 estimated for our model on 1-year mortality or increased dependency on chronic care. As expected, we found that older patients with comorbid conditions tended to have a higher risk of long-term mortality or dependency on chronic care after having survived 90 days post-discharge. Pre-existing long-term mechanical ventilation increased the risk of long-term mortality or care dependency, likewise because these patients have a reduced survival time in general. The protective effect of pre-existing dependency on chronic care might simply indicate that the risk to develop dependency on chronic care for the first time is higher compared to switching to a higher degree of dependency, if a patient was already receiving chronic care.

Patients with sepsis can suffer from a broad spectrum of clinical sequelae in the areas of physical disability, cognitive impairment, mental health impairment, recurrent infection and sepsis, exacerbation of chronic conditions, all of which decrease overall functioning and quality of life (4, 19). Since concrete sequelae can be highly variable across patients and their measurement in administrative data is dependent on validity of ICD-coding (19), we selected the increase in the dependency on chronic care as an objective indicator of cumulative, overall functioning. It has to be acknowledged that long-term outcomes of acute care cannot solely be attributed to the initially treating hospital, since they are also influenced by other health-care providers responsible for the further treatment as well as other factors (50). Little is known on how to enhance long-term recovery of survivors during acute in-patient care on the ICU or the ward (4, 51, 52). Because of this, attributing long-term outcomes of sepsis care to the initial hospitalization is especially problematic. This might explain why 90-day mortality and the composite 1-year endpoint did not correlate in our study. Therefore, short-term mortality may serve as the better indicator of quality of acute sepsis care. On the other hand, a reduction in short-term mortality after changes in treatment regiments might come at the cost of an increase in long-term mortality or worsening of other patient-centered outcomes (4, 16). Including indicators of long-term sequelae to a measurement of the quality of care can therefore help to interpret differences between providers as well as changes across time both in quality assurance and population surveillance (16).

The problem of reliability adjustment has been extensively discussed in methodological literature (35, 38–42), but is currently not applied in prominent voluntary performance measurement programs in Germany or the methodology of the mandatory quality indicators for German hospitals (20,

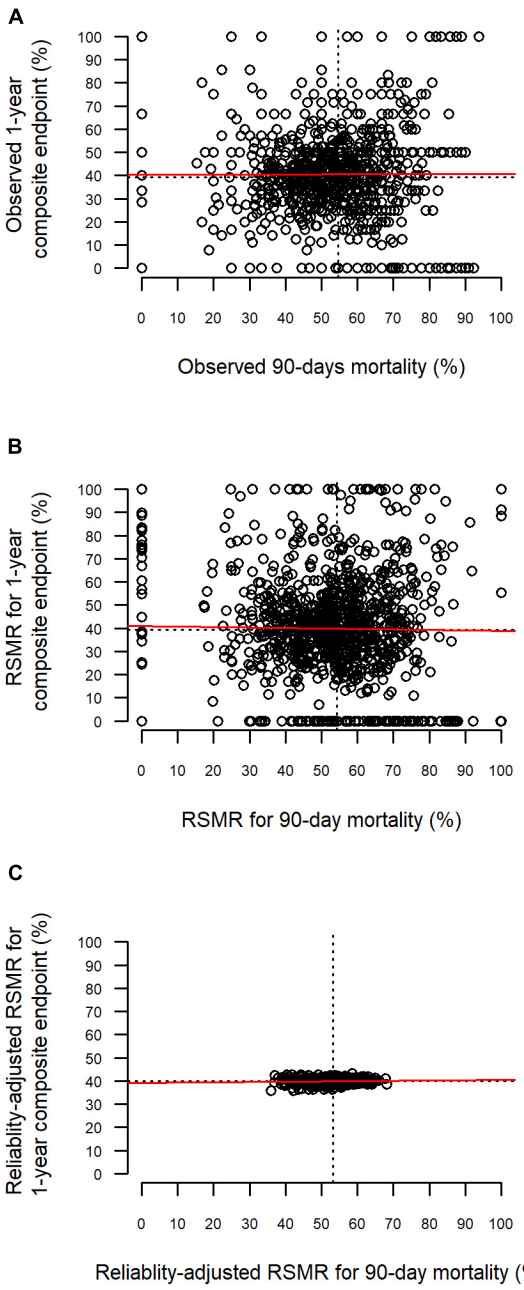

FIGURE 3
Relationship between 90-day mortality and the 1-year composite endpoint. Each point represents one hospital. The red line represents the linear relationship based on least-squares estimation. One-year composite endpoint defined by death or increased dependency on chronic care during 1 year after discharge. **(A)** Relationship between observed rates. **(B)** Relationship between risk-standardized rates (RSMR). **(C)** Relationship between reliability-adjusted RSMR.

53, 54). When case numbers are small, it is hard to tell if extremely high or low outcome rates are due to chance or true differences in quality of care (39). Since there typically is a time-lag between data collection and report of quality indicators, the validity of a quality indicator to predict future performance is important. Shrinkage estimators shrink the estimate of the rate toward the average rate of the population, with the amount of shrinkage negatively proportional to the number of cases. This shrunken estimator has been shown to be a better predictor for future performance compared to classical methods based on logistic regression (38, 39). In our study, reliability adjustment resulted in a great reduction in variability in endpoints between hospitals compared to raw endpoints as well as compared to non-reliability-adjusted RSMR. This effect was stronger for the 1-year-composite endpoint, given the smaller case numbers per hospital. Shrunken estimators are especially relevant for quality indicators used in public reporting or pay-for-performance systems, where wrongfully assigning low-volume hospitals a below-average performance due to unreliable estimates would result in unwarranted negative financial consequences. Nevertheless, if the aim is the identification of possible shortcomings of care for further investigation in continuous quality improvement programs or by peer-reviews, it might be important not to miss possible signals and therefore to also take non-reliability-adjusted estimates into consideration–especially if case-numbers per hospital tend to be low (55).

4.3. Practical usage of the presented methodology

The developed methodology could be used for the purposes of quality measurement and between-hospital comparisons. It could also be useful in population surveillance to monitor the changes in mortality and morbidity on a population level across time in Germany (19, 56). It can be applied to data of the same structure and content, i.e., health claims data of the AOK or of other German public health care insurers, which all obtain largely the same information collected for administrative purposes. The German Institute for Quality and Efficiency in Health Care has recently been instructed to develop mandatory quality indicators for acute sepsis care by the Joint Federal Committee–the institution responsible for quality assurance of health care in Germany (57). Since combined data of all public health insurers are used to calculate mandatory quality indicators of German hospitals, the problem of low case volume and lacking reliability of estimates might be overcome in this context. Thus, the presented methodology could be applied both in voluntary performance measurement in the context of the QSR-program as well as in the context of mandatory quality assurance for German hospitals. For any purpose, the risk-adjustment models should be recalculated using the respective current population and reference period to allow adequate comparisons. For this reason, we refrained from validating the reported model in a separate

external cohort, since the methodology is not intended to be used this way.

4.4. Strengths and limitations

Our study has several strengths. It presents the first claims-based risk-adjusted quality indicators for long-term outcome of acute sepsis care, which include risk factors measured before the index hospitalization. This is an important improvement compared to previous claims-based models, which only relied on information documented during the hospital stay (10–12). Operationalization of variables was done in a rigorous process, based on a multiprofessional panel of experts who care for patients with sepsis (19). Based on the large sample size, complex risk-adjustment models with decent predictive validity were derived.

Our study also has several limitations, mostly associated with general shortcomings of administrative health data (7). These data are limited in content and provide no information on vital signs, microbiological results or medication during the hospital stay. Therefore, several known risk factors for short-term and long-term patient outcomes, like presenting signs and symptoms or severity of initial critical illness could not be assessed (49, 51). On the other hand, predictive validity was comparable to models incorporating clinical data (22, 24, 44, 49), and previous studies found no relevant differences between risk-standardized rates based solely on administrative data compared to administrative data enhanced by clinical information (11, 35). Administrative data are also limited in accuracy and completeness of coding of information (7). This results in possible information biases affecting the case selection, as well as identification of risk factors and outcomes. Lacking accuracy and mostly undercoding has been described for the ICD-coding of sepsis (58, 59). This can have huge effects on the validity of performance measures and provider comparisons, especially if the quality of coding varies across hospitals (7, 60). Based on our data, in average only one third of German patients coded with sepsis per hospital and year were included, which–together with the problem of undercoding of sepsis–results in decreased reliability of estimates and reduced power to detect hospitals, which are outliers in risk-adjusted endpoints. Our study was based on data gathered before the introduction of the new Sepsis-3 definitions (1). Therefore, we included patients with ICD-codes for sepsis with organ dysfunction or septic shock according to sepsis-1/sepsis-2 definitions, since severe sepsis according to old sepsis definitions shows a high overlap with the new definitions (61). We used a composite outcome of mortality and increase in long-term morbidity. While this allows to address the competing risk between both endpoints (21), it leads to difficulties in interpreting differences in hospital performance. Multistate models provide a comprehensive methodology to address competing risks between outcomes (62). But since there does not yet exist a method to obtain hospital-specific estimates of risk-adjusted quality indicators from such models, further methodological development is needed to apply them in the context of provider comparisons.

5. Conclusion

We presented a methodology for claims-based risk-adjusted quality indicators on short-term and long-term mortality and morbidity after acute sepsis care. Beside the limitations of administrative health data, this methodology could provide a valuable tool in assessing and monitoring outcome quality achieved by German hospitals caring for patients with sepsis. Future studies should recalculate the risk-adjustment models based on current data incorporating the new Sepsis-3 definitions and may embrace multi state modeling to address mortality and morbidity jointly. To increase reliability and validity of measures of outcome quality, data sources should cover the full population and hospitals need to improve ICD-10-coding of sepsis.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The data used in this study cannot be made available in the manuscript, the **Supplementary material**, or in a public repository due to German data protection laws (Bundesdatenschutzgesetz). Therefore, they are stored on a secure drive in the Wissenschaftliches Institut der AOK to facilitate replication of the results. Generally, access to data of statutory health insurance funds for research purposes is possible only under the conditions defined in the German Social Law (SGB V §287). Requests for data access can be sent as a formal proposal, specifying the recipient and purpose of the data transfer, to the appropriate data protection agency. Access to the data used in this study can only be provided to external parties under the conditions of the cooperation contract of this research project and after written approval by the AOK. For assistance in obtaining access to the data, please contact wido@wido.bv.aok.de.

Ethics statement

The studies involving human participants were reviewed and approved by Ethik-Kommission der Friedrich-Schiller-Universität Jena. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

DS, CF-S, and MS: concept and design. CF-S, NR, MS, CG, and LW: acquisition of data. LW, DS, NR, and PS: statistical analysis and planning. LW and DS: drafting of the manuscript. DS: supervision. CG, AS, and PS: administrative support. LW: conduction and had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to interpretation of results and critical revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

CF-S was funded by grants from the German Federal Ministry of Education and Research, outside the submitted work and the German Innovations Fund of the Federal Joint Committee in Germany (G-BA), inside and outside the submitted work. DS leads the coordinating bureau of the German Quality Network sepsis–a quality initiative to improve hospital care for sepsis–and was partly funded *via* this project from 2015 to 2022. KR was shareholder with less of 0.5% of InflaRx NV a Jena/Germany based Biotech Company that evaluates an immunmodulatory approach for the adjunctive treatment of COVID-19. PS was funded by grants from the German Federal Ministry of Education and Research, outside the submitted work and the German Innovations Fund of the Federal Joint Committee in Germany (G-BA) outside the submitted work. AS was funded by grants from the German Federal Ministry of Education and Research, outside the submitted work.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1069042/full#supplementary-material

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Risk factors and outcomes of lower respiratory tract infections after traumatic brain injury: a retrospective observational study

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Background: Traumatic brain injury (TBI) is a public health problem with a high burden in terms of disability and death. Infections are a common complication, with respiratory infections being the most frequent. Most available studies have addressed the impact of ventilator-associated pneumonia (VAP) after TBI; therefore, we aim to characterize the hospital impact of a broader entity, lower respiratory tract infections (LRTIs).

Methods: This observational, retrospective, single-center cohort study describes the clinical features and risk factors associated with LRTIs in patients with TBI admitted to an intensive care unit (ICU). We used bivariate and multivariate logistic regressions to identify the risk factors associated with developing LRTI and determine its impact on hospital mortality.

Results: We included 291 patients, of whom 77% (225/291) were men. The median (IQR) age was 38 years (28–52 years). The most common cause of injury was road traffic accidents 72% (210/291), followed by falls 18% (52/291) and assault at 3% (9/291). The median (IQR) Glasgow Coma Scale (GCS) score on admission was 9 (6–14), and 47% (136/291) were classified as severe TBI, 13% (37/291) as moderate TBI, and 40% (114/291) as mild TBI. The median (IQR) injury severity score (ISS) was 24 (16–30). Nearly 48% (141/291) of patients presented at least one infection during hospitalization, and from those, 77% (109/141) were classified as LRTIs, which included tracheitis 55% (61/109), ventilator-associated pneumonia (VAP) 34% (37/109), and hospital-acquired pneumoniae (HAP) 19% (21/109). After multivariable analysis, the following variables were significantly associated with LRTIs: age (OR 1.1, 95% CI 1.01–1.2), severe TBI (OR 2.7, 95% CI 1.1–6.9), AIS thorax (OR 1.4, 95 CI 1.1–1.8), and mechanical ventilation on admission (OR 3.7, 95% CI 1.1–13.5). At the same time, hospital mortality did not differ between groups (LRTI 18.6% vs. No LRTI 20.1%, $p = 0.7$), and ICU and hospital length of stay (LOS) were longer in the LRTI group (median [IQR] 12 [9–17] vs. 5 [3–9], $p < 0.01$) and (median [IQR] 21 [13–33] vs. 10 [5–18], $p = 0.01$), respectively. Time on the ventilator was longer for those with LRTIs.

Conclusion: The most common site/location of infection in patients with TBI admitted to ICU is respiratory. Age, severe TBI, thoracic trauma, and mechanical ventilation were identified as potential risk factors. LRTI was associated with prolonged ICU, hospital stay, and more days on a ventilator, but not with mortality.

KEYWORDS

traumatic brain injury, hospital-acquired pneumonia, ventilator-associated tracheitis, ventilator-associated pneumonia, multiple trauma, acute brain injury

Background

Traumatic brain injury (TBI) is a public health issue and a leading cause of mortality and disability in the younger population. Additionally, TBI impacts the quality of life of older adults, who usually have a reduced capacity to recover after these events (1, 2). TBI is associated with changes in the immune system mediated through inflammatory and autonomic pathways (3, 4) that seem to increase the susceptibility to infections during and after hospitalization (3–5). Among individuals with TBI who suffer nosocomial infections, a frequent source is the respiratory system or what we will denominate lower respiratory tract infections (LRTIs), including ventilator-associated pneumoniae (VAP), ventilator-associated tracheitis (VAT), and healthcare-associated pneumonia (HAP) (3, 6).

The most frequent sources of infection in previous cohorts of TBI have been respiratory and urinary, followed by surgical site infections. Regarding respiratory infections, a greater proportion of studies have focused on VAP. The frequency of VAP in these studies ranges from 31 to 47%, and some of them have found a positive correlation between VAP and several outcomes, including longer hospital stays and higher rates of mortality and disability. The severity of TBI, chest trauma, smoking history, drug abuse, and interventions, such as transfusions, sedation, and the need for a tracheostomy, are associated with VAP (7–11).

Other types of LRTIs might play a relevant role in the hospital course and outcomes of these patients (10). LRTIs could be considered a continuum spectrum of a single disease and, therefore, it might be valuable to describe its epidemiology and associated factors (12–14). This would allow a better understanding of this phenomenon and, accordingly, the development of measures to prevent and manage these complications. By identifying potential risk factors, we can highlight areas of care susceptible to improvement. In this study, our objectives are (a) to describe the epidemiology of lower respiratory tract infections (LRTIs) in our TBI cohort, (b) to determine factors associated with LRTI, and (c) to determine whether LRTI is associated with clinical outcomes (mortality, LOS).

Materials and methods

This is a retrospective, observational, single-center cohort of patients with traumatic brain injury (TBI) admitted to the intensive care unit (ICU). Using the electronic medical record, we searched for patients admitted to the ICU from August 2009 to December 2019 with the diagnosis of TBI. Once selected, the diagnosis was confirmed, and data were validated through a medical chart review. The Ethics Committee of Clínica Universidad de La Sabana approved this study and waived the need for informed consent as only routinely collected clinical data were recorded.

Data collection and storing

One or more dedicated and trained physicians collected clinical data through a medical chart review. These data included demographics, medical history, injury severity, and characteristics during the hospital stay. Data were collected using a Case report form (CRF) built on Research Electronic Data Capture (REDCap, version 8.11.11, Vanderbilt University, Nashville, Tenn.) hosted by the Universidad de Sabana. All study data were de-identified and stored securely by the Translational Science in Infectious Diseases and Critical Care Research Group at Universidad de La Sabana.

Definitions

Lower respiratory tract infection (LRTI) is used as a broad term that includes hospital-acquired pneumoniae (HAP), ventilator-associated pneumoniae (VAP), and ventilator-associated tracheobronchitis (VAT). These entities were diagnosed using the definition of IDSA/ATS guidelines (15). The IDSA guideline criteria were also followed to assess the diagnosis of other infectious complications, including catheter-associated urinary tract infection (CA-UTI), surgical site infection (SSI), and catheter-related bloodstream infection (CRBSI) (16–18). TBI severity was determined using the Glasgow Coma Scale (GCS). Subjects with mild head injury (GCS 13–15) were included in this cohort when they were admitted to ICU; usually, this occurs when there is a risk of clinical deterioration, other body part injuries, and/or comorbid conditions. The severity of trauma and body regions compromised was established using the Abbreviated Injury Score (AIS) and the Injury Severity Score (19). ISS is the sum of the squares of the highest AIS scores in the three most severely injured regions; it ranges from 1 to 75; the higher the score, the more severe the injury. Isolated TBI was defined as AIS head $\geq$3 and injury to any other region with AIS $<$ 3. Patients with TBI and multiple traumas had AIS head $\geq$3 and trauma to any other body region with AIS $\geq$ 3.

Outcomes

The primary outcome was the diagnosis of LRTI during hospitalization. Clinical data were analyzed, and predictors of this primary outcome were identified. The secondary outcomes were hospital survival and the length of ICU and hospital stay.

Statistical analysis

We excluded patients for whom information on discharge or clinical severity was missing. The Shapiro–Wilk test was used to detect departures from normality, and numerical variables were reported as mean (DS) or median (IQR) according to distribution. Categorical data are reported as numbers and percentages. Logistic regression models were used to explore the predictor variables for the primary outcome. Potential predictors for the primary outcome were identified in a univariate analysis. Then, a multivariable model was constructed adjusting for TBI severity, the severity of the trauma, and illness severity scores (APACHE II, SOFA), with results reported as odds ratios (95% CI). For testing the goodness of fit, we used the Hosmer–Lemeshow test. In secondary outcomes analyses, differences in mortality and length of stay between subjects with and without LRTIs were analyzed using the chi-square test for differences in proportions and the Mann–Whitney *U*-test for non-parametric data. A two-tailed *p*-value of 0.05 or less was used to define statistical significance. Statistical analyses were performed using R (version 4.2.1) and Studio (version 2022.07.0) as the integrated development environment.

Results

From August 2009 to December 2019, 291 patients were enrolled. The baseline and clinical characteristics of the patients are presented in Table 1. The median (IQR) age was 38 (28–52) years, and men accounted for 77% (225/291) of the TBI admissions to the ICU. Road traffic accidents were the leading cause of TBI at 72% (210/291), followed by falls 18% (52/291) and assault at 3% (9/291). Median (IQR) GCS on admission was 9 (6–14), and 47% (136/291) were classified as severe TBI, 13% (37/291) as moderate TBI, and 40% (114/291) as mild TBI. Isolated TBI accounted for 21% (63/291), while the rest of the patients had associated injuries to at least one body region with AIS $\geq$ 3. In terms of lesions in other parts of the body, the more frequently compromised (AIS $\geq$ 3) were the thorax 29% (86/291), limbs 28% (84/291), and abdomen 14% (49/291). The median stay in the ICU was 7 (IQR, 4–13), and the median (IQR) hospital stay was 13 days (7–25 days). The frequency of patients requiring invasive ventilatory support was 83% (244/291), and the median (IQR) time on a ventilator was 5 days (3–9 days). Hospital mortality for this cohort was 19% (56/291), and survival time to death was 7 days (IQR, 4–13).

Infection complications were present in 48% (141/291) of patients, and from those, 77% (109/141) corresponded to LRTIs, 14% (20/141) to CA-UTI, 15% (22/141) to SSI, and 9% (14/141) to CRBSI. Regarding absolute frequency, 38% (109/291) had an LRTI, 7% (20/291) had a CA-UTI, 7% (22/291) had an SSI, and 5% (14/291) had a CRBSI. We obtained bacterial growth in 60% (62/109) of LRTI through bronchoalveolar lavage (BAL) of 16% (17/109) and tracheal aspirate of 32% (45/107). Most frequently, isolated bacteria were *Staphylococcus aureus* at 18% (20/109), *Klebsiella pneumoniae* at 10% (11/109), *Enterobacter cloacae* at 8% (9/109), Escherichia *coli* at 7% (8/109), *Pseudomonas aeruginosa* at 6% (7/109), and *Serratia marcescens* at 5% (6/109), among others with minor proportions. Among patients with LRTIs, 55% (61/109) were classified as TAV, 19% (21/109) as hospital-acquired pneumoniae (HAP), and 33% (37/109) as VAP. The median

TABLE 1 Baseline and clinical characteristics of patients.

Demographic characteristics	*n* = 291
Age, median (IQR)	38 (28-52)
Male sex *n* (%)	225 (77)
Cause of injury	***n* (%)**
Road accident	210 (72)
Fall	52 (18)
Assault	9 (3)
Blast	3 (1)
Other	16 (5)
Clinical presentation	***n* (%)**
GCS score	
Mild (3–15)	114 (40)
Moderate (9–12)	37 (13)
Severe (3–8)	136 (47)
AIS head score	
Mild injury (1–2)	84 (29)
Moderate (3)	75 (25)
Severe (4–6)	132 (45)
Injury type	
Blunt	272 (93)
Penetrating	19 (7)
Injury severity score median (IQR)	24 (16–30)
Severity of trauma	***n* (%)**
ISS 1–15	63 (21)
ISS 16–24	93 (32)
ISS $\geq$ 25	125 (47)
AIS thorax $\geq$ 3	86 (29)
AIS limbs $\geq$ 3	84 (28)
AIS abdomen $\geq$ 3	49 (14)
AIS spine $\geq$ 3	30 (8)
AIS neck $\geq$ 3	15 (5)
APACHE II median (IQR)	13 (8–17)
SOFA	5 (3–7)

The major extracranial injury was defined as any non-head AIS score of $\geq$3. Mild trauma was defined as ISS of 1–15, moderate trauma ISS of 16-−24, and severe trauma ISS of $\geq$25. ISS, Injury Severity Score; AIS, Abbreviated Injury Score; GCS, Glasgow Coma Scale.

TABLE 2 Univariate comparison of baseline characteristics of TBI patients with and without LRTIs.

	No LRTI ($n = 182$)	LRTI ($n = 109$)	p-value
Age	37 (25–50)	43 (32–55)	**0.016**
Sex male (%)	137 (76%)	88 (81%)	0.3
APACHE II median (IQR)	12 (6–17)	14 (11–18)	**0.016**
SOFA median (IQR)	4 (3–6)	5 (4–7)	**0.009**
GCS median (IQR)	12 (7–14)	7 (5–13)	**0.026**
ISS median (IQR)	22 (14–29)	26 (18–33)	**0.015**
AIS head median (IQR)	3 (2–4)	4 (3–4)	**0.016**
MV on admission *n* (%)	140 (76%)	104 (95%)	**<0.001**
Days on MV Median (IQR)	4 (3–7)	9 (5–12)	**<0.001**
Hospital LOS Median (IQR)	10 (5–18)	21 (13–33)	**<0.001**
ICU LOS Median (IQR)	5 (3–9)	12 (9–17)	**<0.001**
Mortality	34 (18.6%)	22 (20.1%)	0.75

MV, mechanical ventilation; LOS, length of stay. Bold values indicate statistically significant.

number of days in the hospital before presenting an LRTI was 5 (IQR, 3–9).

Univariate comparison between cohorts with and without LRTIs (Table 2) revealed that patients who had an LRTI were significantly older (median [IQR] 43 years [32–55] vs. 37 years [IQR 25–50], $p = 0.016$) and had more severe head injuries according to GCS (median [IQR], 7 [5–13] vs. 12 [7–14], $p < 0.01$) and AIS head (median [IQR], 4 [3–4] vs. 3 [2–4], $p < 0.01$). APACHE II and SOFA scores were also higher for those patients with LRTIs (median [IQR], 14 [11–18] vs. 12 [6–17], $p = 0.017$) and 5 [4–7] vs. 4 [3–6], $p < 0.01$). In terms of the overall severity of the injury, including other body regions, severity by ISS was worse for the LRTI cohort (median [IQR], 26 [18–33] vs. 22 [14–29], $p = 0.014$). While hospital mortality did not differ between groups (LRTI 18.6% vs. No LRTI 20.1%, $p = 0.7$), ICU LOS was longer in the LRTI group (median [IQR] 12 [9–17] vs. 5 [3–9], $p < 0.01$). Furthermore, hospital LOS was also longer for those with LRTIs when compared to patients without LRTIs (median [IQR] 21 [13–33] vs. 10 [5–18], $p = 0.01$). Time on the ventilator was significantly longer for those with LRTIs (median [IQR] 9 [5–12] vs. 4 [3–7], $p < 0.01$).

Potential predictors for the primary outcome (LRTIs) were identified in the bivariate analysis ($p < 0.1$) and included age, ISS, mean blood pressure on admission, GCS, AIS of the head and the thorax, hemoglobin on admission, serum glucose on admission, SOFA, APACHE II, and invasive mechanical ventilation on admission. After multivariable analysis, the following variables remained significantly associated with LRTI ($p < 0.05$): age (OR 1.1, 95% CI, 1.01–1.2), severe TBI (OR 2.7, 95% CI, 1.1–6.9), AIS thorax (OR 1.4, 95% CI, 1.1–1.8), and mechanical ventilation on admission (OR 3.7, 95% CI, 1.1–13.5) (Table 3).

In univariate analysis, LRTI was not significantly associated with mortality (OR 1.01, 95% CI 0.88–1.18, $p = 0.7$). Variables associated with mortality ($p < 0.1$) in the univariate analysis included AIS head (OR 1.1, 95% CI 1.07–1.13, $p < 0.01$), ISS (OR 1.01, 95% CI 1.001–1.1, $p < 0.01$), oxygen saturation on admission (OR 0.5, 95% CI, 0.3–0.9, $p = 0.03$), severe TBI (CGS ≤ 8) (OR 1.2, 95% CI 1.08–1.31, $p \leq 0.01$), SOFA score (OR 1.03, 95% CI 1.01–1.05, $p < 0.001$), APACHE II score (OR 1.02, 95% CI 1.01–1.03, $p < 0.001$), and blood transfusions (OR 1.1, 95% CI 1.01–1.22, $p = 0.02$).

Variables associated with mortality in the multivariable analysis included AIS head, APACHE II score, and transfusion of blood components (Table 4). Multivariate logistic regression also failed to demonstrate a significant association between LRTIs and mortality.

TABLE 3 Multivariate logistic regression analysis for LRTI in TBI patients admitted to ICU.

Variable	OR (95% CI)	p value
Age	1.1 (1.01–1.20)	**0.04**
ISS	1.0 (0.98–1.03)	0.7
MBP on admission	1.0 (0.99–1.03)	0.22
AIS head	1.13 (0.85–1.48)	0.39
AIS thorax	1.42 (1.13–1.79)	**<0.01**
Hemoglobin on admission	1.09 (0.98–1.24)	0.12
Glucose on admission	1.0 (1.0–1.01)	0.06
SOFA admission	0.98 (0.85–1.14)	0.87
APACHE admission	0.93 (0.87–0.99)	0.053
MV on admission	3.7 (1.24–13.5)	**0.026**
GCS ≤ 8	2.7 (1.11–6.94)	**0.032**

Bold values indicate statistically significant.

TABLE 4 Multivariate logistic regression analysis for mortality in TBI patients admitted to ICU.

Variable	OR (95% CI)	*p value*
AIS head	2.25 (1.54–3.47)	**<0.001**
ISS	0.99 (0.95–1.02)	0.56
$SatO^2$ on admission	0.4 (0.01–2.1)	0.65
Severe TBI	0.5 (0.18–1.56)	0.25
Transfusions	2.2 (1.10–4.7)	**0.032**
SOFA admission	0.96 (0.82–1.13)	0.87
APACHE admission	2.2 (1.1–4.7)	**<0.001**

Bold values indicate statistically significant.

Discussion

In this study, we found that a diagnosis of infection was made in almost half of the patients, with the respiratory system being the prevailing source. Among the different types of LRTIs, the most frequent was VAT. Patients who presented an LRTI had a more severe injury to the head and other body regions, had greater disease severity scores, and were older. We identified the following potential predictors for developing LRTIs after TBI in the ICU: age, severe TBI, trauma to the thorax, and being on mechanical ventilation. When comparing outcomes, those who presented with an LRTI stayed longer in the ICU and the hospital and spent more days on mechanical ventilation. However, mortality was not different even after adjusting for age and severity of trauma. This is consistent with a recent large prospective multicenter study that focused on VAP (10).

Previous cohorts had characterized the epidemiology of infections in TBI and found a respiratory source in frequencies as high as 94% of cases (20, 21). We assessed the diagnosis of LRTI through the ATS/IDS guidelines, which include clinical, radiological, and microbiologic criteria. Interestingly in our cohort, the most common type of LRTI was VAT, diagnosed in patients with fever, new or increased sputum production, microbial isolation in tracheal aspirate, and no radiographic evidence of pneumonia (15). Diagnosis and treatment of VAT are controversial and not readily recognized by some, partly due to the difficulty in evaluating infiltrates in a portable X-ray in the ICU. Moreover, severely traumatized patients might have potential confounders like lung contusion and aspiration. However, in the available literature, VAT has been associated with worse clinical outcomes, including progression to VAP, more extended ICU stay, and time on mechanical ventilation (13, 14). Our results underline the importance of a continuous and individualized evaluation of cases at a higher risk of LRTI, always considering differential diagnoses and context when suspecting a respiratory infection. This approach might lead to an earlier and more precise antibiotic prescription for those with a straightforward diagnosis and to avoid the widespread use of antibiotics when not readily indicated. Furthermore, we must strengthen our bundles of care in mechanical ventilation for this population to prevent and decrease LRTIs.

Patients with LRTI in our cohort were older and more severely traumatized. However, after multivariate analysis, the potential risk factors that remained were age, the severity of TBI, thoracic trauma, and being on mechanical ventilation. Other studies have found different variables associated with LRTIs, including blood transfusions, barbiturates infusion, spinal trauma, and ISS (11, 12, 14). Thoracic trauma represents a structural lung disruption that leads to inflammatory changes but does not necessarily end in a respiratory infection (22–24). As differentials, lung contusion, or aspiration warrants a thorough evaluation before diagnosing LRTI and prescribing antibiotics.

We found the severity of TBI as a potential risk factor for LRTIs. Patients with worse TBI might need higher and longer doses of sedation and are more frequently on advanced respiratory support (25, 26). These variables (sedation and mechanical ventilation) have been identified as predictors of LRTI (11). Additionally, we want to highlight that some clinical and preclinical evidence has highlighted that TBI might induce a state of immune depression through inflammatory and autonomic pathways (27, 28). This might facilitate the occurrence of sepsis, not only in the acute phase but also afterward (4). Several animal models have shown evidence that TBI induces cell death mechanisms, including apoptosis, programmed necrosis, or necroptosis (29, 30). Defects in membrane integrity and the release of intracellular components that act like damage-associate molecular patterns (DAMP) induce the further release of cytokines and assembling inflammasomes (8).

The IMPACT study demonstrated that plasma cytokine concentrations are associated with organ dysfunction, mortality, and poor outcomes in TBI [32]. Further research is needed on how this state of immune depression affects outcomes in the TBI population.

Regarding outcomes, patients who suffered from LRTIs had longer ICU and hospital stays and spent longer on respiratory support than those without LRTIs. However, mortality was not significantly different between those cohorts. Previous studies found that LRTI was associated with longer hospital stays, mechanical ventilation, and healthcare costs, coinciding with our results. On the contrary, the results regarding mortality might differ among cohorts (7, 13, 14). One meta-analysis included 15 studies of VAP in TBI and found longer hospitalization but no significant difference in mortality (11). These findings could be related to the awareness of the risk of infection and early antibiotic prescription in cases suspected to have LRTI, which avoids the progression of sepsis and death. However, antibiotics are sometimes not indicated, leading to overuse and increased bacterial resistance. Another explanation for no difference in mortality could be the heterogeneity in the type and severity of TBI, associated injuries, and criteria used for diagnosis of LRTI. These variables might be a difficulty when comparing cohorts and analyzing outcomes.

The main limitation of this study is that patient enrollment was retrospective using electronic medical records. Data collection relied on previous registries, which makes some information challenging to confirm. However, we used standardized definitions and scores to address this limitation and to confirm admission and hospital diagnoses. Outcomes and complications were also evaluated using a thorough medical chart review. Another limitation we acknowledge is that it was a single-center study, which means the generalizability of results can be compromised.

In conclusion, LRTI is a frequent complication in patients with TBI and impacts clinical outcomes. Potential predictors of LRTI

were identified; however, these findings are meant to be translated in the future into new hypotheses that deepen our understanding of the immune response in patients with TBI and ultimately lead to the design of novel prognostic and therapeutic tools.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Universidad de La Sabana. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

EC: data analysis, statistical analysis, writing, and edition. MY, EV, and JO: data gathering, review, and edition. LE: data gathering, writing, and edition. NB: data gathering and edition. IM-L: writing, review, and edition. LR: data analysis, writing, review, and edition. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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