A novel nomogram to predict 90-day mortality of patients with sepsis

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Research

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Abstract

Background

Sepsis is a prevalent disease among intensive care units and continues to be a frequent cause of death. This study aimed to establish a nomogram for mortality prediction in patients with sepsis.

Methods

We carried out a retrospective, single-center study based on 231 patients with sepsis and data was collected from May 2018 to October 2020. Patients were randomly split into training and validation cohorts. In the training cohort, multivariate logistic regression analysis and a stepwise algorithm were performed to identify risk factors, which were presented with a predictive nomogram. The receiver operating characteristic (ROC), calibration plots and decision curve analysis (DCA) were used to estimate the performance of the nomogram in both the training and validation cohorts.

Results

A total of 231 patients with sepsis were enrolled in the study, and the 90-day mortality was 31.6%. There were 161 and 70 cases in training and validation cohorts respectively. Statistical analyses showed that Age, international normalized ratio (INR), lactate (Lac), and thrombomodulin (TM) were the risk factors for 90-day mortality. The area under the curve was 0.810 (95% CI, 0.739 to 0.881) in training cohort and 0.813(95% CI, 0.708 to 0.917) in the validation cohort. Calibration curve showed good performance of this nomogram. Decision curve analysis demonstrated that the nomogram was clinical utility.

Conclusion

This nomogram offering a probability of mortality for a given patient can benefit outcome improvement and clinicians in making clinical decision.

Introduction

Sepsis is a life-threatening organ dysfunction initiated by the body's overwhelming response to infection [1]. Past decades witnessed sepsis as an important public health problem in the worldwide. Although significant advances have made in intensive care and supportive technology, there is high morbidity and mortality in sepsis. More unfortunately, it imposes heavy medical and financial burden on families and society. Fleischmann et al reported the incidence rate was 437 sepsis cases per 100 000 person-years and the hospital mortality was 17% in the worldwide during the last decade [2]. Interestingly, in China, the mortality of sepsis is higher, and the incidence rate of sepsis in ICU is 20.6% [3]. The pathogenesis of sepsis is very complex, involving coagulation disorders, inflammation imbalance, immune dysfunction,

mitochondrial damage and endothelial damage [4]. A better understanding of this disease's pathophysiological processes and identifying its high risk of short-term mortality are of great significance for medical intervention and prognostic improvement. There are numerous studies of risk factors for mortality in patients with sepsis [5–9], but most of them only pay attention to biomarkers involving inflammatory states and certain organ functions, and combining different risk factors to develop a predictive nomogram is rarely performed. Therefore, the main objective of this study is to construct a predictive nomogram in order to individually predict the probability of 90-day mortality in sepsis.

Material And Methods

Patients and data collection

A total of 231 patients who had been diagnosed with sepsis admitted to ICU in the 908th People's Liberation Army Hospital, Nanchang, China, from May 2018 to October 2020. We selected adult patients (> 17 years of age) with a diagnosis of sepsis according to the Third International Consensus Definitions for Sepsis (Sepsis-3)[10]: (1) Patients with infection confirmed by the positive results of microbial cultivation and (2) the Sequential Organ Failure Assessment (SOFA) score ≥ 2 [4]. Excluded were patients (1) under 18 years of age, (2) pregnancy, (3) hemorrhagic shock, (4) cancer, (5) acute coronary syndrome, (6) cardiopulmonary arrest. The following variables were retrospectively collected: baseline demographic data (age and gender), site of infection, comorbid conditions and mortality in 90 days. The severity of illness was evaluated by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score [11] and the Sequential Organ Failure Assessment (SOFA) score[12] respectively, and they were calculated on a basis of clinical and laboratory values. The APACHE II score and SOFA score were calculated on the first day of ICU admission. The alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin (TBil), serum creatinine (Cr), platelet count (PLT), prothrombin time (PT), international normalized ratio (INR), activated partial thrombin time (APTT), fibrinogen (FIB), thrombin time (TT), D-dimer, fibrinogen degradation product (FDP), thrombin-antithrombin complex (TAT), $\alpha 2$ -plasmininhibitor-plasmin complex (PIC), thrombomodulin (TM), and tissue plasminogen activator-inhibitor complex (t-PAIC), were recorded. Other clinical variables, such as mean arterial pressure (MAP), temperature, heart rate, hemoglobin(HB), potential of hydrogen (PH), arterial partial oxygen pressure (PaO₂), arterial partial pressure of carbon dioxide (PaCO₂) and lactate (Lac), were also recorded.

Study design

Statistical analysis

Data for continuous variables were presented as means $\pm$ standard deviation or median with interquartile range (IQR). They were compared using Student's t-test (normal distribution) or Mann-Whitney (non-normal distribution). Categorical variables, expressed as counts and percentages, were compared using χ^2 test or Fisher's exact test. The variance inflation factor (VIF) was used to test collinearity between continuous variables, and an arithmetic square root of $VIF \leq 10$ was regarded as non-collinearity. Clinical

variables in the training cohort were entered into multivariate logistic regression analysis and backward step-wise selection was applied by using the likelihood ratio test with Akaike’s information criterion as the stopping rule [13]. In order to provide clinicians with a quantitative tool to predict 90-day death of sepsis, we built the predictive nomogram on the basis of multivariable logistic analysis in the training cohort. The performance of this nomogram was composed of calibration and discrimination. Calibration curves were used to evaluate the calibration of the predictive model, accompanied with the Hosmer-Lemeshow test. The discriminative ability of the predictive nomogram was assessed by a receiver operating characteristic (ROC) curve. For clinical usefulness, net benefit was examined in both of the training and validation cohorts by decision curve analysis (DCA). All the statistical analyses were performed with R version 4.0.1 (R Core Team, Vienna, Austria) and SPSS 25.0 software (SPSS Inc, Chicago, IL, USA). The two-sided P values < 0.05 were considered statistically significant.

Results

Clinical characteristics of patients

After screening by the inclusion and exclusion criteria, a total of 231 patients were included into the study. For these cases, the median age was 70 years old (range from 18 to 96 years old) and males accounted for 61.9%. A total of 73 patients passed away within 3 month during the study period, resulting in the mortality of 31.6%. The survival patients generally had lower level of t-PAIC, TAT, PT, INR, APTT, TT, FDP, D-dimer, Creatinine, Lac, Heartrate, SOFA, APACHEII, and higher levels of PLT, HB, and PaO2 in the two cohorts. Besides, the survival patients exhibited higher level of serum PH value in validation cohort. The other detailed clinical characteristics and results of univariate analysis are shown in Table 1.

Table1 Patients’ baseline characteristics at ICU admission

Clinical characteristics	Training cohort			Validation cohort		
	Survival patients (n =112)	Non-survival patients (n = 49)	p value	Survival patients (n =46)	Non-survival patients (n =24)	p value
Male, n (%)	69(61.6)	30(61.2)	0.963	29(63.0)	15(62.5)	0.964
Age ≥ 57(y), n (%)	47(42.0)	32(65.3)	0.006	30(65.2)	22(91.7)	0.016
Comorbidity						
Diabetes, n (%)	17(15.2)	10(20.4)	0.414	17(37.0)	9(37.5)	0.964
Hypertension, n (%)	42(37.5)	26(53.1)	0.066	21(45.7)	12(50.0)	0.729
COPD, n (%)	6(5.4)	6(12.2)	0.126	8(17.4)	6(25.0)	0.450
CKD, n (%)	10(8.9)	6(12.2)	0.518	2(4.3)	3(12.5)	0.209
Source of infection						
Pulmonary, n (%)	71(63.4)	33(67.3)	0.629	27(58.7)	19(71.2)	0.087
Urinary tract, n (%)	8(7.1)	1(2.0)	0.195	5(10.9)	0(0)	0.094
Abdominal, n (%)	27(24.1)	14(28.6)	0.550	13(28.3)	3(12.5)	0.136
Skin (%), n (%)	6(5.4)	2(4.1)	0.732	2(4.3)	1(4.2)	0.972
TM ≥ 13.1(TU/mL), n (%)	17(15.2)	22(44.9)	0.000	17(37.0)	17(70.8)	0.007
TAT(ng/ml)	8.2(4.6-18.0)	17.2(5.7-46.8)	0.002	8.7(5.6-17.0)	13.4(6.2-30.9)	0.162
PIC(ug/mL)	1.16(0.62-2.16)	1.04(0.57-2.28)	0.742	1.10(0.75-1.48)	1.43(0.69-2.83)	0.421
t-PAIC(ng/ml)	12.2(7.6-24.1)	21.7(11.3-41.7)	0.003	14.2(9.4-23.9)	21.3(13.8-47.1)	0.020
PT (s)	14.2(12.7-16.2)	16.4(14.0-21.4)	0.000	13.7(13-15.3)	15(13.6-19.6)	0.008
INR	1.2 (1.1-1.3)	1.4(1.2-1.8)	0.000	1.14(1.08-1.27)	1.25(1.13-1.60)	0.008
APTT (s)	31.6(26.6-38.4)	37.4(32.0-47.7)	0.000	31.4(26.7-40.5)	33.9(29.2-48.7)	0.087

FIB (s)	2.9±1.09	2.6±1.2	0.143	2.9±0.9	2.7±1.3	0.308
TT (s)	15.8(14.5-17.3)	17.2(14.8-18.7)	0.003	15.5(14.0-17.4)	16.8(14.9-19.4)	0.070
FDP(μg/L)	8.69(3.67-18.92)	14.45(4.53-38.00)	0.030	7.56(4.51-13.12)	11.37(6.99-27.95)	0.033
D-dimer(μg/L)	2.59(1.03-5.97)	4.91(1.65-11.00)	0.016	2.19(0.87-4.53)	3.19(2.54-7.76)	0.015
Platelet(× 10 ⁹ /L)	179±90	138±94	0.010	182±108	209±128	0.358
Hemoglobin(g/L)	111±29	100±31	0.038	109±31	104±31	0.525
ALT(U/L)	31.9(12.9-73.5)	21.5(13.3-116.8)	0.597	27.3(13.3-58.7)	29.6(11.1-64.2)	0.921
AST(U/L)	43.0(23.3-84.3)	42.1(26.4-131.2)	0.483	33.2(19.8-72.5)	30.3(19.1-76.7)	0.843
TBil(μmol/L)	13.5(7.9-22.5)	13.9(7.4-32.5)	0.514	14.5(6.8-23.4)	17.6(10.9-28.1)	0.192
Cr (μmol/ml)	92.6(62.3-163.8)	136(76.5-241.4)	0.017	70.3(54.5-132.5)	113.4(78.3-150.0)	0.056
Temperature(°C)	36.7(36.5-37.5)	36.6(36.3-37.3)	0.350	36.7(36.2-37.3)	36.4(36.0-36.8)	0.176
Heart rate(min-1)	96±20	106±25	0.013	98±26	107±26	0.179
MAP (mmHg)	90±17	88±22	0.547	91±17	87±18	0.352
SOFA	7(5-10)	9(7-15)	0.000	7(5-10)	9(6-13)	0.065
APACHEII	21±6	24±6	0.008	22±7	27±7	0.004
PH	7.41 (7.35-7.45)	7.38(7.29-7.50)	0.133	7.42(7.34-7.49)	7.29(7.19-7.43)	0.006
PaCO ₂ (mmHg)	36(31-42)	34(29-40)	0.149	34(28-41)	39(32-46)	0.040
PaO ₂ (mmHg)	110(81-157)	93(64-140)	0.017	112(80-167)	97.1(64-152)	0.366
Lac (mmol/L)	1.7(1-3.2)	3.2(1.5-6.6)	0.000	2.0(1.2-3.3)	3.8(1.8-9.5)	0.010

COPD chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *TM* thrombomodulin, *TAT* thrombin-antithrombin complex, *PIC* α₂-plasmininhibitor-plasmin complex, *tPAIC* tissue plasminogen activator-inhibitor complex, *PT* prothrombin time, *APTT* activated partial thrombin time, *FIB* fibrinogen, *INR* international normalized ratio, *TT* thrombin time, *FDP* fibrinogen degradation product, *ALT* alanine transaminase, *AST* aspartate transaminase, *TBil* total bilirubin, *MAP* mean arterial pressure, *SOFA*

Sequential Organ Failure Assessment, *APACHEII* Acute Physiology and Chronic Health Evaluation II, *PH* potential of hydrogen, *PaO₂* arterial partial oxygen pressure, *PaCO₂* arterial partial pressure of carbon dioxide, *Lac* lactate.

Development of an Individualized Prediction Model

Multiple logistic regression analysis identified the age, INR, Lac, and TM as independent predictors (Table 2). This model that contained the above independent predictors was developed and presented as the nomogram (Fig 1).

Table 2 Factors independently associated with 90-day mortality of patients with sepsis in the multivariate logistic analysis

Variables	OR	95% CI	P value
Age (≥57 y vs.<57 y)	1.20	0.36-2.04	0.005
TM(≥13.1 TU/mL vs. <13.1 TU/mL)	1.30	0.39-2.21	0.005
INR	1.52	0.23-2.80	0.021
Lac(mmol/L)	0.17	0.04-0.29	0.008

INR international normalized ratio, *TM* thrombomodulin, *Lac* lactate,

Validation of the prediction nomogram

The calibration curve of this nomogram for the probability of 90-day mortality demonstrated an excellent conformity between prediction and observation in the training and validation cohorts although the logistic calibration curve and nonparametric curve slightly deviated from ideal line (Fig 3). In addition, the Hosmer-Lemeshow test showed a nonsignificant statistic ($P > 0.05$), which indicated that there was no violation of perfect fit.

Clinical application of the nomogram

The decision curve analysis (DCA) was performed in the training and validation cohorts in order to assess the clinical usefulness of the predictive nomogram. It is presented in Fig. 4A and B, respectively. The decision curve showed that the nomogram could provide a good clinical utility. The result showed that if the threshold probability of a patient or doctor is approximate > 15%, using the nomogram to predict 90-day death can reap more benefit than either the treat-all-patients scheme or the treat-none scheme.

Discussion

In this study, the 90-day mortality was 31.6%, which is higher than other studies [2, 3, 5]. The major reason for this difference in mortality may be different follow-up days. Nomograms which base on a combination of risk factors are frequently used to estimate prognosis and it can well show the significance of factors in the outcome. Risk factors for short-term mortality in sepsis have been studied in recent decades, but a large number of previous reports have only described potential risk factors without developing nomogram, resulting in predicting prognosis inaccurately. In this study, we created a nomogram to predict 90-day mortality for patients with sepsis. This nomogram incorporates age, INR, Lac, and TM, which were identified by multiple logistic regression analysis. As a result, the usefulness of this nomogram for prognosis in patients with sepsis has the advantage of accurate prediction and the outcome prediction can be more individualized.

We all know that coagulopathy is frequently observed in sepsis [14] and plays a vital role in multiple organ dysfunction syndrome [15]. Lyons et al reported that the increased severity of coagulopathy can lead to increased mortality [16]. Besides, hemostasis-related parameter has also been reported as a predictor of sepsis-related mortality [17–19]. In this study, we found that the INR value in death group was significantly higher than in survival group and it was an independent factor for 90-day death identified by multivariate analysis. However, it is less likely to use INR alone to accurately assess the outcomes of sepsis patients [5].

Serum lactate levels are often considered as a marker of tissue hypoxia [20] and it is commonly used to estimate prognosis and guide clinical treatment [21]. Interestingly, the higher level of lactate has always been found in critically ill patients, particularly in sepsis and septic shock patients [22]. Previous studies revealed that lactate levels correlate strongly and positively with disease severity and mortality in the context of sepsis [23–25]. Additionally, the sepsis-3.0 guidelines recommended persistence of a serum lactate more than 2 mmol/L as a new criterion for the clinically identification of septic shock [10]. In agreement with previous studies, we found that the lactate level in death group was significantly higher than in survival group and presented as an independent risk factor for sepsis mortality.

Increased levels of serum TM have been found in both pediatric and adult sepsis [26, 27]. During sepsis, the primary site of deterioration is endothelium because it is damaged directly by mass proinflammatory cytokines [28]. TM, an integral endothelial cell membrane protein, is cleaved and released into the bloodstream during sepsis and septic shock, thereby leading to elevated levels of serum TM [29, 30]. Additionally, previous studies have shown that increased serum TM level is associated with disease severity and a high risk of death in sepsis [27, 30]. In this study, we observed that the TM levels measured were significantly increased in death group when compared with the survival group, and the higher TM levels were associated with poor outcome.

ROC analysis is a very important method to evaluate the performance of a model [31]. In this study, the ROC curve showed that the AUC was 0.810 in the training cohort and 0.812 in the validation cohort, which indicates that our predictive model has a good ability to predict. In other word, the predictive model has good discrimination. However, an AUC alone to assess a model in improving clinical decision-making is

inadequate. Therefore, decision curve analysis was used to further assess the performance of the model because it can evaluate the net benefit of model-assisted decisions under different threshold probabilities. In this study, the decision curve showed that treatment directed by nomogram was obviously superior to the treat-all-patients project or the treat-none project. It's prognosis predicted by this nomogram that can add more net benefit for patients with sepsis in the training and validation cohorts. Besides, the calibration curve showed that the model was a good fit. Overall, all of these findings put together indicate that the predictive nomogram is highly accurate in predicting sepsis-related mortality.

Some potential limitations of this study should be noted. First, this database contained data obtained from a single center, and the size of this study population is small. Therefore, the results obtained may have limited external validity because we did not use an external population to validate the predictive nomogram. Another limitation of this study is that the data was collected in a retrospective manner. In the future, a multicenter study with external validation should be performed to further confirm performance of the nomogram.

Conclusion

We developed a novel predictive nomogram that incorporated patients' age, INR, Lac, and TM, which can be conveniently used to facilitate accurate prediction of the 90-day mortality in patients with sepsis.

Abbreviations

COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; TM: thrombomodulin; TAT: thrombin-antithrombin complex; PIC: α 2-plasmininhibitor-plasmin complex; tPAIC: tissue plasminogen activator-inhibitor complex; PT: prothrombin time; APTT: activated partial thrombin time; FIB: fibrinogen; INR: international normalized ratio; TT: thrombin time; FDP: fibrinogen degradation product; ALT: alanine transaminase; AST: aspartate transaminase; TBil: total bilirubin; MAP: mean arterial pressure; SOFA: Sequential Organ Failure Assessment; APACHEII: Acute Physiology and Chronic Health Evaluation II; PH: potential of hydrogen; PaO₂: arterial partial oxygen pressure; PaCO₂: arterial partial pressure of carbon dioxide; Lac: lactate; IQR: median with interquartile range; VIF: variance inflation factor; DCA: decision curve analysis; ROC: receiver operating characteristic; 95% CI: 95% Confidence interval; ICU: intensive care unit.

Declarations

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None

Authors' contributions

QBZ, LPH and JCS designed this study. LPH collected the data. NQZ, LCZ and QWL were responsible for the statistical analysis. QBZ and LPH were the first writing authors of the manuscript. JCS finalized this manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate

The study was approved by the Ethics Committee of all the study centers. Written informed consent was waived by the Ethics Commission of 908th hospital.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

No individual participant data is reported that would require consent to publish from the participant.

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Figures

Figure 1

a nomogram for predicting 90-day mortality of patients with sepsis. This nomogram was developed in the training cohort, including the Age, INR, Lac, and TM.

Figure 2

ROC curve for the nomogram of 90-day mortality in patients with sepsis. A. ROC curve for the training cohort; the AUC was 0.810 (95%CI, 0.739 to 0.881). B. ROC curve for the validation cohort; the AUC was 0.813(95% CI, 0.708 to 0.917).

Figure 3

A calibration plot of the predicted and observed probabilities of 90-day mortality in the training cohort (A) and in the validation cohort (B).

Figure 4

Decision curve analysis of clinical intervention in patients with the nomogram in the training cohort (A) and validation cohort (B).