

Establishment and Verification On A Death Risk Model of Sepsis Patients Within 30 Days

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Abstract

Background/Objective:

To establish and validate an individualized nomogram to predict the probability of death within 30 days in patients with sepsis would help clinical physicians to make correct decision.

Methods

We collected data of 1,205 patients with sepsis. These included 16 indexes like age and blood, randomly assigned to the modeling and verification groups. In the modeling group, the independent risk factors related to death within 30 days were analyzed. Besides, a nomogram was established to draw the receiver-operating characteristic (ROC) curve of the subjects. Subsequently, the discriminant ability of the model was evaluated by the area under the ROC curve (AUC). Then, a calibration chart and Hosmer-Lemeshow test were employed to evaluate the calibration degree of the model, and the Decline Curve Analysis (DCA) test was used to evaluate the clinical effect of the model.

Results

The different independent risk factors related to the death of sepsis patients within 30 days included pro-brain natriuretic peptide (pro.bnp), albumin, lactic acid (lac), oxygenation index, mean arterial pressure (map), and hematocrit (hct). The AUC of the modeling and verification groups were 0.815 and 0.806, respectively. Moreover, the P-values of the Hosmer-Lemeshow test in the two groups were 0.391 and 0.100, respectively, and the DCA curves of the two groups were both above the two extreme curves.

Conclusion

Our model presents good significance for predicting the death of sepsis patients within 30 days. Therefore, there is a need to implement this model in clinical practice, as prompt prediction could help tailor treatment regimens and enhance survival outcomes.

Introduction

Sepsis has a high fatality rate, leading to increased costs in healthcare[1–4],and identifying severe sepsis patients with a predicted high risk of death and early interventions are the key strategies for improving prognosis[5]. Clinically, to predict outcome of patients with sepsis, various severity scores have been widely used. However, these methods have shortcomings. For example, the APACHEII score is widely applied to assess the prognosis of critically ill sepsis patients but lacks pertinence[6], studies have pointed out that APACHE II score underestimates the risk of death in patients with sepsis in ICU [7]. Similarly, the Simplified Acute Physiology Score II (SAPS II) showed poor calibration in external validation

studies [8, 9]. On the other hand, the SOFA score describes the development of multiple organ dysfunction syndromes, but also shows defects when evaluating prognosis[10]. To date, there is a lack of evaluation methods for the short-term prognosis of sepsis patients. Therefore, this study aims to establish a risk prediction model for sepsis patients to predict their death risk within 30 days and only intervene in the high-risk patients to reduce the mortality rate.

Materials And Methods

Subjects: This study included 1,205 patients diagnosed with sepsis from June 1, 2013, to September 1, 2020. Our inclusion criteria were as follows: 1. A diagnosed infection; 2. Infection caused the SOFA score to increase by 2 points or more. The exclusion criteria were: 1. Less than 18 years old; 2. Patients with leukemia, lymphoma, and end-stage tumor; 3. Patients with uncertain prognosis indicators; 4. Patients with some missing sepsis indicators.

Observation indexes

Basic patient information (gender and age) and blood sample indexes, including oxygenation index, high sensitivity -C reactive protein (crp), creatinine (cr), emergency procalcitonin (pct), activated partial thromboplastin time (aptt), albumin, prothrombin time (pt), pro.bnp, pH value, lactic acid (lac), hematocrit (hct), platelet (plt), and the mean arterial pressure and heart rate at the time of hospital admission, were recorded for the first time within 24 hours after hospital admission. The international common unit at present was taken as the index unit.

Ethics statement

This study was approved by the Ethics Committee of Dongyang People's Hospital, and the written informed consents of all patients were obtained. All data were analyzed anonymously, and no personal information was recorded during sessions. This study was conducted following the principles outlined in the Helsinki Declaration and its amendments.

Methods: The patient data (in excel, pct>100 is marked as 100; pro.bnp>35000 is marked as 35000) were collected. The createDataPartition function in R statistical package was employed to randomly divide patients into modeling and verification groups according to a death ratio of 7:3.

In the modeling group, the visreg function evaluated whether there is a linear relationship between each continuous variable and death. Since the continuous variables lacked a linear relationship with death, they were converted into classified variables. Moreover, the one-factor analysis related to death was performed using the twogrps function (found in the CBCgrps package), which can automatically distinguish whether the data are per normal distribution. Thus, the correlation test method was selected. Multiple collinearity tests were conducted on meaningful variables in the single-factor analysis, and variance expansion coefficient and VIFs values were adopted to enhance interpretation. VIFs \geq 10 indicated

no multiple collinearities among variables. Therefore, multivariate analysis was included after excluding multiple collinearities.

Significant variables in multivariate analysis were used to establish prediction models, which were presented as a nomogram. The nomogram could directly show the relationship between each variable and death and calculate the risk of death individually[11].

The model was evaluated from three perspectives: discrimination, correction, and clinical significance.

AUC evaluated the discrimination of the model. The AUC value between 0.5 and 1.0 indicated that the model was meaningful. The closer the AUC value is to 1, the better the discrimination ability of the model. Specifically, the AUC>0.75 demonstrated that the model had a good discrimination ability[12].

The calibration of the model was evaluated by calibration chart and Hosmer-Lemeshow chi-square test. The bootstrap method was applied in the modeling and verification groups, proving that the model had high stability. The fitting curve showed a high overlap with the standard curve, indicating a good calibration degree. The Hosmer-Lemeshow test, first discovered by Hoslem in R language, was employed, and its p-value was greater than 0.05, suggesting that the model fitting was good[13].

The DCA curve assessed the clinical validity of the model. Interpretation of the curve was as follows: the ordinate denoted the benefit of the evaluation model, and the abscissa denoted the risk value of illness; the model curve was the curve represented by the model, with the 'All' and 'None' curves taken as reference. It was considered that the further the model curve is from the two extreme curves, the greater the clinical significance[14, 15].

Statistical analysis

In this study, the continuity of the measured data, which followed a normal distribution, was analyzed by T-test and expressed as mean±standard deviation. Data that were not normally distributed were analyzed by the Wilcoxon rank-sum test (sample size was less than 5000) and expressed as quartile. Finally, classification variables were analyzed by chi-square test and expressed as a percentage, and the above statistical analysis was completed in R software.

Results

Herein, 1,205 patients were included. The modeling group included 844 cases with 124 death, whereas 361 cases were included in the verification group with 67 death. Thus, the mortality was about 15.8%. In the modeling group, univariate analysis showed that 11 indicators like PCT, MAP, and creatinine were related to prognosis (Table 1).

Table 1
Univariate analysis between survivors and no survivors ^a

Variables	Total (n = 844)	survivals (n = 720)	No survivals (n = 124)	p
Gender, n (%)				0.379
female	333 (39)	289 (40)	44 (35)	
male	511 (61)	431 (60)	80 (65)	
Pt, n (%)				< 0.001
<15(s)	325 (39)	295 (41)	30 (24)	
15-25(s)	492 (58)	406 (56)	86 (69)	
>25(s)	27 (3)	19 (3)	8 (6)	
Aptt, Median (IQR)	46.6 (41.3, 53)	46.2 (41.3, 52.7)	48.75 (41.9, 54.5)	0.073
Oxygenation.Index, n (%)				< 0.001
>300	407 (48)	370 (51)	37 (30)	
<150	68 (8)	42 (6)	26 (21)	
150-300	369 (44)	308 (43)	61 (49)	
Cr, n (%)				< 0.001
<100(mmol/L)	401 (48)	360 (50)	41 (33)	
100-200(mmol/L)	311 (37)	260 (36)	51 (41)	
201-300(mmol/L)	63 (7)	53 (7)	10 (8)	
301-400(mmol/L)	28 (3)	18 (2)	10 (8)	
>400(mmol/L)	41 (5)	29 (4)	12 (10)	
Albumin, Mean \pm SD	28.11 \pm 4.68	28.52 \pm 4.58	25.72 \pm 4.56	< 0.001
Map, n (%)				< 0.001
70-105(mmHg)	678 (80)	608 (84)	70 (56)	
<70(mmHg)	102 (12)	56 (8)	46 (37)	
>105(mmHg)	64 (8)	56 (8)	8 (6)	

Variables	Total (n = 844)	survivals (n = 720)	No survivals (n = 124)	p
Hct, n (%)				< 0.001
0.3-0.459	501 (59)	450 (62)	51 (41)	
<0.3	337 (40)	266 (37)	71 (57)	
>0.459	6 (1)	4 (1)	2 (2)	
Pct, Median (IQR)	13.95 (2.83, 48.8)	13.07 (2.52, 44.91)	16.86 (3.9, 88.58)	0.009
Crp, Median (IQR)	169.6 (117.89, 200)	169.35 (120.33, 200)	172.6 (90.72, 200)	0.734
Ph, Median (IQR)	7.41 (7.35, 7.45)	7.41 (7.36, 7.45)	7.34 (7.24, 7.42)	< 0.001
Plt, n (%)				< 0.001
100-300(10*9/L)	501 (59)	443 (62)	58 (47)	
<50(10*9/L)	109 (13)	72 (10)	37 (30)	
50-99(10*9/L)	190 (23)	165 (23)	25 (20)	
>300(10*9/L)	44 (5)	40 (6)	4 (3)	
Pro.bnp, n (%)				< 0.001
<2000(pg/ml)	402 (48)	373 (52)	29 (23)	
2000-10000(pg/ml)	290 (34)	236 (33)	54 (44)	
10001-20000(pg/ml)	75 (9)	56 (8)	19 (15)	
>20000(pg/ml)	77 (9)	55 (8)	22 (18)	
Lac, Median (IQR)	2.4 (1.6, 4.1)	2.3 (1.5, 3.6)	3.9 (2.18, 7.7)	< 0.001
Age, Median (IQR)	75 (64, 83)	74 (63, 83)	78.5 (67.75, 85.25)	0.001
heart.rate, Median (IQR)	124 (108, 142)	122 (107, 140)	133.5 (120, 152.5)	< 0.001

a Continuous variables are described by means and quarterbacks. Categories varies are analyzed by χ^2 test and continuous variables are analyzed by Wilcoxon rank sum test.

Multiple collinear tests were performed on the meaningful indexes in single-factor analysis. However, their VIFs values were all less than 10, proving no obvious collinear relationship among the factors (see

attached Table in Supplementary Dataset). Multivariate logistics analysis was conducted on death-related variables within 30 days based on univariate analysis. Here, brain pro-natriuretic peptide, lactic acid, albumin, oxygenation index, mean arterial pressure, and hematocrit were all independent risk factors (Table 2).

Table 2
Multivariate logistic regression analysis of involved variables.

Variables	B	SE	WaldX2	P	OR(95%CI)
(Intercept)	12.552	9.298	1.350	0.177	2.827*10 ⁵ (0.003-2.255*10 ¹³)
Pt15-25(s)	0.091	0.269	0.338	0.735	1.0950(0.650-1.874)
Pt>25(s)	-0.274	0.615	-0.445	0.657	-0.761(0.214-2.431)
Oxygenation.Index<150	1.076	0.370	2.911	0.003	2.933(1.411-6.032)
Oxygenation.Index150-300	0.445	0.255	1.741	0.082	1.560(0.948-2.587)
Cr100-200(mmol/L)	-0.126	0.274	-0.461	0.645	0.881(0.513-1.505)
Cr201-300(mmol/L)	-0.852	0.498	-1.712	0.087	0.427(0.154-1.087)
Cr301-400(mmol/L)	0.071	0.572	0.124	0.901	1.073(0.335-3.120)
Cr>400(mmol/L)	-0.002	0.515	-0.003	0.997	0.998(0.353-2.680)
albumin	-0.087	0.027	-3.265	0.001	0.916(0.869-0.965)
Map<70(mmHg)	1.554	0.283	5.497	<0.001	4.732(2.714-8.243)
Map>105(mmHg)	0.272	0.447	0.608	0.543	1.313(0.512-3.005)
Ph	-1.947	1.230	-1.584	0.1133	0.143(0.013-1.610)
Plt<50(10 ⁹ /L)	0.381	0.314	1.214	0.225	1.463(0.783-2.685)
Plt50-99(10 ⁹ /L)	-0.146	0.305	-0.480	0.631	0.864(0.467-1.549)
Plt>300(10 ⁹ /L)	-0.554	0.588	-0.942	0.346	0.575(0.156-1.643)
Pro.bnp2000-10000(pg/ml)	0.860	0.282	3.045	0.002	2.363(1.367-4.148)
Pro.bnp10001-20000(pg/ml)	0.893	0.403	2.217	0.027	2.443(1.095-5.348)
Pro.bnp>20000(pg/ml)	1.185	0.422	2.810	0.005	3.271(1.421-7.462)
Lac	0.121	0.041	2.945	0.003	1.129(1.042-1.225)
Heart.rate	0.003	0.005	0.558	0.577	1.003(0.993-1.012)
Hct<0.3	0.727	0.250	2.912	0.004	2.070(1.272-3.395)
Hct>0.459	1.532	1.087	1.410	0.159	4.628(0.471-3.851)

Subsequently, the independent risk factors were selected to establish a nomogram (Figure 1). The specific values of each independent risk factor matched the corresponding scores. Then, the scores were summed to obtain the total score, indicating the corresponding death risk. For example, the patient's albumin content was 27.3g/L; oxygenation index was ≈ 300 ; the mean arterial pressure was 70-105mmhg; pro. bnp was 10,001-20,000pg/ml; the lactic acid value was 7.3mmol/L; hct was ≈ 0.299 . Each item had a corresponding score in β (XM) terms of the nomogram, marked by a red dot. By calculation, the Total score was 2.36, and in Pr (death), the corresponding mortality rate was 21.8% (marked by a red arrow).

Interpreting the model's discrimination, the goodness of fit, and clinical validity were performed using the ROC curve to perform the discrimination of models (Figure 2A). Its AUC value was 0.815, showing a good discrimination ability for the model. The optimum threshold of this model was 0.117, with a specificity of 69.6% and a sensitivity of 77.4%. The calibration chart (Figure 2B) and Hosmer-Lemeshow test were used to assess the goodness of fitting, and the p-value of the Hosmer-Lemeshow test was 0.391, suggesting good fitting. Finally, the DCA curve (Figure 2C) was used to assess clinical effectiveness. The DCA curves of both the modeling and verification groups were above the two extreme curves, indicating that good clinical significance.

Lastly, the verification population was interpreted: In the modeling group, discrimination (Figure 3A), the goodness of fitting (Figure 3B), and clinical effectiveness (Figure 3C) were interpreted, and the AUC value of the verification group was 0.806. The P-value of the calibrated Hosmer-Lemeshow test was 0.100, and the overlap between the fitting curve and the standard curve was high, indicating a good prediction effect and good fitting. Hence, the DCA curve suggested a good clinical efficacy.

Discussion

This study has established a nomogram. It exhibits different indexes as the independent risk factors causing the death of sepsis patients within 30 days. These include the pro. bnp, lactic acid, albumin, hematocrit, oxygenation index for the first time after hospital admission, and the average arterial pressure at admission. This model will help clinicians to analyze the prognosis of sepsis patients and formulate possible intervention measures. Notably, the model was evaluated based on different perspectives, including discrimination, calibration, and clinical effectiveness, and all their results suggest that the model has good significance.

Sepsis is caused by an inability of the immune system to eliminate invading pathogens and immune disorders [16, 17]. It is often manifested as multiple organ dysfunction, including coagulation disorder, cardiac dysfunction, renal insufficiency, nutritional disorder, etc. Many indexes such as PCT[18],CRP[18], renal insufficiency[19], lactic acid[20–22], pro. bnp[23, 24], albumin[25, 26], and coagulation[27, 28] have been reported to have a good effect on the diagnosis and prognosis evaluation of sepsis. This study presents that PCT, CRP, platelet, coagulation, and renal function indicators have less significance in assessing the short-term prognosis of sepsis patients. The PCT and CRP indicators are among the commonly detected indexes in patients with sepsis and are helpful to diagnose and evaluate the severity

of sepsis. However, their values for prognosis evaluation are controversial. Some studies have found no significant correlation between the prognosis of severe patients and the PCT and CRP levels[28, 29]. Abnormal coagulation is common in patients with severe sepsis. Compared to previous studies, this study indicates that the initial coagulation index was not an independent risk factor for the death of patients with sepsis. Besides, it could be related to the presently increased clinical interventions (platelet and plasma transfusion), which could timely correct coagulation functioning. Previous studies have suggested that creatinine has significance in evaluating the prognosis of sepsis patients [19, 30]. However, our study shows that the initial creatinine value has little significance in evaluating prognosis. Thus, the mature and early application of the CRRT technology could be the reason for the declining renal function indicator values in assessing the prognosis of sepsis patients [31].

Lactic acid is one of the indexes of oxygen metabolism, which could gauge prognosis in sepsis and many other critical diseases[20–22]. Pro-bnp is an index reflecting cardiac functioning. Sepsis could trigger septic cardiomyopathy. A study has reported that the death rate of septic patients with septic cardiomyopathy complications increases [32]. Moreover, inappropriate rehydration during treatment could also increase the pro-bnp index. Whether it is caused by sepsis or improper medical treatment, the abnormal pro-bnp increase is considered one indicator for the poor prognosis of sepsis patients[33]. Albumin is an important nutritional index, and since its consumption in sepsis patients increases, malnutrition triggers poor prognosis [25, 26].

The low MAP suggests that sepsis patients are in a state of low perfusion shock, indicating that the disease has entered a severe stage. Elsewhere, studies have reported that the mortality rate of septic shock could reach 33.5%-61%[34, 35], which significantly increases the mortality rate of patients with sepsis.

Many studies have explored the relationship between sepsis and acute respiratory distress syndrome (ARDS), and it is generally believed that sepsis combined with ARDS would increase the mortality rate[36]. Nevertheless, few studies have assessed the relationship between sepsis and oxygenation index. This study suggests that the early decline of the oxygenation index is an independent risk factor for the prognosis of sepsis. Besides, ARDS, cardiac dysfunction, and excessive fluid resuscitation are the reasons for the decreasing oxygenation index and should be actively prevented and treated in clinical medicine.

Furthermore, this study suggests that hematocrit has certain significance in evaluating the short-term prognosis of sepsis patients. Whether the hematocrit is lower or higher than the normal level, it eventually affects the prognosis. Hence, correcting anemia and changing blood concentration could improve the prognosis of sepsis patients.

Unlike previous studies, the independent risk factors related to the death of patients with sepsis within 30 days have been found in this study and presented using a nomogram.

Clinically, various scoring systems had been widely used in the patients with sepsis, but the ability of those scoring systems is insufficient in accurately and reliably predicting mortality in the sepsis patient population. Arabi et al. evaluated four scoring systems in ICU patients with sepsis, reporting poor calibration for all four scores [9]. Compared to the old scoring system, the predictive factors included in this study are objective and simple, and the model has good significance in discrimination, calibration and clinical validity.

Thus, this study could provide a short-term prognosis of sepsis patients in a more intuitive, concrete, and vivid manner when compared with previous studies. Besides, it comprehensively evaluates the model, suggesting that the model is helpful for clinical decision-making.

The limitation of this study

(1) in a retrospective study, selection bias cannot be avoided; (2) it is a single-center study, and real external verification data are lacking.

Declarations

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Author contributions: Chen Jianping set the research objectives, led and supervised the research activities; Wang Bin was responsible for the specific method design, model establishment, and writing the original manuscript draft; Ouyang Jian participated in data collection and preliminary data cleaning.

Data Usability Statement: The minimum basic data describing the original code for establishing our prediction model in R software are uploaded as supporting information. However, due to ethical reasons, the clinical data of patients in our hospital cannot be publicly obtained. Therefore, if anyone is interested in our data, please contact Wang Maofeng (Director of Data Access Committee of Dongyang Hospital Affiliated to Wenzhou Medical University; Email: 13967995216@163.com) and promise to sign a confidentiality agreement for non-commercial purposes.

Conflict of interest: All authors declare no conflict of interest.

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Figures

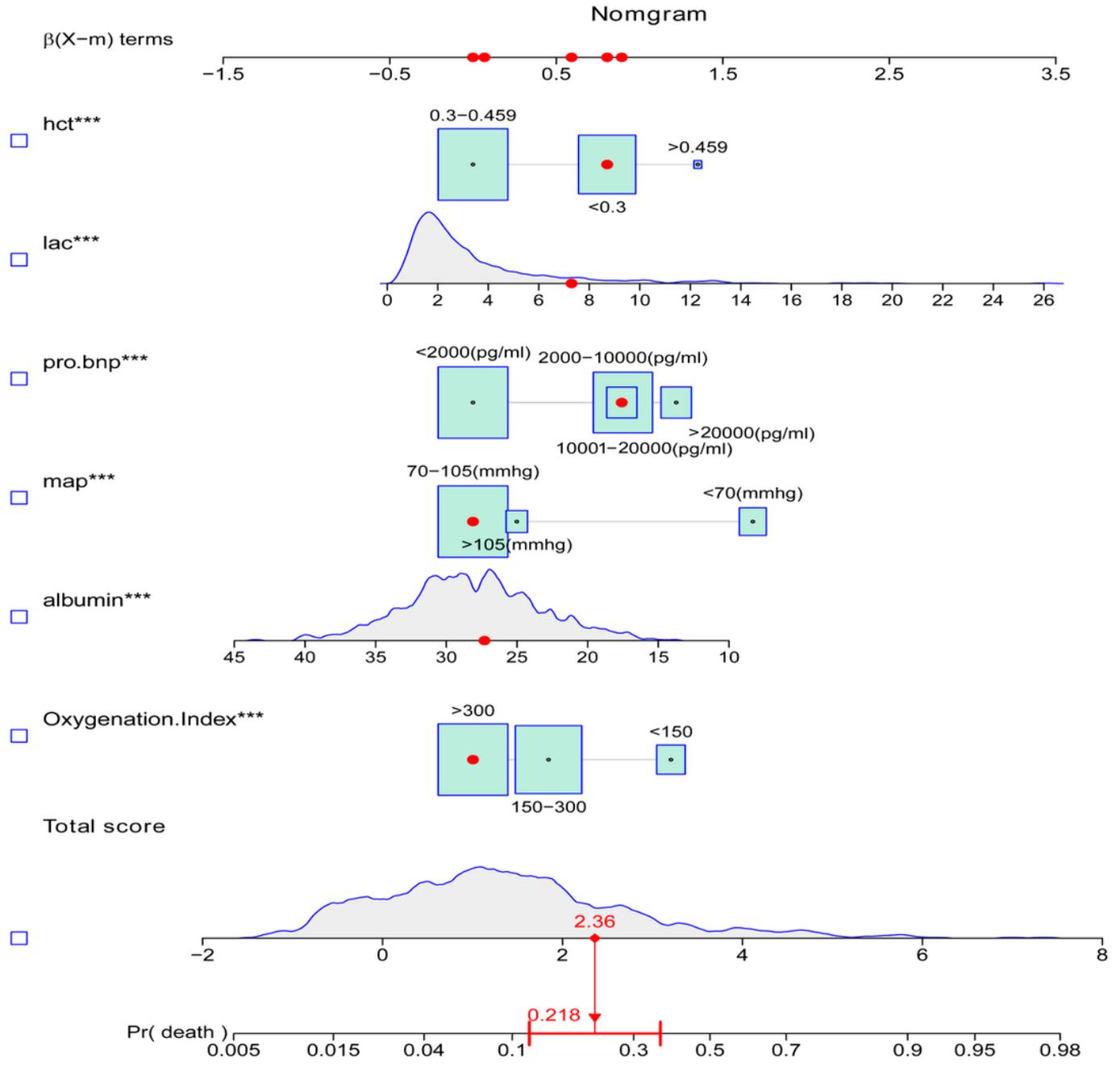


Figure 1

Nomogram for predicting the risk of short-term (30 day) death in patients with sepsis

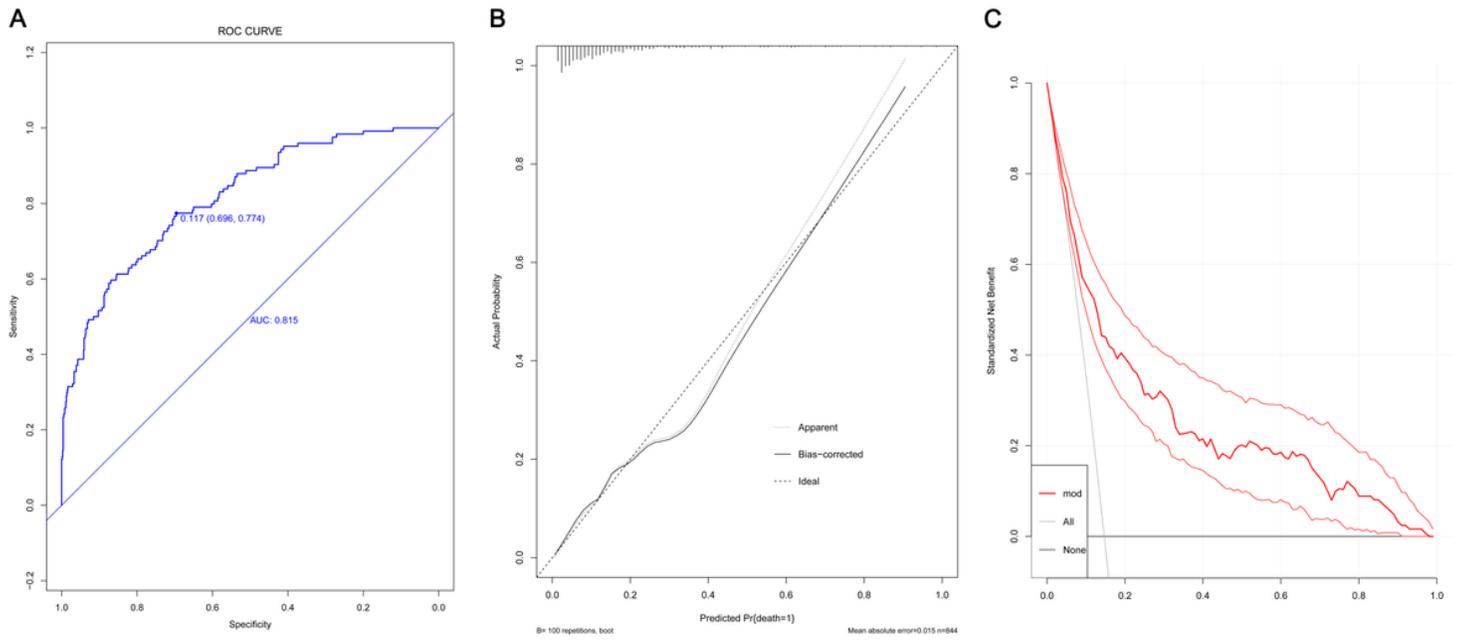


Figure 2

ROC curve,calibration chart and DCA curve in the modeling population

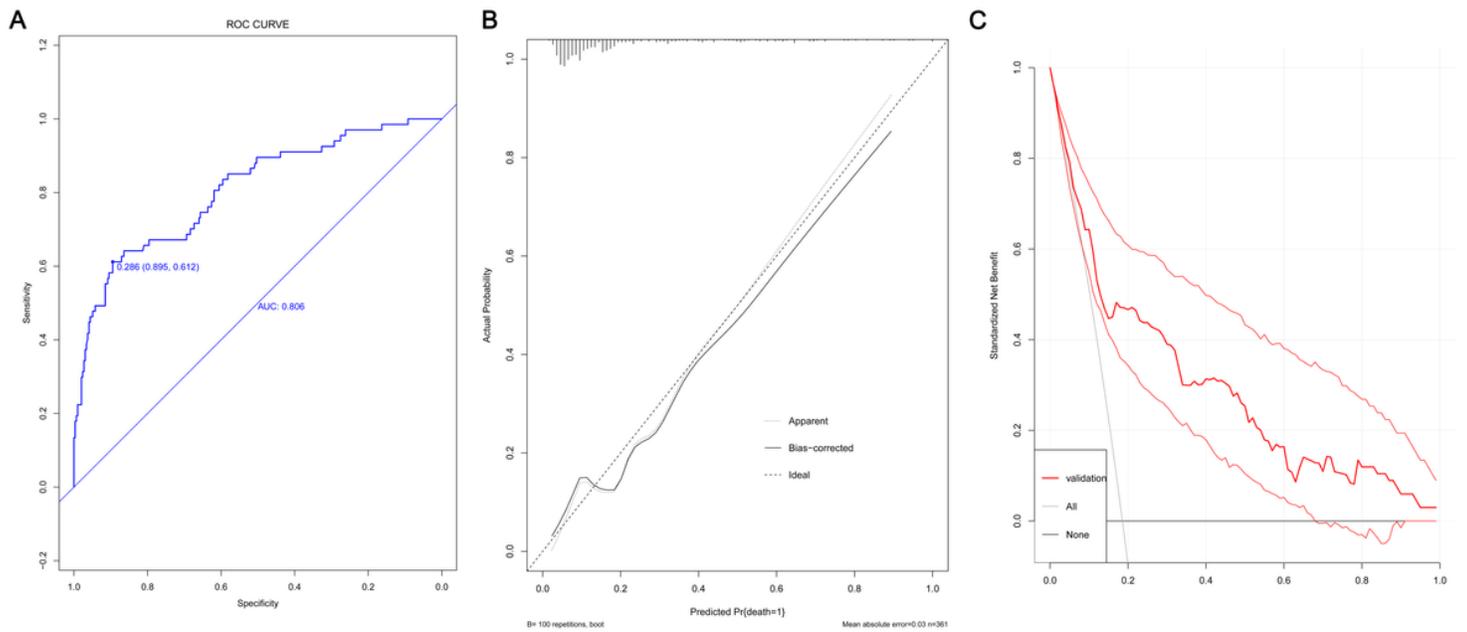


Figure 3

ROC curve,calibration chart and DCA curve in the validation population

Supplementary Files

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

- [AttachedTable.docx](#)
- [Dataofmodelingpopulation.csv](#)
- [Dataofvalidationpopulation.csv](#)