

Development and Validation of a Risk Factor-Based Nomogram to Early Predict in-Hospital Mortality in Adult Patients With Suspected Infection Admitted to the Intensive Care Unit: a Retrospective Cohort Study

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Research

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Abstract

Background

The over-consumption of time for data collection in the Sequential Organ Failure Assessment (SOFA) score and the poor performance of the quickSOFA (qSOFA) score in predicting poor prognosis among patients with suspected infection in intensive care unit (ICU) may delay the treatment towards sepsis. The aim of this study is to develop a prediction model to early identify patients with suspected infection who are under a high risk of in-hospital mortality in ICU.

Methods

Patients with suspected infection were retrospectively retrieved from the Medical Information Mart for Intensive Care (MIMIC III) database. Objective variables whose results can be obtained within a short period of time were integrated into the uni- and multi-variate logistic regression to screen the independent predictors for the in-hospital mortality in ICU patients with suspected infection. Then, the prediction nomogram was constructed by these independent predictors in the training set, and undergone internal validation and sensitivity analysis.

Results

A total of 7000 patients with suspected infection were included into the final analysis. In the training set, multivariate logistic regression revealed that patient's age, elixhauser index, the first result of lactate, red blood cell distribution width (RDW), white blood cell (WBC), lymphocyte, PH value and bicarbonate as well as the first hour's mean value of respiratory rate, temperature and SpO₂ since ICU admission were the independent predictors for the in-hospital mortality. Then, a nomogram for predicting the in-hospital mortality in ICU patients with suspected infection was developed in the training set and exhibited strong discrimination and calibration as well as great clinical usefulness in both of the training and validation sets as well as the sensitivity analysis.

Conclusions

The nomogram shows good predictive performance in ICU to identify adult patients with suspected infection who are likely to die in hospital, which may facilitate clinicians to initiate necessary treatment towards sepsis timely and finally improve the prognosis of septic patients.

Introduction

The Third International Consensus Definitions Task Force defined sepsis as "life-threatening organ dysfunction due to a dysregulated host response to infection." [1] For clinical operationalization, the task force recommends using a change in baseline of the total Sequential Organ Failure Assessment (SOFA) score of 2 points or more to represent organ dysfunction in patients with suspected infection and then defined this cohort of patients as sepsis. [2] Whereas, as the level of creatinine and bilirubin as well as

urine output in the SOFA score can not be timely captured, the calculation of SOFA score may delays the initiation of treatment towards sepsis.[3] To solve this defect, the task force developed a parsimonious clinical model called quickSOFA (qSOFA) to promptly identify adult patients with suspected infection who are likely to have poor outcomes, which can prompt the clinicians to further investigate for organ dysfunction with SOFA score and initiate appropriate therapy if such actions have not already been undertaken. However, as the qSOFA score has been verified to have well predictive performance for the in-hospital mortality in patients with suspected infection outside the intensive care unit (ICU) (AUROC = 0.81; 95% CI, 0.80–0.82) but poor among encounters in ICU (AUROC = 0.66;95%CI, 0.64–0.68),[4] this benchmark may be not applicable to the prediction of poor outcome in patients with suspected infection who are entered into ICU directly or in patients who are suspected to have infection after ICU admission. Based on these, developing a predictive model to predict poor outcome in patients with suspected infection under an ICU setting is of great significance.

Therefore, in the present study, we aimed to develop and validate an prediction nomogram to promptly and accurately predict the in-hospital mortality in ICU patients with suspected infection, and then compared the predictive performance of this nomogram with the SOFA and qSOFA scores.

Methods

Data source

We conducted an observational study by retrieving data from the Medical Information Mart for Intensive Care (MIMIC III) open source clinical database, which contains de-identified health-related data of over forty thousand patients who received treatment in critical care units of the Beth Israel Deaconess Medical Center between 2001.06 and 2012.10.[5, 6] The MIMIC III database can be freely utilized after successful application and ethical approval from the Institutional Review Boards of both Beth Israel Deaconess Medical Center (Boston, MA, USA) and the Massachusetts Institute of Technology (Cambridge, MA, USA). Since all data are de-identified in this database to remove patients' information, the requirement for individual patient consent is not indispensable.

Study population and data extraction

Since Johnson AEW et al has successfully extracted the suspected infection population from the MIMIC III database according to the Sepsis-3 task force definition as the combination of culture and antibiotic start time to occur within a specific time epoch,[4, 7] we followed the structure query language (SQL) code edited by them to extract patients suspected of infection within 24 hours before or after ICU admission (the code is available online at <https://github.com/alistairewj/sepsis3-mimic/tree/master/query>). The following exclusion criteria were set: (1) age < 18; (2) with bad data (missing value account for 50% or more); (3) entering into ICU for more than twice; (4) suspected of infection one day before or after ICU admission. Besides, patients entering into the cardiac surgical intensive care unit were excluded because their post-operative physiologic derangements do not translate to the same mortality risk as the other ICU patients. The baseline characteristics of the extracted cohort between this study and that of Johnson et

al was exhibited in **Additional file 1: Table S1**. The data from the table showed that the study population we extracted was similar to that of Johnson et al, indicating that we successfully isolated the cohort with suspected infection as with the Sepsis-3 criteria. Then, patients from the Metavision system (one of the electronic health record systems in MIMIC III) were randomly distributed into a training set and a validation set at a ratio of 7:3 to develop and validate the prediction nomogram, respectively. Sensitivity analysis was conducted in patients from the Carevue system (another electronic health record systems in MIMIC III). The Metavision system contains clinical data between 2008 and 2012, while data in the Carevue system is between 2001 and 2008. The data extraction process was illustrated in **Additional file 2** **Figure S1**. For the final cohort, we retrospectively collected the following data: (1) demographic data including age, gender, ethnicity and the body mass index (BMI); (2) the elixhauser comorbidity index; [8] (3) in-hospital mortality; (4) length of ICU stay; (5) mean value of vital signs during the first hour of ICU stay; (6) the simplified acute physiology score (SAPS) to assess the severity of illness; [9] (7) SOFA and qSOFA which were calculated using data from the first 24 hours of ICU stay. Besides, the first result of the following laboratory indexes since ICU admission were extracted, they are lactate, PCO₂, PO₂, PH, platelet, red blood cell distribution width (RDW), white blood cell (WBC), lymphocyte, neutrophil, bicarbonate, chloride, and glucose. We included these laboratory indexes into this study because their results can be obtained within a short time (normally within 1 hour), which was in line with the design concept of the prediction nomogram.

Statistical analysis

The distribution of continuous variables was judged by Shapiro-Wilk tests. Data were expressed as mean \pm standard deviation (SD) for parametric continuous data and as median [interquartile ranges] for non-parametric distribution. Categorical data were expressed as number (percentages). Parametric and non-parametric variables were compared by unpaired Student's test and Mann-Whitney U test, respectively. The Chi-Squared test was used to compare categorical variables between groups.

Logistic regression analysis was conducted in the training set to identify independent risk factors for the in-hospital mortality in patients with suspected infection. Specifically, variables related to the in-hospital mortality in the univariate analysis ($p < 0.1$) were entered into a stepwise multivariate logistic regression analysis, in which both forward selection and backward elimination were used to test at each step for variables to be included or excluded. The Akaike Information Criterion (AIC) was used as the selection criteria to eliminate predictors, [10] and variables with $p < 0.05$ were considered as the independent risk factors and used to create the nomogram. The following variables were integrated into the logistic regression analysis: (1) patients' age; (2) elixhauser index; (3) the vital signs and the laboratory indexes described above. Collinearity between these continuous variables were tested by the variance inflation factor (VIF) and an arithmetic square root of $VIF \leq 2$ was considered as non-collinearity.

The predictive performance of the nomogram was evaluated and compared with SOFA and qSOFA scores in both of the training and validation sets. The predictive validity was assessed by an area under the curve of the receiver operating characteristic (AUROC) between the nomogram and SOFA or qSOFA score. The construct validity was determined by examining the predictive agreement using the Cronbacha. [11]

The calibration curve was generated by the bootstrap method with 1000 resampling to evaluate the calibration of the nomogram. Besides, integrated discrimination improvement (IDI) index was calculated to compare discrimination slopes between the nomogram and SOFA or qSOFA score[12]. Besides, the DCA curve was generated to assess the net benefit of medical intervention conforming the nomogram and qSOFA score at different threshold probabilities in the training and validation sets. Sensitivity analysis was conducted in patients from the Carevue system to assess robustness of the prediction nomogram.

Statistical analyses were performed using R software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria). Missing values were addressed with multiple imputation in the process of logistic regression and model construction. The imputation technique involves creating multiple copies of the data and replacing missing values with imputed values through a suitable random sample from their predicted distribution. A two-tailed p value of < 0.05 was considered statistically significant. All analyses were reported according to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines.[13]

Results

Characteristics of participants

After screening by the inclusion and exclusion criteria, a total of 7000 patients with suspected infection were included into the final cohort. Characteristics at baseline of all participants and those in the hospital survivor and hospital non-survivor groups were exhibited in Table 1. Except for gender and BMI, all of the other features were significantly different between the two groups. Non-survivors were older than survivors (73 [59, 82] vs 64 [51, 78], $p < 0.001$). Patients' illness condition and organ failure were more severe in non-survivors, with $p < 0.001$ in both of the simplified acute physiology score (SAPS II) (51 [40, 63] vs 33 [25, 42]) and the SOFA score (7 [4, 10] vs 3 [2, 5]). The distribution mode of the qSOFA score was different between the two groups ($p < 0.001$), with larger proportion of $qSOFA \leq 1$ in non-survivors and $qSOFA \geq 2$ in survivors. Besides, non-survivors had longer ICU stay time than survivors (3.46 [1.63, 6.99] vs 2.21 [1.3, 4.58], $p < 0.001$).

Table 1
Patients' baseline characteristics ^a

Variable	All patients n = 7000	Survivors n = 6095	Non-Survivors n = 905	P value
Age (years)	65 [52, 79]	64 [51, 78]	73 [59, 82]	< 0.001
Male, n (%)	3774 (54)	3292 (54)	482 (53)	0.698
BMI (kg/m ²)	27.18 [23.64, 31.68]	27.26 [23.68, 31.77]	26.84 [23.26, 31.31]	0.054
Ethnicity, n(%)				< 0.001
Asian	218 (3)	192 (3)	26 (3)	
Black	609 (9)	552 (9)	57 (6)	
Hispanic/Latino	256 (4)	235 (4)	21 (2)	
White	5073 (72)	4456 (73)	617 (68)	
Others	844 (12)	660 (11)	184 (20)	
SAPSII score	35 [26, 45]	33 [25, 42]	51 [40, 63]	< 0.001
SOFA score	4 [2, 6]	3 [2, 5]	7 [4, 10]	< 0.001
qSOFA score, n (%)				< 0.001
0	295 (4)	279 (5)	16 (2)	
1	1904 (27)	1774 (29)	130 (14)	
2	3792 (54)	3255 (53)	537 (59)	
3	1009 (14)	787 (13)	222 (25)	
ICU length-of-stay (day)	2.34 [1.32, 4.92]	2.21 [1.3, 4.58]	3.46 [1.63, 6.99]	< 0.001

^a Continuous data are presented as median [interquartile range], whereas categorical data are presented as frequency (percentage).

BMI: body mass index; SOFA, sequential organ failure assessment; qSOFA, quickSOFA; SAPSII: simplified acute physiology score.

Development of a prediction nomogram

The SOFA and qSOFA scores as well as the characteristics of the predictors integrated into the logistic regression analysis in the training and validation sets were exhibited in **Additional file 3: Table S2**, which showed that both sets had no statistical difference in almost all the variables.

As the nomogram was developed in the training set, we exhibited in Table 2 the characteristics of the variables in the training set which were included into the logistic regression. Except for the level of chloride ($p = 0.688$), all of the other variables were statistically different between survivors and non-survivors. The VIF of the variables in Table 2 was calculated and none of them had an arithmetic square root of $VIF \leq 2$, indicating that there was no collinearity between variables. After conducting the logistic regression, the risk factors independently associated with the in-hospital mortality of ICU patients with suspected infection were screened out and shown in **Table 3**. Then, a model integrating lactate, elixhauser index, age, RDW, WBC, lymphocyte, PH value, bicarbonate as well as the mean values of respiratory rate, temperature and SpO_2 was established, and then a nomogram based on this model was plotted. **(Fig. 1)** After calculating by the nomogram, a patient with a total point of over 225 will have a probability of the in-hospital death of more than 50% and then, be considered to be under the risk of in-hospital death.

Table 2
 Characteristics of variables that included into logistic regression ^a

Variable	Patients in the training set n = 4900	Survivors n = 4288	Non-Survivors n = 612	P value
Age (years)	64.98 [51.73, 78.78]	63.83 [50.89, 77.89]	72.76 [59.3, 82.39]	< 0.001
Elixhauser index	3 [0, 8]	2 [0, 7]	6 [2, 11]	< 0.001
Laboratory tests ^b				
Lactate (mmol/L)	1.6 [1.1, 2.6]	1.6 [1.1, 2.4]	2.15 [1.4, 3.9]	< 0.001
PCO ₂ (mmHg)	40 [35, 47]	40 [35, 47]	39 [33, 47]	0.003
PO ₂ (mmHg)	120 [78, 213]	123 [80, 216]	101 [68, 199]	< 0.001
PH	7.38 [7.32, 7.44]	7.38 [7.32, 7.44]	7.35 [7.25, 7.42]	< 0.001
Platelet (K/uL)	213 [152, 279]	215 [155, 279]	196 [119.75, 280]	< 0.001
RDW (%)	14.5 [13.6, 15.9]	14.4 [13.5, 15.7]	15.4 [14.1, 17.2]	< 0.001
WBC (K/uL)	10.8 [7.6, 14.9]	10.6 [7.5, 14.5]	12.7 [8.4, 18.2]	< 0.001
Lymphocyte (%)	10 [6, 16]	10.1 [6, 16.3]	7.95 [4.5, 12.6]	< 0.001
Neutrophil (%)	82 [73, 88.2]	81.6 [73, 88]	83.7 [74, 89.1]	0.004
Bicarbonate (mEq/L)	24 [21, 26]	24 [21, 26]	21 [17, 25]	< 0.001
Chloride (mEq/L)	105 [102, 109]	105 [102, 109]	106 [101, 110]	0.688

^a Continuous data are presented as median [interquartile range], whereas categorical data are presented as frequency (percentage)

^b Laboratory tests recorded the first result of each patients' ICU stay

^c Vital signs is calculated on the first hour since ICU admission

SOFA, sequential organ failure assessment; qSOFA, quickSOFA; RDW, red blood cell distribution widths; WBC, white blood cell.

Variable	Patients in the training set n = 4900	Survivors n = 4288	Non-Survivors n = 612	P value
Glucose (mg/dL)	128 [105, 162]	127 [105, 160]	136 [105, 179.25]	0.001
Vital signs ^c				
Mean heartrate (min ⁻¹)	88.4 [75.33, 102.5]	88 [75, 101.75]	91.63 [79.6, 107.35]	< 0.001
Mean systolic pressure (mmHg)	120.5 [107, 136.5]	121.5 [108, 137]	115 [101.63, 132.25]	< 0.001
Mean diastolic pressure (mmHg)	64.8 [56.55, 74.47]	65 [57, 74.5]	62.5 [53.42, 72.7]	< 0.001
Mean respiratory rate (min ⁻¹)	18.8 [16.14, 22.33]	18.64 [16, 22]	20.5 [17.31, 24.46]	< 0.001
Mean temperature (°C)	36.67 [36.11, 37.22]	36.69 [36.17, 37.22]	36.5 [35.78, 37.11]	< 0.001
Mean SpO ₂ (%)	97.5 [95.5, 99.33]	97.5 [95.5, 99.33]	97.33 [94.83, 99.33]	0.015
^a Continuous data are presented as median [interquartile range], whereas categorical data are presented as frequency (percentage)				
^b Laboratory tests recorded the first result of each patients' ICU stay				
^c Vital signs is calculated on the first hour since ICU admission				
SOFA, sequential organ failure assessment; qSOFA, quickSOFA; RDW, red blood cell distribution widths; WBC, white blood cell.				

Table 3. Factors independently associated with the in-hospital mortality in ICU patients with suspected infection in the multivariate logistic analysis

Variables	OR	95% CI	P value
Lactate (mmol/L)	1.20	1.15 1.26	< 0.001
Elixhauser index	1.05	1.03 1.06	< 0.001
Age (years)	1.02	1.01 1.03	< 0.001
RDW (%)	1.16	1.12 1.21	< 0.001
Mean respiratory rate (min ⁻¹)	1.05	1.03 1.07	< 0.001
PH	0.19	0.08 0.46	< 0.001
Bicarbonate (mEq/L)	0.96	0.94 0.98	< 0.001
Mean temperature (°C)	0.83	0.76 0.92	< 0.001
WBC (K/uL)	1.01	1.00 1.02	< 0.001
Lymphocyte (%)	0.99	0.98 1.00	0.004
Mean SpO2 (%)	0.96	0.94 0.99	0.005
RDW, red blood cell distribution widths; WBC, white blood cell; OR: odds ratio.			

Hosmer-Lemeshow test: $p = 0.72$

Figure 1. The nomogram for the prediction of in-hospital mortality in patients with suspected infection in ICU.

Model performance

The predictive validity for the in-hospital mortality in ICU patients with suspected infection using the nomogram was statistically greater than that of the qSOFA score (AUROC: 0.772 vs 0.611; $p < 0.001$) and SOFA score (AUROC: 0.772 vs 0.743; $p = 0.015$) in the training set. In the validation set, the predictive validity of the nomogram was still statistically greater than that of qSOFA score (AUROC: 0.764 vs 0.625; $p < 0.001$), but similar to that of SOFA score (AUROC: 0.764 vs 0.739; $p = 0.141$). **(Fig. 2)** The predictive agreement between the nomogram and the SOFA or qSOFA score for the in-hospital mortality in ICU patients with suspected infection was evaluated by Cronbach α . Results showed that the nomogram had greater statistical agreement with the SOFA score (training set: Cronbach $\alpha = 0.757$; 95% CI, 0.723–0.789; validation set: Cronbach $\alpha = 0.744$; 95% CI, 0.693–0.789) but lower with the qSOFA score (training set: Cronbach $\alpha = 0.322$; 95% CI, 0.293–0.349. validation set: Cronbach $\alpha = 0.345$; 95% CI, 0.302–0.388). Besides, the IDI index between the nomogram and the qSOFA score was 0.125 (95% CI, 0.109–0.142) in the training set and 0.113 (95% CI, 0.090–0.136) in the validation set, which demonstrated that compared with the qSOFA score, the prediction validity of the nomogram was improved by 12.5% and 11.3% in the training and validation sets, respectively. **(Table 4)** Calibration curve was depicted for both of the training and validation sets and the bias-corrected line is formed using a bootstrap method. **(Fig. 3)** The figure

showed that the apparent curve and bias-corrected curve were slightly deviated from the reference line, but a good conformity between observation and prediction is still observed.

Table 4

Comparison of the prediction performance of the models for the in-hospital mortality of ICU patients with suspected infection ^a

Predictive Model		AUROC	P value	IDI	P value	Cronbach α
Training set	Nomogram	0.772 [0.752–0.792]				
	SOFA score	0.743 [0.721–0.765]	0.015	0.012 [-0.004–0.029]	0.136	0.757 [0.723–0.789]
	qSOFA score	0.611 [0.590–0.632]	< 0.001	0.125 [0.109–0.142]	< 0.001	0.322 [0.293–0.349]
Validation set	Nomogram	0.764 [0.734–0.793]				
	SOFA score	0.739 [0.707–0.771]	0.141	0.008 [-0.017–0.033]	0.528	0.744 [0.693–0.789]
	qSOFA score	0.625 [0.596–0.655]	< 0.001	0.113 [0.090–0.136]	< 0.001	0.345 [0.302,0.388]
^a The P value was drew by comparing of the nomogram with SOFA or qSOFA.						
SOFA, sequential organ failure assessment; qSOFA, quickSOFA; AUROC, area under the receiver operating characteristic curve; IDI, integrated discrimination improvement.						

Figure 2 The ROC curve of the prediction nomogram, SOFA score and qSOFA score in the training set (a) and validation set (b).

Figure 3 Calibration curves constructed by bootstrap approach in the training set (a) and validation set (b).

Clinical usefulness of the nomogram

Considering the clinical usefulness, the DCA for the nomogram was depicted and compared with the qSOFA score. **(Fig. 4)** Results indicated that medical intervention guided by the nomogram could add more net benefit than the qSOFA score when the threshold probability (PT) > 0.1 in both of the training and validation sets.

Figure 4 The DCA curve of medical intervention in patients with the nomogram and qSOFA score in the training set (a) and validation set (b).

Stability of the model performance

Sensitivity analysis was conducted in the Carevue system. The predictive validity, predictive agreement, calibration and clinical usefulness of the nomogram were compared with SOFA and qSOFA scores by using AUROC and IDI index, Cronbach α , calibration curve, and DCA curve, respectively. Results showed that the predictive validity of the nomogram was statistically greater than that of the qSOFA score (AUROC: 0.760 vs 0.611, $p < 0.001$; IDI: 0.130; 95% CI, 0.117–0.142; $p < 0.001$). The predictive agreement also followed a pattern similar to that in the training and validation sets (nomogram vs SOFA: Cronbach $\alpha = 0.753$; 95% CI, 0.727–0.777. nomogram vs qSOFA: Cronbach $\alpha = 0.338$; 95% CI, 0.319–0.358). Good conformity between observation and prediction is still observed in the calibration curve. Besides, the prediction nomogram still exhibited better clinical usefulness than the qSOFA score in ICU patients with suspected infection. These results further consolidated the stably and well predictive performance of the prediction nomogram. **(Additional file 4: Figure S2; Additional file 5:Table S3)**

Discussion

In this retrospective analysis by MIMIC III database, we conducted the logistic regression to screen independent risk factors for the in-hospital mortality of patients with suspected infection in ICU. Then, variables including patient's age, elixhauser index, the first result of lactate, RDW, WBC, lymphocyte, PH and bicarbonate as well as the first hour's mean value of respiratory rate, temperature and SpO₂ since ICU admission were screened out and integrated into a best-fit prediction model visualized as a prediction nomogram. To the best of our knowledge, this is the first study to develop a nomogram to predict the in-hospital mortality in patients with suspected infection under an ICU setting. The results from this study have some implications and require further consideration.

First, both of the qSOFA score and the nomogram are designed to early identify adult patients with suspected infection who are likely to have poor outcomes. However, the nomogram performed better than the qSOFA score in predicting the in-hospital mortality in patients with suspected infection in ICU. Considering that the qSOFA score had good predictive performance in the out-of-hospital, emergency department, and general ward settings but poor performance in ICU, the nomogram we developed may effectively makes up for the defect of the qSOFA score and a combined use of the two models may provide timely and accurate prediction of poor outcome in patients with suspected infection in both of the non-ICU and ICU settings and then to prompt the clinicians to further investigate for organ dysfunction with SOFA score and to initiate appropriate therapy towards sepsis.

Second, as can be seen from the Cronbach α , the nomogram and SOFA score show high consistency in recognizing the patients with suspected infection who are under high risk of in-hospital death, which indicates that the septic patients identified by the SOFA score from the suspected infection cohort are to a large extent consistent with the suspected infection patients with poor outcome identified by the

nomogram. In addition, as can be seen from the AUROC, the predictive validity of the nomogram in predicting poor outcome is similar or even stronger than that of the SOFA score. All of these demonstrate that the nomogram is appropriate for the prediction of poor outcome in the potentially septic population. Besides, in order to make timely and objective prediction, we included into the prediction nomogram with laboratory indexes and other indicators that can be obtained within a short time, while those time-consuming laboratory tests, such as hepatic and renal function, and subjective indicators, such as the Glasgow Coma Scale (GCS) and medical intervention, were excluded from the model construction process. Therefore, the predictive efficiency of the nomogram is higher than the SOFA score, which avoids the delay of the early fluid resuscitation and antibiotic administration in the treatment of sepsis.[14] However, it should be noted that the nomogram can not be used for the diagnosis of sepsis for that it is designed for the prediction of in-hospital mortality but not for the evaluation of organ dysfunction. Consequently, sepsis should still be diagnosed according to the Sepsis-3 criteria.[1] The flow chart for the diagnosis of sepsis by the combined use of the nomogram as well as the qSOFA and SOFA score is exhibited in **Additional file 6: Figure S3**.

Third, the Sepsis-3 Task Force did not include lactate as a part of the diagnostic criteria for sepsis for that evidence from them showed that integrating lactate into the qSOFA did not improve the predictive validity for ICU mortality and/or prolonged ICU stay. However, by conducting the logistic regression analysis, we found that lactate has the highest odds ratio (OR) value compared with all the other independent risk factors related to the in-hospital mortality in patients with suspected infection, which indicated that lactate is the most important predictor and has the strongest power for the prediction of in-hospital mortality in ICU patients with suspected infection. Supporting our conclusion, Sepsis-1 definition also included increased lactate level as part of the severe sepsis criteria which was equivalent to the sepsis criteria in Sepsis-3.[15] Therefore, although lactate was excluded from the diagnostic criteria of sepsis in Sepsis-3, its clinical significance should not be underestimated. Several studies have shown that increased levels of lactate can be used to identify suspected infection patients with normal vital signs and without significant organ dysfunction who are under an increased risk of death from sepsis.[16–18] In consequence, the dynamic monitoring of blood lactate still plays an important role in the identification and management of sepsis, which may contribute to risk-stratify patients with suspected sepsis and facilitate aggressive early treatment.[19–22] To support this view, the Surviving Sepsis Campaign issued interim guideline after the publication of Sepsis-3 that the 3 h and 6 h bundle therapies should be continued for sepsis with lactate levels above 2.0 mmol/L.[3]

Fourth, except for lactate, RDW has the highest OR value in the multivariate logistic regression, indicating that it may significantly affect the prognosis of patients with suspected infection in ICU. This finding is consistent with some previous studies that RDW can be used to estimate the short-term mortality of non-hematologic diseases, such as sepsis-associated encephalopathy,[23] stroke,[24] cardiovascular diseases,[25, 26] and liver diseases.[27, 28] Studies had indicated that the inflammatory response and oxidative stress during sepsis may contribute to the adverse effect of RDW,[29–32] but the exact mechanisms under the relationship between RDW and the in-hospital mortality of patients with suspected infection are still unclear. Therefore, more studies are necessary to clarify the specific mechanism of the

positive relationship between RDW and short-term poor prognosis, which may provide new target for the improvement of prognosis in patients with sepsis.

One thing should be noted is that if patients suspected of infection have been stayed in ICU for a period of time and the data of creatinine, bilirubin and urine output has been obtained, SOFA score should be calculated directly to diagnose sepsis and guide the relevant treatment. However, if such patients have just been admitted to ICU or the data of the above indicators are lacked, clinicians should adopt the nomogram firstly to identify the patients who are likely to have poor outcomes so as to initiate or escalate sepsis related therapy as soon as possible.

The study has several limitations. First, the retrospective nature of this observational study determined that unidentified confounding factors may affect the results if adding to the model. Second, as data in the MIMIC database is slightly old and internal validation as well as sensitivity analysis were conducted only by data from this database, external validation based on latest data and data from different medical settings are necessary to further evaluate the performance of the developed prediction nomogram. Third, as predicting the in-hospital mortality by a nomogram artificially is inefficient, it is essential to integrate the nomogram into an electronic medical system, which can facilitate the clinicians to make prompt prediction without increasing their working loads and then to conduct appropriate treatment timely.

Conclusion

A prediction nomogram integrating patient's age, elixhauser index, the first result of lactate, RDW, WBC, lymphocyte, PH and bicarbonate as well as the first hour's mean values of respiratory rate, temperature and SpO₂ since ICU admission can be conveniently used in ICU to early identify adult patients with suspected infection who are likely to die in hospital, which may be particular beneficial when a patient suspected of infection has just been admitted to the ICU and the data related to SOFA has not yet been collected. Under this condition, the nomogram can facilitate aggressive early treatment and finally improve the prognosis of patients with sepsis.

Abbreviations

SOFA

Sequential organ failure assessment

qSOFA

quickSOFA

ICU

Intensive care unit

MIMIC III

Medical Information Mart for Intensive Care

RDW

Red blood cell distribution width

WBC
White blood cell
AUROC
Area under the curve of the receiver operating characteristic
IDI
Integrated discrimination improvement index
AIC
Akaike information criterion
VIF
Variance inflation factor
SAPS \square
Simplified acute physiology score
GCS
Glasgow coma scale
OR
Odds ratio

Declarations

Ethics approval and consent to participate

The MIMIC III database has received ethical approval from the Institutional Review Boards of both Beth Israel Deaconess Medical Center (Boston, MA, USA) and the Massachusetts Institute of Technology (Cambridge, MA, USA). All data are de-identified in this database to remove patients' information, the requirement for individual patient consent is not indispensable.

Consent for publication

Not applicable

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding/Support

None.

Authors' contributions

YY, QW and SL analyzed the data and wrote the paper. YFY and KG collected the data. FG, PW and WL checked the integrity of the data and the accuracy of the data analysis. LL and YZ designed the study and revised the paper. All authors read and approved the final manuscript.

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None

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Figures

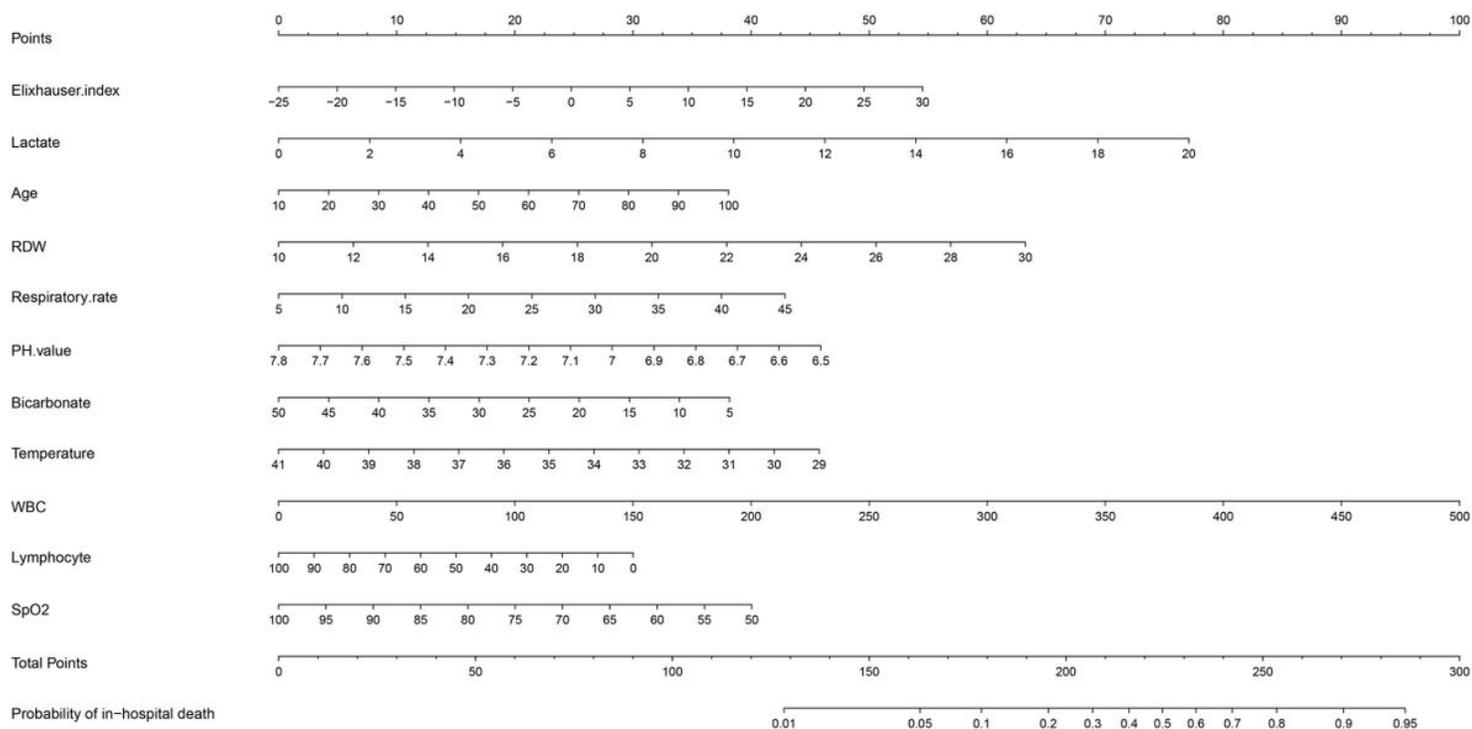


Figure 1

The nomogram for the prediction of in-hospital mortality in patients with suspected infection in ICU.

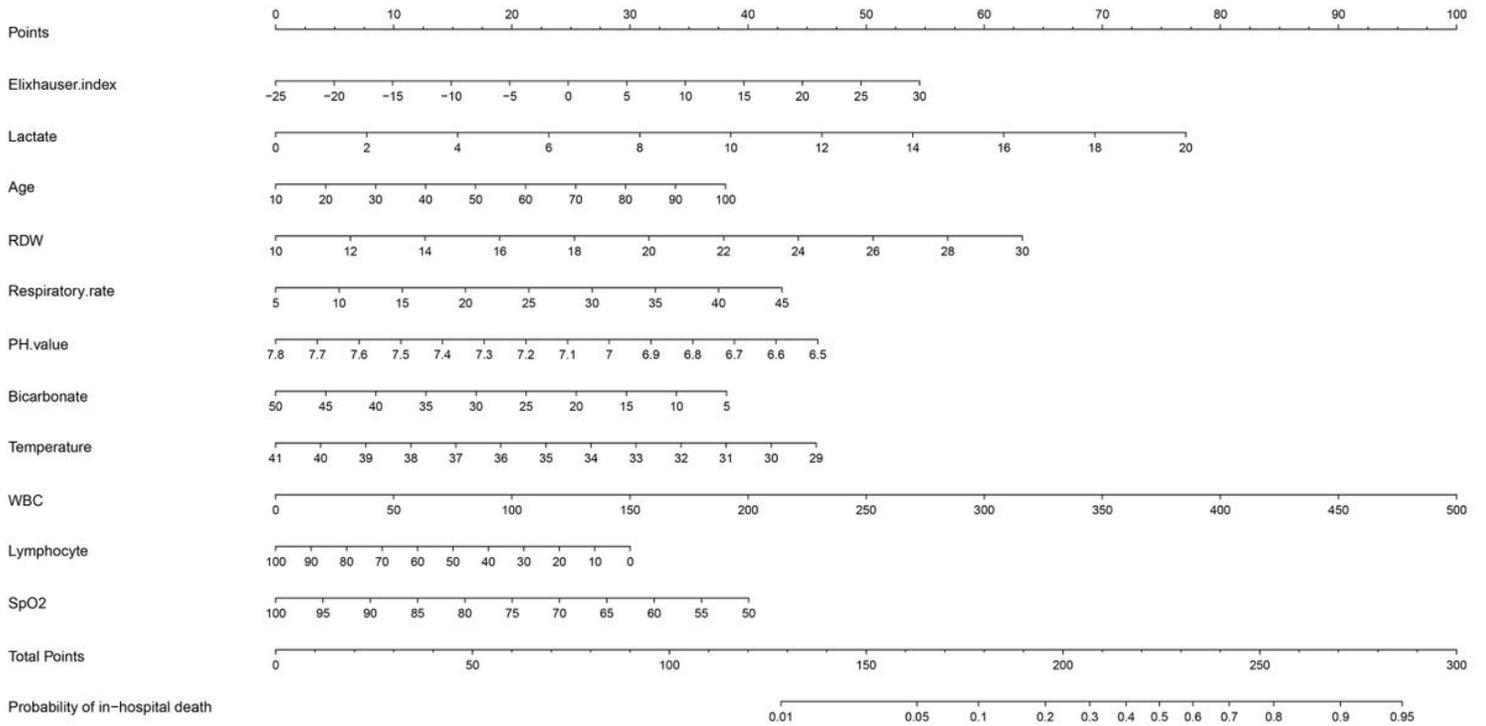


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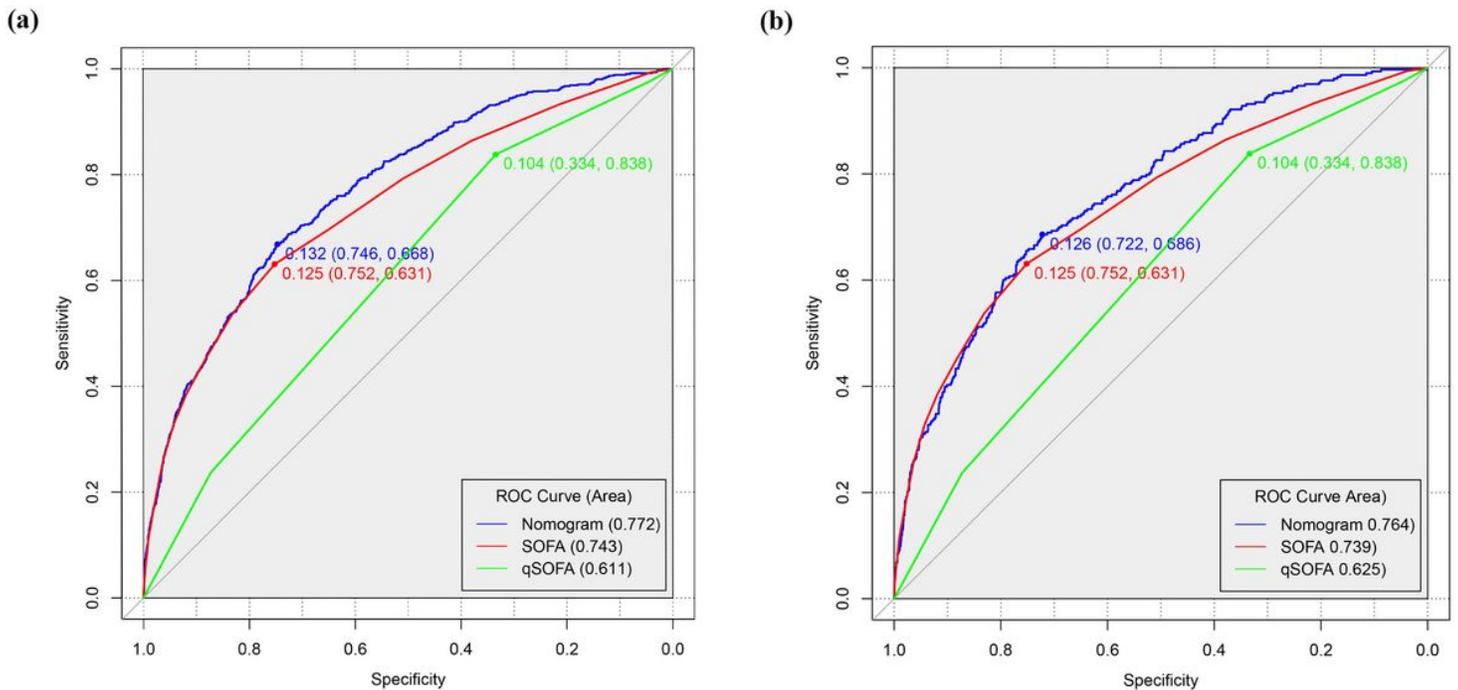


Figure 2

The ROC curve of the prediction nomogram, SOFA score and qSOFA score in the training set (a) and validation set (b).

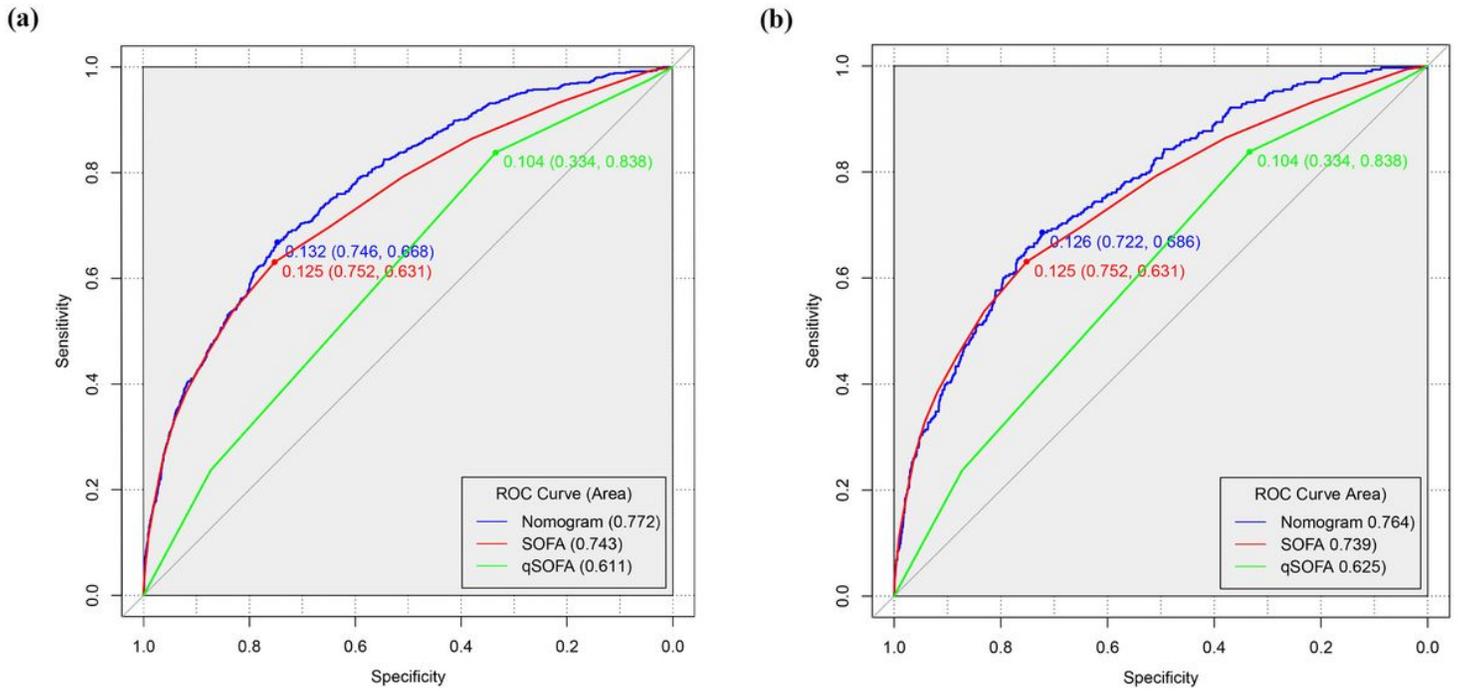


Figure 2

The ROC curve of the prediction nomogram, SOFA score and qSOFA score in the training set (a) and validation set (b).

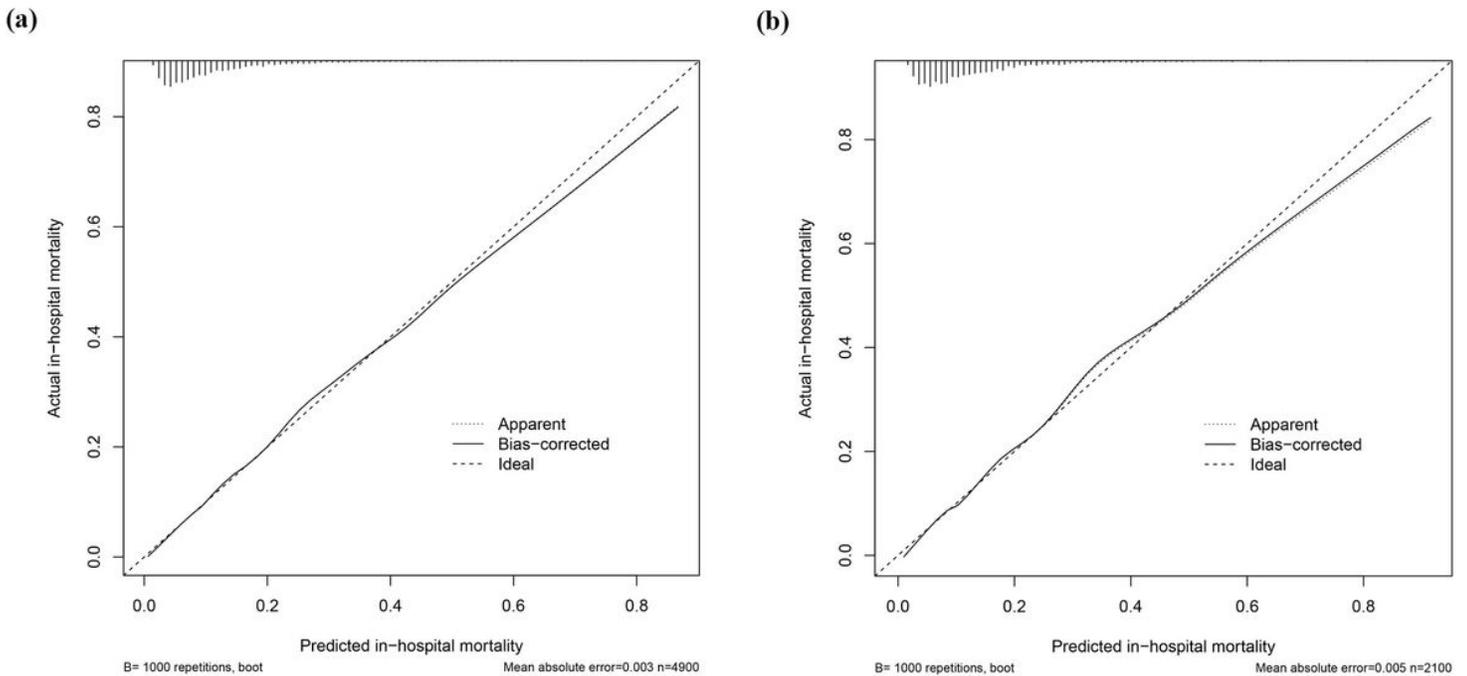


Figure 3

Calibration curves constructed by bootstrap approach in the training set (a) and validation set (b).

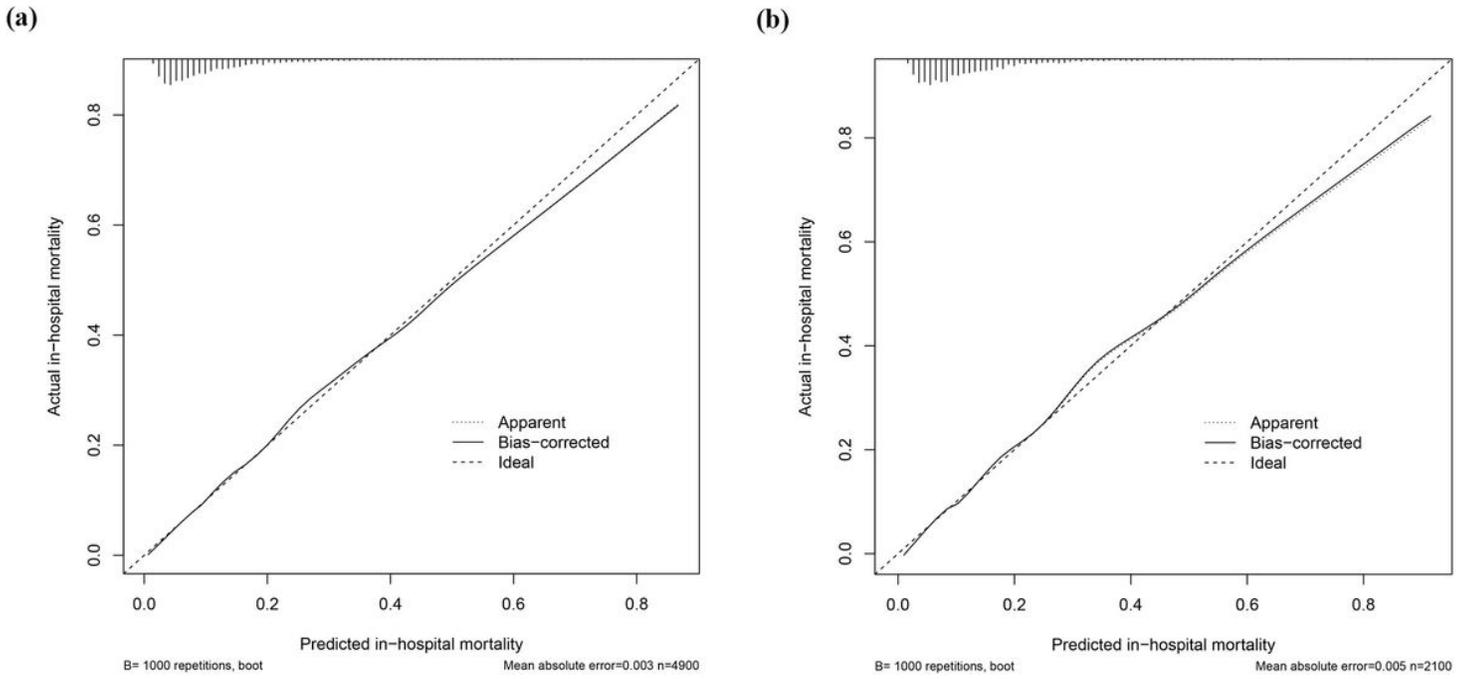


Figure 3

Calibration curves constructed by bootstrap approach in the training set (a) and validation set (b).

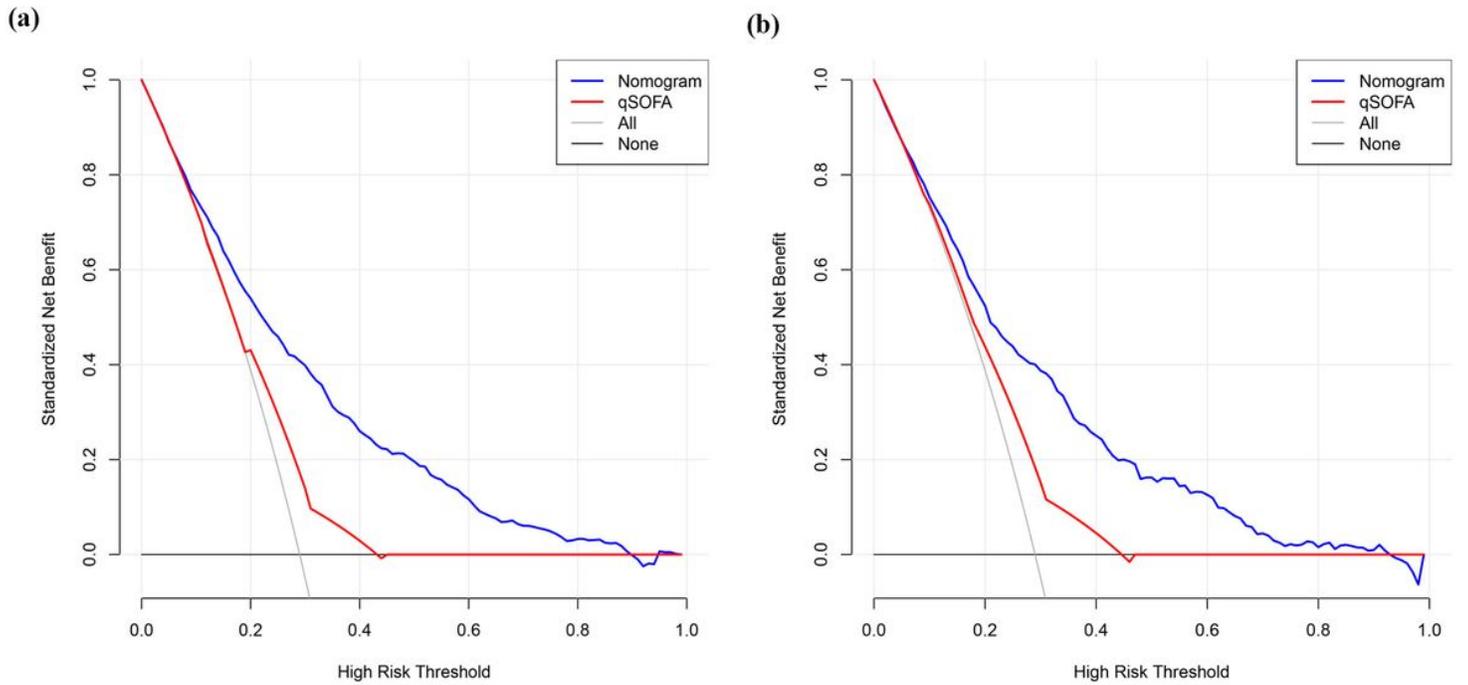


Figure 4

The DCA curve of medical intervention in patients with the nomogram and qSOFA score in the training set (a) and validation set (b).

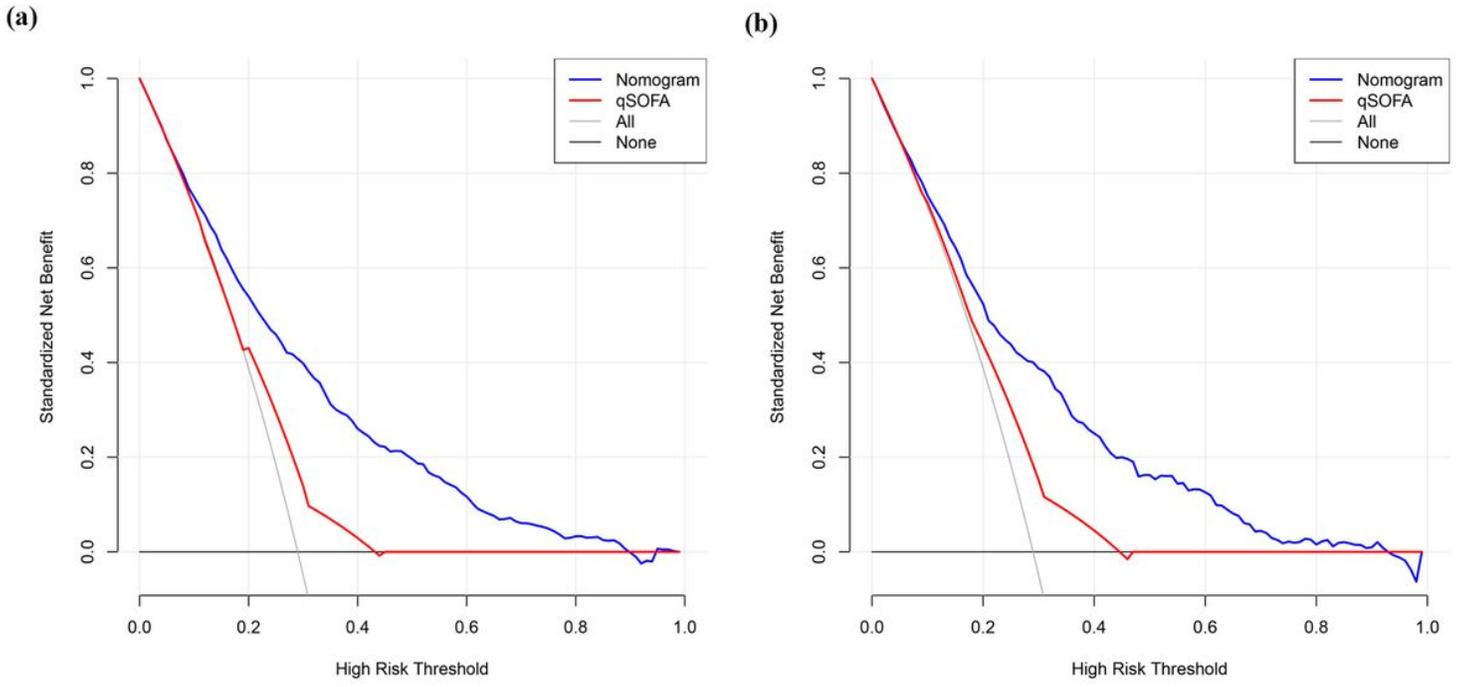


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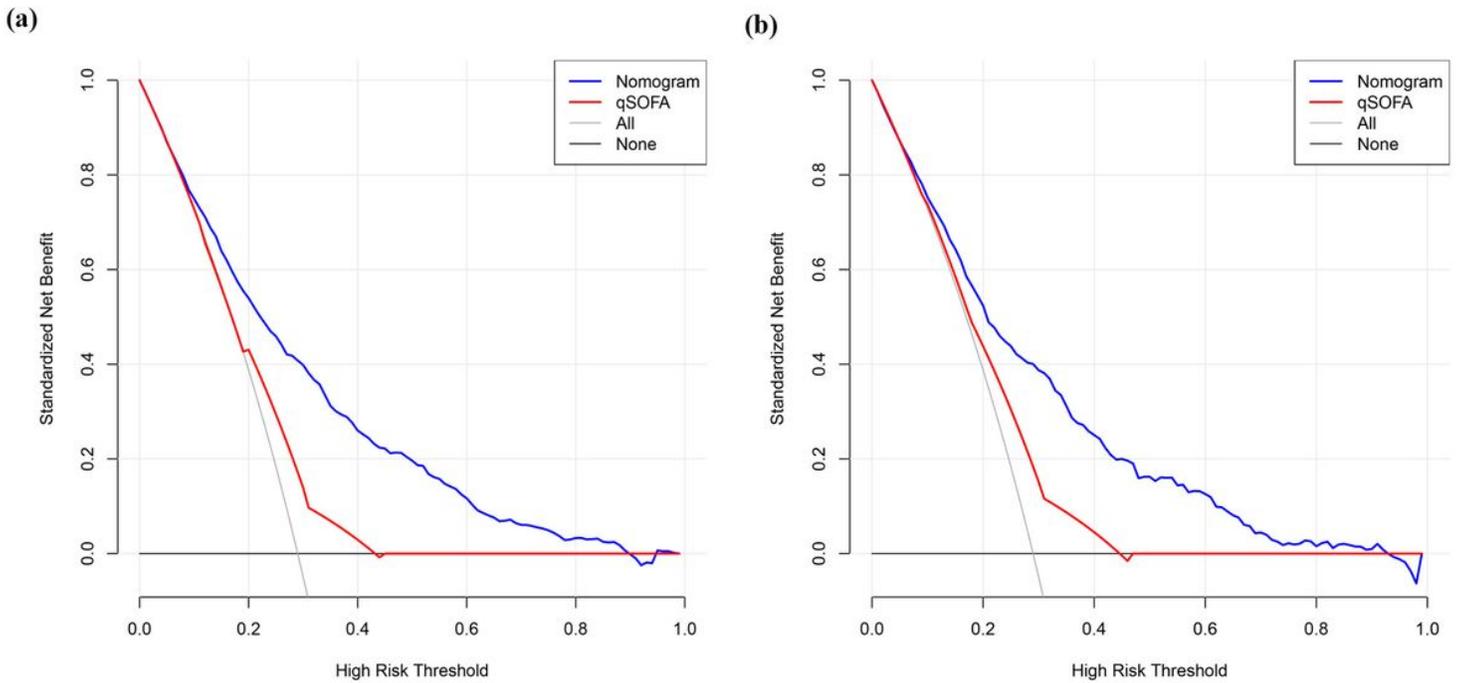


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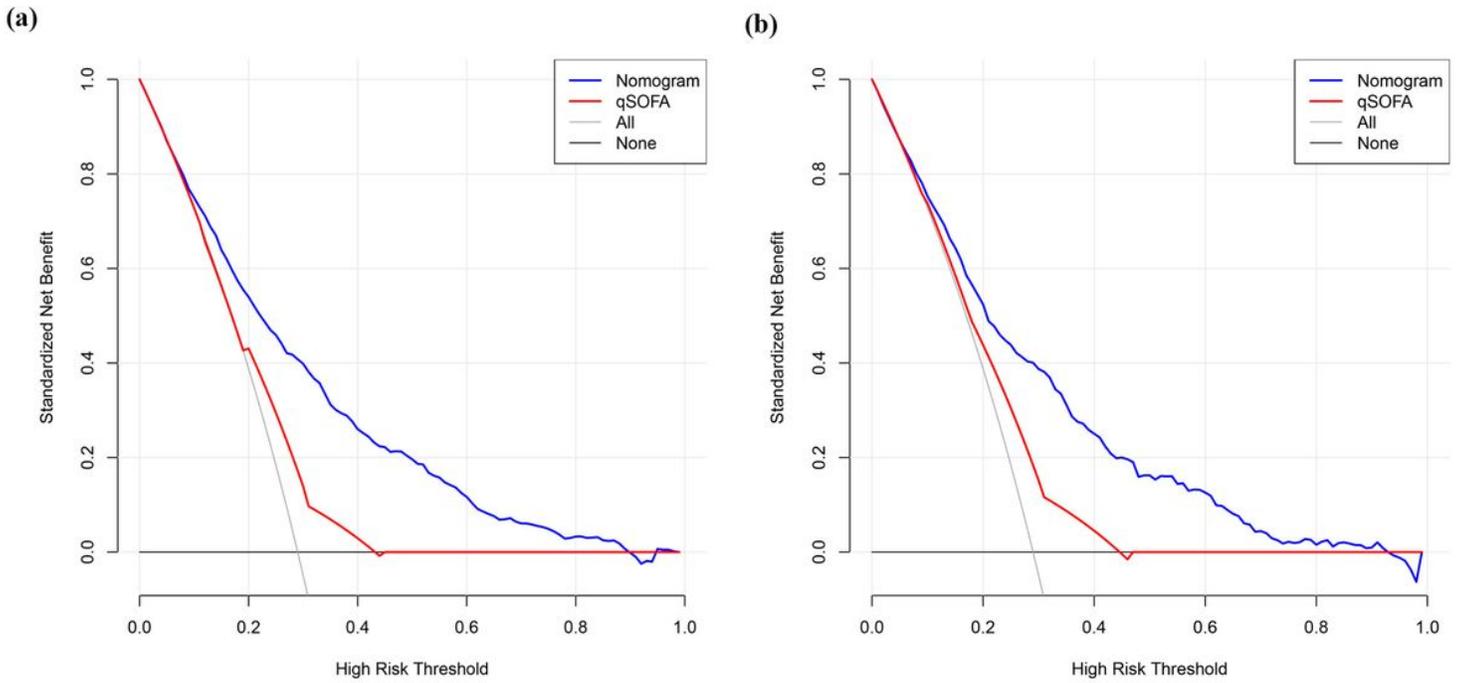


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The DCA curve of medical intervention in patients with the nomogram and qSOFA score in the training set (a) and validation set (b).

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