Establishment of a Highly Predictive Survival Nomogram For Patients With Sepsis: A Retrospective Cohort Study

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Research

Keywords: MIMIC-III, sepsis, SOFA score, nomogram, mortality

Posted Date: February 23rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-218217/v1

Abstract

Background: Sepsis is a critical illness common in intensive care units (ICUs) and emergency rooms worldwide and is associated with high morbidity and mortality. However, exisiting methods to predict mortality from sepsis, such as the Sequential Organ Failure Assessment (SOFA) score, are insufficient. This paper aimed to construct a nomogram for predicting the 30-, 60-, and 90-days mortality risks of patients with sepsis that is more accurate than the SOFA score alone.

Methods: Data on sepsis patients were obtained from the Medical Information Mart for Intensive Care (MIMIC) database and analysed retrospectively. The included patients were randomly divided into a training cohort and a validation cohort. The variables included in the training cohort were selected using a backward stepwise selection method with Cox regression, which were then used to construct a prognostic nomogram. In the validation cohort, we compared our prognostic nomogram with the existing SOFA using the area under the time-dependent receiver operating characteristic curve (AUC), net reclassification improvement (NRI), integrated discrimination improvement (IDI), calibration plotting and decision-curve analysis (DCA).

Results: We included a total of 5240 patients in the study, who were divided into the training (n=3667) and validation (n=1573) cohorts. Patient age and the following clinical parameters obtained on the first day of ICU admission were included in the nomogram: SOFA score, metastatic cancer, SpO_2, lactate, body temperature, albumin, and red blood cell distribution width (RDW). The AUCs for the 30-, 60-, and 90-days mortality risks were better for our nomogram than for the SOFA score, with values of 0.766, 0.771, and 0.772, respectively, in the training cohort and 0.759, 0.770, and 0.760, respectively, in the validation cohort. The nomogram also showed good calibration, as indicated by the evidence that the predicted values of the survival risks at 30-, 60-and 90-days were in good agreement with the observed values both in the training and validation sets. In addition, IDI and NRI improved over the entire follow-up period. Finally, DCA was used to verify the clinical value of the model and its impact on actual decision-making. We can see that the net benefit of the nomogram is greater than the SOFA score for any predicted probability, both in the training set and in the validation set, indicating that it has a substantial net benefit in predicting 30-, 60-, and 90-days survival rates.

Conclusions: We established a nomogram that performed better than the SOFA score in predicting the prognosis of patients with sepsis. Further studies with a large sample size are needed to verify the generalizability of the nomogram.

Background

Sepsis, which is defined as an infection with organ failure characterized by a dysregulation of the host's response to the infection, including inflammation and non-immune responses involving multiple systems according to the International Consensus on the Definition of Sepsis and Septic Shock（Version III）in 2016,is common in intensive care units (ICUs) worldwide and has a high morbidity and mortality[1-2]. There

are more than 19 million sepsis cases in the world annually[1], and the fatality rate is reportedly as high as 26.10–42.86%[2].

In the clinic, organ dysfunction can be indicated by an increase in the Sequential Organ Failure Assessment (SOFA) score of 2 points or more, which is associated with an in-hospital mortality rate of more than 10%[3]. SOFA score is a scoring system proposed by the European Society of Critical Care Medicine, which is used to express organ dysfunction. It evaluates the function of six organ systems, including respiration, blood, liver, cardiovascular, central nervous system and kidney, from 0 (no organ dysfunction) to 4 (severe organ dysfunction). The scores of each organ are added together to get the final total score to evaluate the function of multiple organs throughout the body[4] . Randomised controlled trials have confirmed that SOFA score is associated with mortality in ICU patients with suspected infection and has a predictive effect on in-hospital mortality[5-6]. If a patient has a definite site of infection and the SOFA score is greater than or equal to 2, the patient can be diagnosed with sepsis. Septic shock, considered a subtype of sepsis, is characterized by particularly serious circulatory, cellular, and metabolic abnormalities associated with a greater risk of mortality than sepsis alone[7]. Patients with septic shock can be identified by the need for an antihypotensive agent to maintain a mean arterial pressure of 65 mmHg or greater and a serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia[8]. This combination is associated with a hospital mortality rate greater than 40%[32]. A National Institute of Sport, Expertise, and Performance (INSEP) study found that sepsis mortality in the ICU and general hospital was 37.3% and 43.3%, respectively, when using the old sepsis definition in septic shock and 44.3% and 50.9%, respectively, when using the Sepsis-3 definition for sepsis [9].

Early sepsis prognostic assessment is as critical as early sepsis diagnosis and can lead to greater vigilance among medical workers and the provision of timely and appropriate treatment for the patient. Studies have shown that the SOFA and quick SOFA (qSOFA) scores can accurately predict the prognosis of sepsis patients, but nevertheless demonstrate certain limitations[10-11]. For example, improving SOFA does not necessarily reduce mortality, and SOFA scores do not necessarily improve when mortality is reduced. Mortality rates can be significantly affected by factors not included in the SOFA score[4]. The SOFA score was developed more than 20 years ago, and the working group that developed the third definition of sepsis also noted that a number of new markers have emerged that may be superior to existing SOFA indicators, but need to be further validated[6].

A nomogram is a graphical tool based on a statistical prediction model[12] that is used to determine the probability that a single clinical event can occur in a patient. It combines several risk factors to make an accurate prediction and it is widely used for clinical prediction, such as tumor, sepsis and so on[13-14]. However, so far there is no accurate prediction of the prognosis of sepsis at 30, 60 and 90-day.

Here, we aimed to develop a nomogram that can predict the prognosis of patients with sepsis using SOFA score, metastatic cancer, SpO_2, lactate, body temperature, albumin, and red blood cell distribution width (RDW). Notably, the developed nomogram is better than the SOFA score at predicting sepsis prognosis.

This nomogram can potentially be used to inform important treatment decisions in order to decrease the risk of death in patients with sepsis.

Methods

Data source

The Medical Information Mart for Intensive Care-III (MIMIC-III) database was established in 2003 with funding from the National Institutes of Health (NIH) at Beth Israel Deaconess Medical Center and Massachusetts General Hospital, Massachusetts Institute of Technology (MIT)[15]. The current (July 2018) version of the MIMIC-III database is version 1.4 and covers data obtained from 2001 to 2012 from more than 58,000 hospitalizations of patients at Beth Israel Deaconess Medical Center, including 38,645 adult patients and 7875 neonatal patients[16].

This database provides a large amount of real data that can be utilized in clinical research and comprises information related to patients admitted to critical care units at large tertiary care hospitals. Data include vital signs, medications, laboratory measurements, observations and notes charted by care providers, fluid balance, procedure codes, diagnostic codes, imaging reports, hospital length of stay, survival data, and more. All data can be extracted in the SQL language for further analysis. The personnel involved in this research participated in a series of courses provided by the NIH and obtained authorization to access the MIMIC-III database after passing the required assessment (certificate number 38601114). The patient information in the database is anonymous, so informed consent is not required.

Study population

We used ICD-9 codes 99591, 99592, and 78552 to extract data from 7770 patients diagnosed with sepsis, severe sepsis, and septic shock from the MIMIC-III database. According to the new definition of sepsis, septic shock has already included severe sepsis in the old definition. However, since the data collected in the 1.4 version of the database was from 2001 to 2012, the definition of sepsis may still be used in the old version, so we still used the diagnosis of sepsis, severe sepsis and septic shock when extracting the data. The inclusion criteria were as follows:(1) patients who were 18 years of age or older; (2) patients with more than a 24-hour stay in the ICU to ensure sufficient data for evaluation; and(3) patients diagnosed with sepsis according to the Third International Consensus Definitions of Sepsis and Septic Shock (Sepsis-3), including infection and organ failure (SOFA score $\geq$2).For patients who have been admitted to ICU twice or more, we only focus on the information of their first admission to ICU.

Data extraction

All data were translated into SQL for further analysis. The hadm_id variable for each included patient was used to extract the following information from the MIMIC-III database: sex; age; SOFA score; continuous renal replacement therapy (CRRT) use; first care unit (SICU,TSICU,MICU,CCU,CSRU); comorbidities namely congestive heart failure, cardiac arrhythmia, renal failure, liver disease, metastatic cancer (MC), diabetes,

coagulopathy, fluid electrolytes, and blood loss anaemia; laboratory tests namely white blood cell count (WBC), neutrophil percentage (NET), red blood cell distribution width (RDW), haematocrit (HCT), sodium, potassium, albumin, lactate, and blood pH; and vital signs such as(namely) heart rate, respiratory rate, body temperature, and SpO_2。All of the above information and data were extracted from the first 24 h of ICU stay

Statistical analysis and nomogram construction

Continuous variables are expressed as the mean and standard deviation, while categorical variables are expressed as percentages. Multivariate Cox regression was used to select variables for plotting the 30-, 60-, and 90-days survival curves of the patients. The survival-probability nomogram was constructed using Cox regression. The included patients were divided into a training cohort and a validation cohort . The training cohort data were subjected to multifactor Cox regression analysis to control for confounding factors. The analysis presumed that the effects of the predictor variables were constant over time and that there was a linear relationship between the endpoint and predictor variables. Predictor variables that had a highly skewed distribution were subjected to logarithmic transformation to reduce the effect of extreme values, in which case the value of log(variable) could be entered as a predictor variable. SPSS (version 24.0, Chicago, Illinois, USA) and R (version 4.0.2; https://www.r-project.org/) were used for data analysis. A P value <0.05 in a two-sided test was considered statistically significant.

Nomogram validation and performance evaluation

The validity of the nomogram was assessed based on its discrimination performance and by constructing both internal (with the training cohort) and external (with the validation cohort) calibration curves. A comparison can be made between the performance of the two models using receiver operating characteristic (ROC) curve analysis and the area under the ROC curve（AUC）,

The predictive accuracy of the model) was determined by calculating the integrated discrimination improvement (IDI) and the net reclassification improvement (NRI)[17]. NRI is used to compare the diagnostic ability of two indicators at a certain threshold, whether one indicator is more accurate than the other. If the NRI is much higher than 0, it is positive improvement (improved prediction ability); if it is little more than 0, it is negative improvement (decreased prediction ability); if it is equal to 0, it is no improvement. IDI is used to reflect the overall improvement of the model at different thresholds. Similar to NRI, if IDI > 0, it is positive improvement, indicating that the prediction ability of the new model is improved compared with the old model; if IDI < 0, it is negative improvement, and the prediction ability of the new model is decreased; if IDI = 0, it is considered that the new model is not improved. “Positive outcomes are situations such as succeeding, winning, or being cured of an illness, while negative outcomes are situations such as failing, losing, or succumbing to an illness. Finally, the net clinical benefit of the predictive model developed in the present study was assessed using decision-curve analysis (DCA)[18].

Results

Characteristics of the study patients

A total of 7,770 patients diagnosed with sepsis, severe sepsis and septic shock were collected from the database between 2001 and 2012. Finally, after excluding duplicate patients, 5240 patients were included in the study. For the laboratory examination results, the indexes with> 20% missing values were omitted, and the remaining data were filled with the multiple difference complement method. The outcomes were known for all 5240 sepsis patients included from the MIMIC-III database. These patients were randomly assigned to the training (70%, n=3667) and validation (30%, n=1573) cohorts for constructing and validating the nomogram, respectively. The median SOFA score of the entire patient cohort was 6, indicating XXX. The median ages in the training and validation cohorts were 68 and 67 years, respectively; most patients were male (55.7% and 54.9%);. the medical ICU (MICU) was the most common first care unit (69.2% and 69.9%); fluid electrolyte was the most common complication (54.8% and 53.6%). Moreover, most patients in both groups had a WBC count between 10 and 40 k/μl (61.5% and 61.7%); the NET was mainly >70% (78.6% and 78.2%); the median SpO_2 values were 97.14 and 97.19, respectively; and the median albumin levels were 2.90 mg/dl and 2.80 mg/dl, respectively. In both cohorts, the median lactate level was 2.20 mmol/l, the median RDW was 15.40%, the most common sodium level was between 130 and 149 k/μl, the most common potassium level was between 3.5 and 5.6 k/μl, the most common $PaCO_2$ value was between 36 and 45 mmHg, the most common heart rate was between 60 and 100 min-1, the most common respiratory rate was between 20 and 30 min-1, and the most common body temperature was between 36 and 37.2°C. The distributions of all variables are presented in Table 1.

Multivariate Cox regression analysis and construction of a predictive nomogram with the training cohort

Multifactor Cox regression analysis was performed with the data from the training cohort to control for confounding factors. The results of the Cox regression analysis are listed in Table 2. (After performing a comprehensive evaluation of the variables and then applying Occam's razor[18] (the simplest explanation is preferable to one that is more complex), the variables included in the nomogram for predicting the 30-, 60-, and 90-days survival rates in sepsis patients were age (HR=1.02, 95%CI=1.02-1.03), SOFA score(HR=1.07, 95%CI=1.05-1.08), MC(HR=3.03, 95%CI=2.63-3.50), SpO_2(HR=0.97, 95%CI=0.96-0.99), lactate(HR=1.05, 95%CI=1.03-1.08), body temperature, albumin(HR=0.81, 95%CI=0.76-0.87), and RDW(HR=1.12, 95%CI=1.10-1.14). A graphical illustration of the nomogram is shown in Figure 1.

Performance of the nomogram

We evaluated the performance of the nomogram using a variety of metrics, including AUCs, NRI and IDI. The AUCs for the 30-, 60-, and 90-days survival probabilities in the nomogram were 0.766, 0.771, and 0.772, respectively, in the training cohort and 0.759, 0.770, and 0.760, respectively, in the validation cohort (Figure 2).The corresponding median NRI values in the validation cohort were 0.434 (95% CI=0.283 to 0.590), 0.520 (95% CI=0.381 to 0.653), and 0.530 (95% CI=0.414 to 0.681), respectively. The IDI values for

30-, 60-, and 90-days of follow-up examinations were 0.129, 0.143, and 0.150 in the training cohort and 0.102, 0.131, and 0.140 in the validation cohort, respectively.

Validation of the performance of the nomogram

As described above, a nomogram for predicting the outcome of sepsis patients was established by including age, SOFA score, MC, SpO_2, lactate, body temperature, albumin, and RDW. There was a correlation between the calibration and standard curves for the present nomogram in the calibration graphs of the training and validation cohorts, indicating that the predicted values of the survival risks at 30-, 60-, and 90-days were in good agreement with the observed values (Figure 3).

Clinical use

Mathematical models incorporate various data sources and innovative computational methods to portray real-world disease transmission and translate the basic science of infectious diseases into decision-support tools for public health. DCA was used to verify the clinical value of the model and its impact on actual decision-making. We can see that the net benefit of the nomogram is greater than the SOFA score for any predicted probability, both in the training set and in the validation set. So the preferred model is the nomogram, the net benefit of which was larger over the range of SOFA score. The resulting plots show XXX, indicating that it has a substantial net benefit in predicting 30-, 60-, and 90-days survival rates (Figure 4).

Discussion

In this retrospective study using data from the MIMIC-III database, we integrated age, SOFA score, MC, SpO_2, lactate, body temperature, albumin, and RDW to generate prediction models using Cox regression analysis, and the best-fitting model was visualized as a nomogram. the new model has better predictive performance than the model that does not include surgery There was a correlation between the calibration and standard curves for the present nomogram in the calibration graphs of the training and validation cohorts.

Many patients with various complex diseases present to the emergency room and ICU, and accurate evaluations of the severity of critical illnesses, reasonable judgement of prognoses, and selection of appropriate interventions are essential clinical skills for emergency room physicians. Several scores are widely used for such clinical situations, including the SOFA score, Logistic Organ Dysfunction Score (LODS), Acute Physiology And Chronic Health Evaluation II (APACHE) score, and Simplified Acute Physiology Score (SAPS)[19-20]. The SOFA score in particular has been demonstrated to be a valuable tool for predicting short-term mortality in patients with sepsis[21-22]. The present nomogram represents an improvement over the SOFA score.

The AUC of the SOFA score were used to assess the performance of the nomogram prediction model, demonstrating the excellent discriminability of the model. The calibration curves of the new nomogram

matched the standard curve (that is, the identity curve) very well in both the training and validation cohorts; in other words, the predicted 30-, 60-, and 90-days survival probabilities for sepsis patients obtained from the model were in good agreement with the observed values. Moreover, the 28-day DCA curves for both the training and validation cohorts demonstrated that the nomogram produces a net benefit. Together, these results show that clinical patients can benefit from the use of the nomogram based on our prediction model.

In our nomogram, age had a relatively strong influence. Studies have shown that age is an independent risk factor for death in patients with sepsis and that the fatality rate increases linearly with age[23]. Our research revealed the same trend; the nomogram score increased with age, which might be due to elderly patients being more susceptible to infection with gram-negative bacteria[23], having more comorbidities such as cancer[24], and having weaker immune function[25]. The predictions made using the nomogram regarding whether a patient has MC are also related to the immune system, and the inclusion of albumin in the nomogram reflects the tendency of older patients to have a worse nutritional status than their younger counterparts. XXX

[26-27] The haemodynamic performance of patients with septic shock is exceptionally complicated. In sepsis, endothelial cell dysfunction, the interaction of leukocytes/platelets and endothelial cells, coagulation activation, inflammation, abnormal haemorheology, and functional shunting together lead to microcirculatory disorders, insufficient tissue perfusion, and hypoxia, ultimately leading to multiple-organ dysfunction or even septic shock[28-29]. SpO_2 can reflect the body's real-time oxygen supply state and the degree of hypoxia and can therefore serve as a factor associated with sepsis. Additionally, it can be measured more conveniently and rapidly than the arterial blood gas level[19-20], making it an attractive parameter for use in prediction models and justifying its recruitment and inclusion into our nomogram.

Patients with sepsis or septic shock will experience anaerobic metabolism due to microcirculatory disturbances and lactate accumulation. The serum lactate level has traditionally been interpreted as a sign of tissue hypoxia and is often used clinically to indicate the severity and prognosis of sepsis/septic shock[30-31]. Lactate also has a high predictive value in our nomogram, with the score increasing with the lactate level.

The indicator with the highest weight in our nomogram was RDW, which has been used as a prognostic biomarker for cardiovascular disease, stroke, and metabolic syndrome mortality[32]. Another retrospective study based on the MIMIC-III database found that the RDW value was useful in predicting the long-term all-cause mortality of severe sepsis patients[33]. A multicentre observational study showed that RDW is a powerful predictor of the risk of all-cause death and blood infection in critically ill patients[34]. Moreover, an increase in the distribution of red blood cells when patients are discharged from the ICU is a powerful predictor of subsequent all-cause mortality[35]. These observations together show the predictive value of RDW. However, while this index is commonly measured in clinical workups, it is often ignored and, given its importance in the above studies and our results, deserves greater attention.

The limitations of this study include its retrospective design based on the MIMIC-III database. We also internally validated our nomogram using only data from one database. This limitation could be addressed in future studies by using a separate database or data from a separate group or study. XXX Additionally, for septic microbial infections, it is necessary to include the time the cultures were initiated and for antibiotics to be administered within a specific period. This information is difficult to extract from the database and should be addressed in future research on sepsis outcome prediction.

Sepsis is a complex disease, and while the guidelines on sepsis are constantly being updated, the mechanism underlying the pathophysiological changes it induces remains difficult to characterize[36-37]. Our understanding of sepsis could be strengthened by summarizing patient data to provide timely and effective treatment when attempting to control the disease. The nomogram that we constructed here has considerable strengths in providing accurate predictions of mortality risk of patients with sepsis and is easy to use and, therefore, highly suitable for clinical application.

Conclusions

In the information era, data reusability and data sharing strategies are receiving increasing attention worldwide[38-37]. Nomograms are a significant component of modern medical decision-making. The nomogram that we established here better predicts the prognosis of patients with sepsis than the SOFA score. However, this nomogram still needs to be externally validated in another population from a different country. In addition, a larger population will yield better results.

Declarations

Ethics approval and consent to participate

This study was approved by the research ethics committee of Jinan University.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no conflict of interest.

Funding

This study was supported by grants from the National Natural Science Foundation of China (82072232 and 81871585); Project in the Natural Science Foundation of Guangdong Province (2018A030313058); and Planned Science and Technology Project of Guangzhou, China (201804010308).

Authors' contributions

Haiyan Yin and Jun Lyu: conceptualized the study and revising the article; Hui Liu: data analysis, drafting the article, revising the article, and final approval. Luming Zhang: design, experimentation, data acquisition; Fengshuo Xu and Zichen Wang: experimentation, data acquisition; Didi Han and Feng Zhang: statistical analysis and drafting the article for intellectual content.

Acknowledgements

We acknowledge: Department of Clinical Research, The First Affiliated Hospital of Jinan University for their help in statistical analysis.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1 Patient characteristics

Variable	Validation Cohort	Training Cohort
	(n=1573)	(n=3667)
Sex, n (%)		
male	863 (54.9)	2044 (55.7)
female	710 (45.1)	1623 (44.3)
Age, years	67.00 (55.00, 79.00)	68.00 (55.00, 79.00)
SOFA score	6.00 (4.00, 9.00)	6.00 (4.00, 9.00)
CRRT, n (%)	115 (7.3)	313 (8.5)
First care unit, n (%)		
SICU/TSICU	299 (19.0)	691 (18.8)
MICU	1099 (69.9)	2536 (69.2)
CCU	131 (8.3)	313 (8.5)
CSRU	44 (2.8)	127 (3.5)
Comorbidity, n (%)		
congestive heart failure	586 (37.3)	1353 (36.9)
cardiac arrhythmias	635 (40.4)	1537 (41.9)
renal failure	401 (25.5)	883 (24.1)
liver disease	319 (20.3)	710 (19.4)
metastatic cancer	113 (7.2)	257 (7.0)
diabetes	529 (33.6)	1201 (32.8)
coagulopathy	402 (25.6)	999 (27.2)
fluid electrolyte	843 (53.6)	2008 (54.8)
blood loss anaemia	44 (2.8)	84 (2.3)
Laboratory test		
WBC (k/μl)		
<4	135 (8.6)	301 (8.2)
4-10	442 (28.1)	1051 (28.7)
10-40	971 (61.7)	2255 (61.5)
>40	25 (1.6)	60 (1.6)

NET (%)		
<50	118 (7.5)	256 (7.0)
50-70	225 (14.3)	530 (14.5)
>70	1230 (78.2)	2881 (78.6)
RDW (%)	15.40 (14.20, 17.20)	15.40 (14.10, 17.10)
HCT (%)		
<30	421 (26.8)	1068 (29.1)
30-45.9	1102 (70.1)	2477 (67.5)
>45.9	50 (3.2)	122 (3.3)
Sodium (k/µl)		
<130	150 (9.5)	302 (8.2)
130-149	1392 (88.5)	3229 (88.1)
>149	31 (2.0)	136 (3.7)
Potassium (k/µl)		
<3.5	268 (17.0)	558 (15.2)
3.5-5.5	1150 (73.1)	2723 (74.3)
>5.5	155 (9.9)	386 (10.5)
Albumin (mg/dl)	2.90 (2.50, 3.30)	2.80 (2.40, 3.30)
pH		
<7.35	667 (42.4)	1552 (42.3)
7.35-7.45	657 (41.8)	1572 (42.9)
>7.45	249 (15.8)	543 (14.8)
Lactate (mmol/l)	2.20 (1.50, 3.60)	2.20 (1.50, 3.50)
$PaCO_2$ (mmHg)		
<20	22 (1.4)	38 (1.0)
21-35	531 (33.8)	1259 (34.3)
36-45	574 (36.5)	1367 (37.3)
46-70	379 (24.1)	866 (23.6)
>70	67 (4.3)	137 (3.7)

Vital signs		
HR (min-1)		
<60	35 (2.2)	74 (2.0)
60-100	1030 (65.5)	2458 (67.0)
100-120	427 (27.1)	935 (25.5)
>120	81 (5.1)	200 (5.5)
RR (min-1)		
<12	11 (0.7)	23 (0.6)
12-20	730 (46.4)	1620 (44.2)
20-30	767 (48.8)	1885 (51.4)
30-40	65 (4.1)	139 (3.8)
Body temperature (℃)		
32-35.9	174 (11.1)	425 (11.6)
36-37.2	927 (58.9)	2095 (57.1)
37.3-38.5	433 (27.5)	1071 (29.2)
>38.5	39 (2.5)	76 (2.1)
SpO_2 (%)	97.14 (95.77, 98.43)	97.19 (95.76, 98.50)

XXXAbbreviations: SOFA score: Sequential Organ Failure Assessment score ; CRRT: continuous renal replacement theraphy ; SICU: Surgical Intensive Care Unit; TSICU: Trauma Surgical Intensive Care Unit ; MICU: Medical Intensive Care Unit; CCU: coronary care unit; CSRU: Cardiac surgery recovery unit; WBC: white blood cell ; NET□neutrophile granulocyte ; RDW: red cell distribution width ; HCT: hematocrit, PaCO2: partial pressure of carbon dioxide in artery; HR: heart rate; RR: respiratory rate ; SpO2: oxyhemoglobin saturation.

Table 2 Multivariate analyses of disease-specific survival in the training set

	HR	95% CI		P value
Age	1.02	1.02	1.03	<0.001
SOFA score	1.07	1.05	1.08	<0.001
Renal failure				
no	reference			
yes	1.15	1.04	1.28	0.007
Liver disease				
no	reference			
yes	1.28	1.14	1.43	<0.001
Metastatic cancer				
no	reference			
yes	3.03	2.63	3.50	<0.001
Fluid electrolyte				
no				
yes	1.21	1.11	1.32	<0.001
First care unit				
SICU/TSICU	reference			
MICU	1.00	0.89	1.12	0.973
CCU	1.25	1.05	1.48	0.011
CSRU	1.08	0.85	1.36	0.549
SpO_2 (%)	0.97	0.96	0.98	<0.001
pH				
<7.35	reference			
7.35-7.45	1.15	1.05	1.27	0.005
>7.45	1.39	1.21	1.59	<0.001
Lactate (mmol/l)	1.05	1.03	1.08	<0.001
Temperature (°C)				
32-35.9	reference			
36-37.2	0.74	0.65	0.83	<0.001

37.3-38.5	0.58	0.50	0.67	<0.001
>38.5	0.55	0.39	0.79	0.001
Potassium (k/µl)				
<3.5	reference			
3.5-5.5	1.13	1.00	1.28	0.050
>5.5	1.29	1.09	1.53	0.003
Sodium (k/µl)				
<130	reference			
130-149	0.79	0.68	0.92	0.002
>149	0.95	0.74	1.24	0.662
Albumin (mg/dl)	0.81	0.76	0.87	<0.001
RDW (%)	1.12	1.10	1.14	<0.001
NET (%)				
<50	reference			
50-70	0.79	0.66	0.95	0.013
>70	0.84	0.71	0.99	0.039

Figures

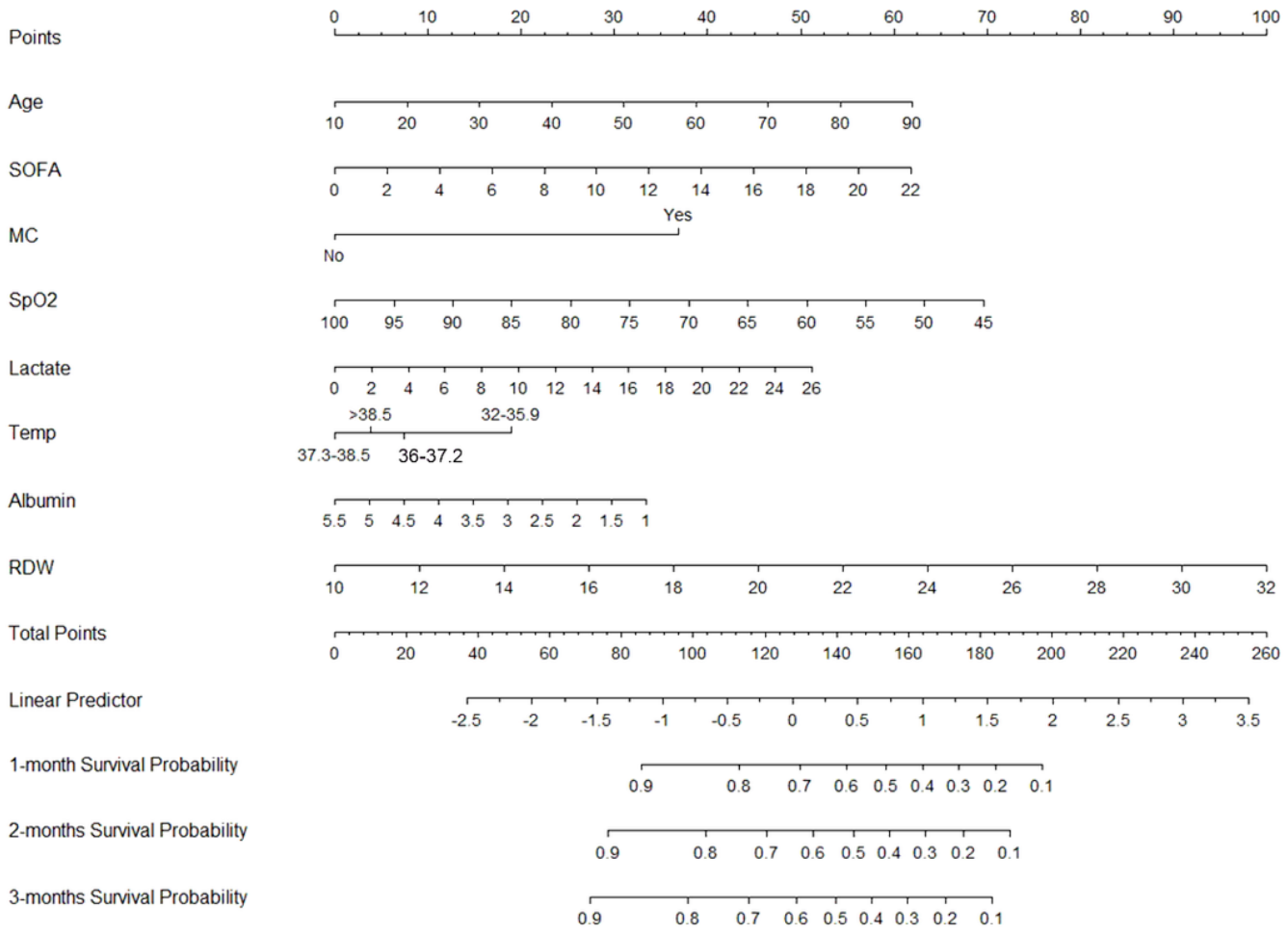

Figure 1

Nomogram predicting 30-, 60-, and 90-day survival. This is the histogram we created to evaluate the 30-day, 60-day, and 90-day survival of patients with sepsis. All parameters in the first column is (the eight parameters from age to red blood cell distribution width) of the score, according to the different parameter values, we can draw a vertical line to get the parameters of the score, the score of eight parameters together, get the value, according to the score values correspond to the following scale of survival rates 30 days, 60 days and 90 days of patients with draw a vertical line can be individualized for 30 days, 60 days and 90 days of survival.

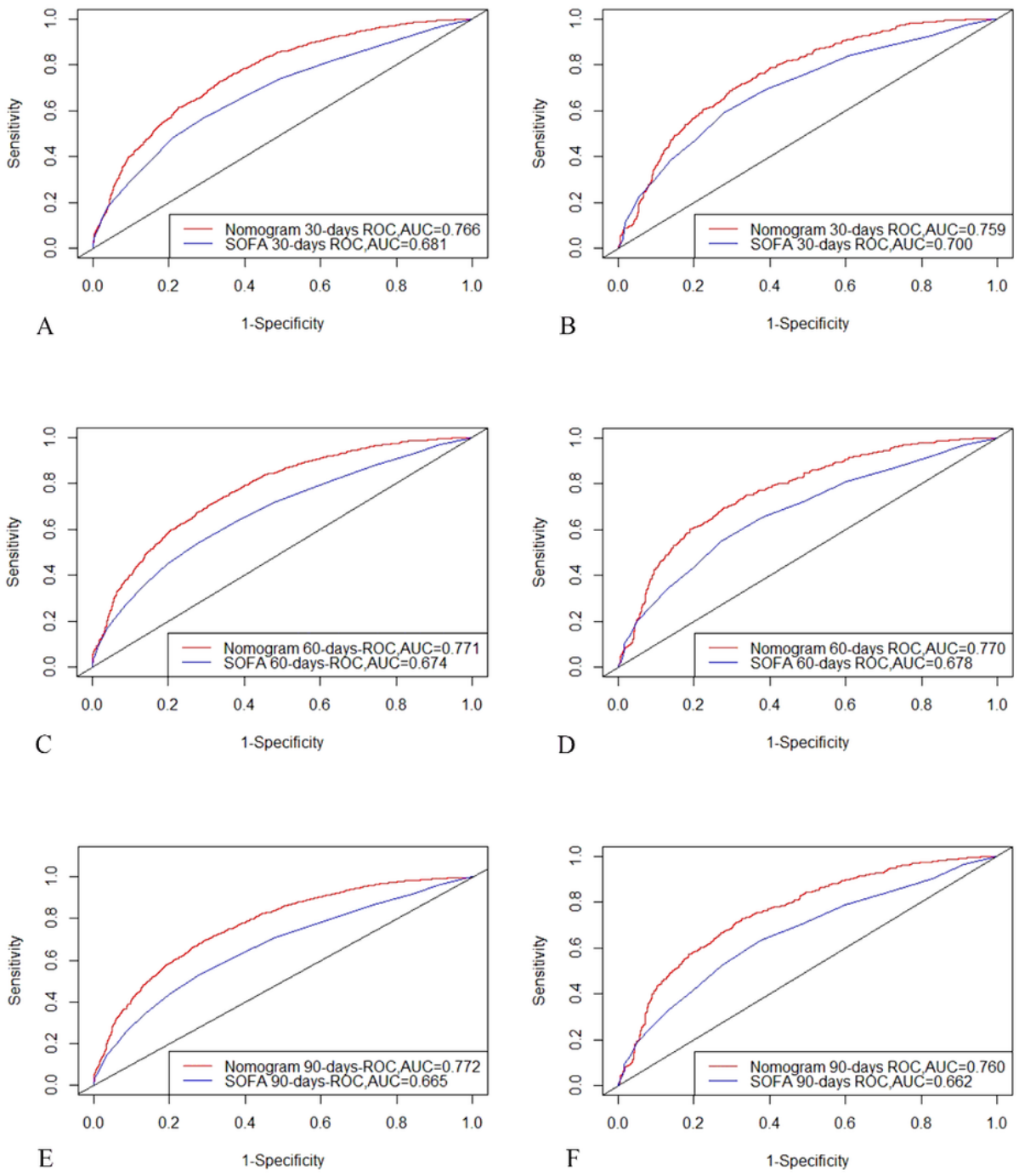

Figure 2

ROC curves for the nomogram and the SOFA models. The AUC can be calculated from the ROC curves to assess the predictive ability of the models.) The AUCs for the 30-, 60-, and 90-days survival probabilities in the nomogram were 0.766, 0.771, and 0.772, respectively, in the training cohort and 0.759, 0.770, and 0.760, respectively, in the validation cohort

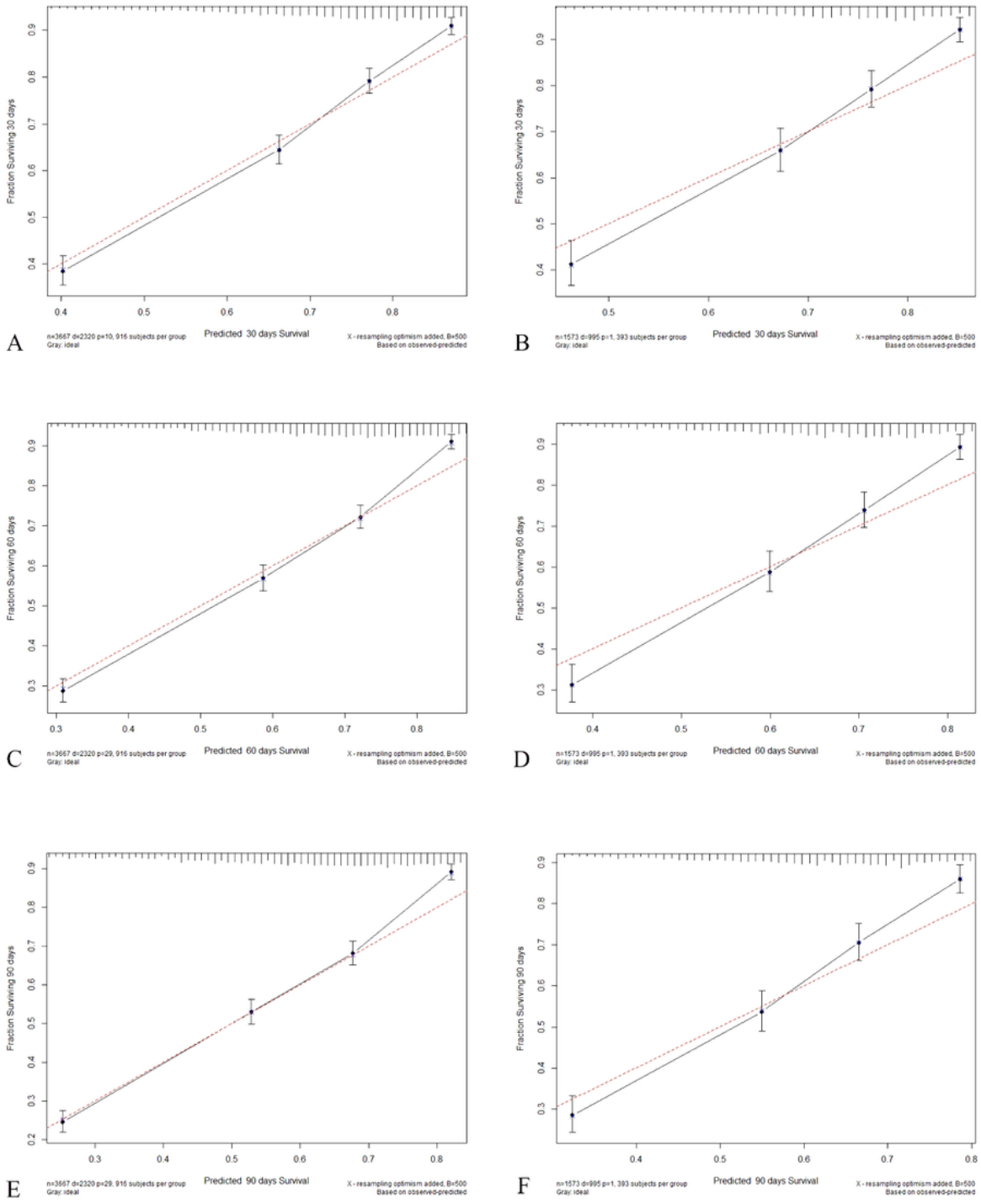

Figure 3

Calibration curves for 30-, 60- and 90-days survival. The abscissa is the predicted survival rate in the histogram and the ordinate is the actual survival rate. The red dotted line is the reference line, where the predicted value is equal to the actual value. The solid black line is the curve fitting line, and the colored part on both sides is 95%CI. Calibration curves depict the calibration of each model in terms of the

agreement between the predicted probabilities and observed outcomes, shown here separately for the training set (A, C, E) and validation set (B, D, F).

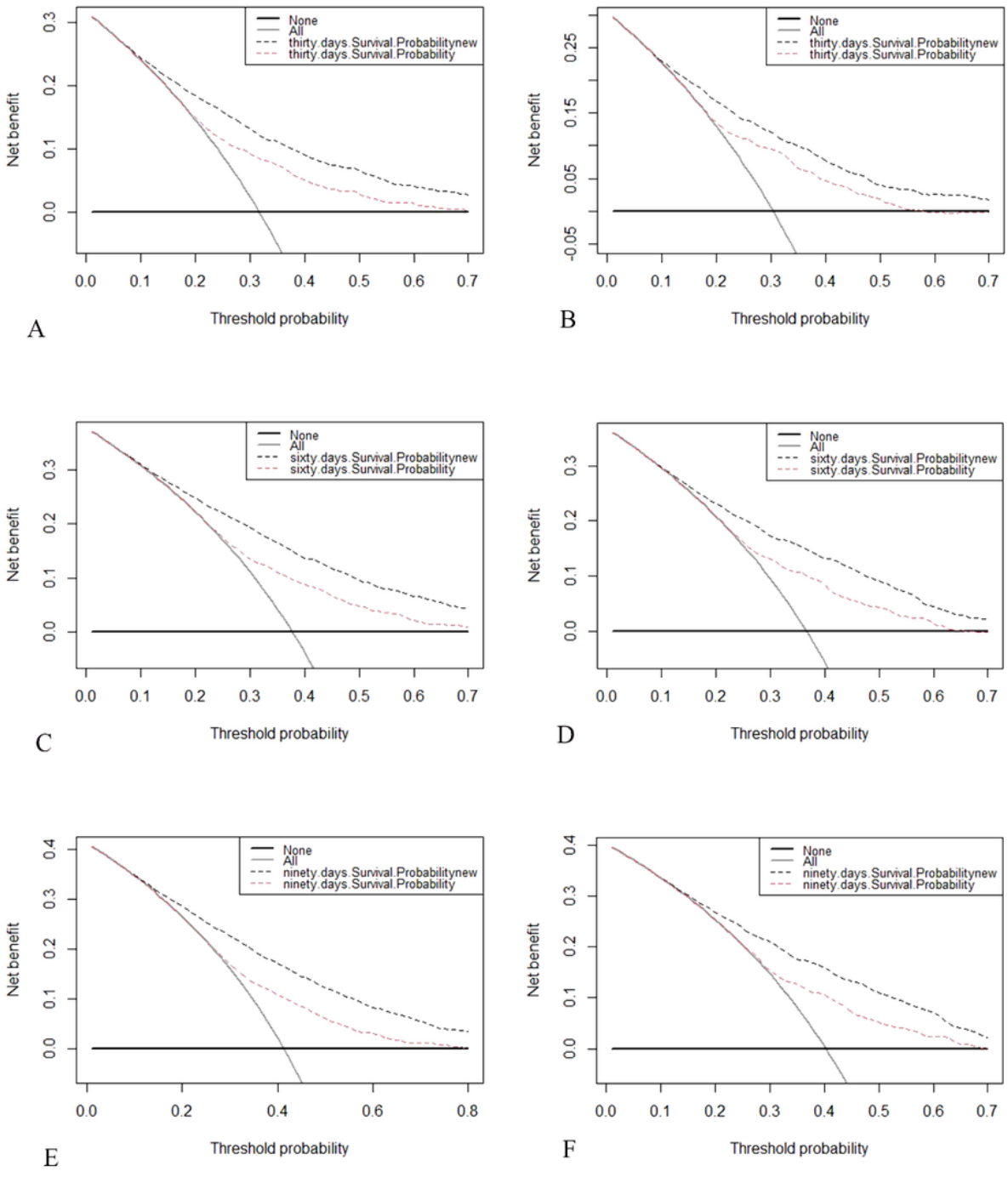

Figure 4

Decision-curve analysis of the training set (A, C, E) and validation set (B, D, F) for 30-, 60- and 90-days survival. In the figure, the abscissa is the threshold probability, and the ordinate is the net benefit rate. The horizontal solid line indicates where all samples are negative and no patient is treated, with a net benefit

of zero. The solid oblique line in gray indicates where all samples are positive, all receive medical treatment, so its net benefit is a backslash with a negative slope. The black dotted line represents the survival probability of the nomogram and the red dotted line represents the survival probability of the SOFA score. We can see that the net benefit of the nomogram is greater than the SOFA score for any predicted probability, both in the training set and in the validation set.