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Original Article

Development and validation of a clinical score combining the sequential organ failure assessment score with inflammation-based markers to predict outcome of patients with sepsis

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Abstract: Background: Whether combining the Sequential Organ Failure Assessment (SOFA) score at admission with inflammation-based markers can improve performance of prediction and risk stratification of patients with sepsis, compared to use of the SOFA score alone, remains unknown. Methods: Data from septic patients included in the Medical Information Mart for Intensive Care database (MIMIC-IV) database were used for model development and internal validation. We developed a predictive nomogram model that included SOFA score, Charlson Comorbidity Index (CCI), red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and mean corpuscular volume (MCV) values. The primary outcome was the performance of the risk score. Results: Data from 4704 septic patients included in the database were used for the primary cohort and to build the model. The multivariate analyses included SOFA score, CCI, RDW, NLR, LMR, and MCV values. These values were used for nomogram model construction. The nomogram model showed good calibration, and had better discrimination in terms of area under the receiver operating characteristic (AUROC) curve results than use of the SOFA score alone (0.724 (95% CI: 0.705-0.743) vs. 0.585 (95% CI: 0.562-0.609), respectively; P<0.001). It also had better classification in terms of net reclassification improvement (20.5% (95% CI: 16.2%-24.7%; P<0.001)) and integrated discrimination improvement (6.0% (95% CI: 5.1%-6.8%; P<0.001)). The validation cohort results supported these findings. Conclusion: The results suggested that this simple-to-use nomogram model provided a relatively accurate risk of death prediction in patients with sepsis.

Keywords: Sequential organ failure assessment score, red cell distribution width, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, mean corpuscular volume, nomogram, sepsis

Introduction

Sepsis is characterized by systemic inflammation and acute organ dysfunction due to infection [1], The short-term mortality rate is relatively high (30%-50%) [2]. Identifying patients with sepsis in the intensive care unit (ICU) who are at an increased risk of death during the early phase of sepsis can assist with development and provision of timely and adequate interventions [3].

Risk prediction systems are used in the ICU. These systems include use of underlying medical comorbidities and physiologic data to estimate patient mortality and outcomes. The commonly used Sequential Organ Failure Assessment (SOFA) score [4] consists of six distinct organ dysfunction measures. Its use over time to assess illness severity and predict future organ dysfunction and mortality in patients who are critically ill has been validated [5].

SOFA score values are highly reliable and routinely available for prediction and risk stratification of patients with sepsis. However, no components of the score include the contribution of the dysregulated systemic inflammation associated with disease progression during sepsis [6]. Use of inflammation-based markers (e.g., red

cell distribution width (RDW) [7], neutrophil-to-lymphocyte ratio (NLR) [8], lymphocyte-to-monocyte ratio (LMR), and mean corpuscular volume (MCV) [9]) to identify critically ill patients at risk of death from sepsis has been examined. It remains unknown whether combining the SOFA score recorded at admission with these inflammation-based markers improves performance of prediction and risk stratification of patients with sepsis, compared to the SOFA score alone.

In this study, we examined a nomogram model that combined use of the SOFA score at admission with RDW, NLR, LMR, and MCV values. We also investigated whether the new model had better performance for prediction and risk stratification in patients with sepsis than SOFA only.

Materials and methods

Study design

We performed a retrospective analysis of data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database [10]. These high-quality, comprehensive ICU patient data are third-party anonymized and publicly available. The patients were admitted to ICUs at the Beth Israel Deaconess Medical Center (2008-2019). The Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology institutional review boards (IRBs) approved use of the database (certification number 31723135). IRB approval from our institution was not required because pre-existing IRB approval applied.

Study population

Data associated with septic patients were eligible for inclusion in the analysis [1]. A sepsis diagnosis in MIMIC-IV was consistent with the third sepsis definition. Specifically, data from patients with clinically confirmed or suspected infection and a ≥2-point acute SOFA score change were screened for inclusion in the analysis [1]. The presence of infection was identified according to ICD-9 and ICD-10 codes. Only patients with a post-24 h ICU admission sepsis onset were included in the analysis. The definition of sepsis onset in the MIMIC-IV database is discussed elsewhere. The exclusion criteria were: (1) patient age <18 years; (2) an ICU stay <24 h; (3) an admission with outliers present (values greater than the mean ± three times the standard deviation). If a patient was admitted to the ICU more than once, only data associated with the first ICU stay were analyzed. Patients who were not excluded were randomly assigned to a primary cohort group or an internal validation cohort group at a 7:3 ratio, respectively.

Data extraction

A structured query programming language approach was used to extract the data. Baseline characteristics for the 24 h period immediately post-ICU admission were extracted: age, gender, admission type, Charlson Comorbidity Index (CCI), severity at admission measured by SOFA score, and Simplified Acute Physiology Score II (SAPS II), use of mechanical ventilation, renal replacement therapy (RRT), and vasopressor administration. Vital sign data (e.g., mean arterial pressure (MAP), heart rate, temperature (°C), and respiratory rate) were also extracted. Clinical pathology data for hemoglobin concentration, white blood cell, neutrophil, lymphocyte, and platelet counts, RDW, MCV, pH, lactate concentration, and PaO_2/FiO_2 were also extracted. Neutrophil count divided by the lymphocyte count was used to calculate NLR. Lymphocyte count divided by the monocyte count was used to calculate LMR. The value associated with the greatest severity was used if a variable was recorded more than once during the initial 24-h period. The primary outcome variable for the analysis was the performance of the risk score.

Statistical analysis

Results for continuous variables were presented as mean (standard deviation) or median (interquartile range) values and were compared using the Student's t-test for variables with data that met the normal distribution assumption. Mann-Whitney U tests were used for the analysis of variables with data that did not meet the normal distribution assumption. Categorical variables were described using proportions. Chi-square test or Fisher's exact test were used for between-group comparisons.

Uni- and multivariate analyses were used to examine the associations of SOFA score, CCI, NLR, LMR, MCV, and RDW with in-hospital mor-

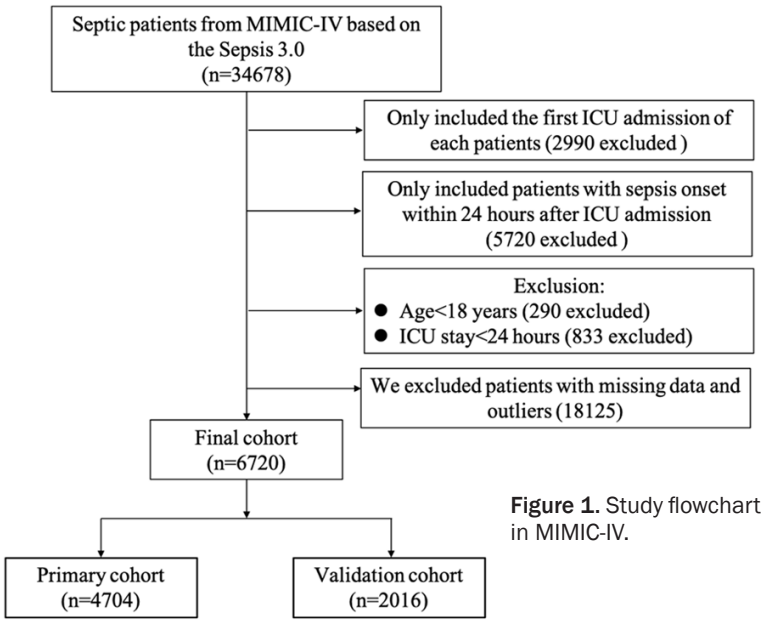

Figure 1. Study flowchart in MIMIC-IV.

tality in the primary model. Model overfitting error was controlled using a backward step-down process based on the Akaike information criterion. A nomogram was constructed based on the results of a logistic regression analysis. Nomogram accuracy and validity were evaluated based on calibration, discrimination, and clinical utility. Calibration curves were used to analyze the extent of agreement between predictions of the nomogram and the clinical data. The area under the receiver operating characteristic (AUROC) curve analysis was performed to compare the predictive performance between the nomogram model and SOFA score alone (bootstrap). Bootstrapping validation was performed in the primary cohort. The AUROCs between the primary cohort and validation cohort were also compared using bootstrap. To assess the clinical usefulness of the predictive nomogram, decision curve analysis (DCA) was used to quantify the net benefits at different threshold probabilities. Net reclassification was also used to determine if the nomogram improved risk classification beyond that achieved using the SOFA score alone. In the analysis, in-hospital mortality results of 0-0.2, 0.2-0.4, and 0.4-1 were defined as low risk, moderate risk, and high risk, respectively. Net reclassification improvement (NRI) was used to assess reclassification improvement over risk categories. Integrated discrimination improvement (IDI) was used as a continuous version of the NRI that did not require risk categories that were defined a priori. Nomogram accuracy and validity were validated in the validation cohort.

A risk score for each patient was calculated based on the nomogram model, and patients in the primary cohort were classified eventually into groups by tertile of the risk score. Multivariate modeling of the association between groups and mortality was performed with logistic regression. Baseline variables that were considered clinically relevant or that showed a univariate relationship with outcome ($P<0.10$) were entered into a multivariate logistic regression model as covariates, and included age, gender, SOFA score, CCI, SAPS II, use of mechanical ventilation, and initial lactate level.

Statistical analyses were performed using the software application, R (version 4.0.3). $P<0.05$ was considered significant.

Results

Baseline characteristics

An examination of the database found that 6,720 patients met the definition of sepsis. The study flowchart is presented in **Figure 1**. For the 4704 patients in the primary cohort, the mean SOFA score was 3.69 (1.89), and the in-hospital mortality rate was 14.3%. The validation cohort consisted of 2016 patients who achieved a mean sofa score of 3.73 (1.90), with an in-hospital mortality rate of 14.7%. There were no intergroup differences for baseline characteristics between the development and validation cohorts. Results for baseline characteristics of the patients in the primary and validation cohorts are presented in **Table 1**.

Prognostic nomogram of modified SOFA scores for 28-day mortality

Uni-and multivariate logistic regression analyses revealed that SOFA score, CCI, NLR, LMR, MCV, and RDW were independent risk factors for in-hospital mortality, with adjusted odds

Table 1. Baseline characteristics and outcomes of the primary cohort and validation cohort

Baseline	Primary cohort (n=4704)	Validation cohort (n=2016)
Age (years)	67.0 [56.0, 78.0]	67.0 [56.0, 78.0]
Male, n (%)	2586 (55.0)	1155 (57.3)
BMI	29.09 (8.03)	28.91 (8.15)
Admission Type, n (%)		
Emergency	2921 (62.1)	1260 (62.5)
Elective	165 (3.5)	61 (3.0)
Urgent	945 (20.1)	405 (20.1)
Other	673 (14.3)	290 (14.4)
Charlson Comorbidity Index	6.0 [4.0, 8.0]	6.0 [4.0, 8.0]
SOFA	3.69 (1.89)	3.73 (1.90)
SAPS II	53.0 [40.0, 72.0]	54.0 [41.0, 73.0]
Intervention in the first 24 h, n (%)		
Vasopressor	1964 (41.8)	866 (43.0)
Renal replacement therapy	200 (4.3)	86 (4.3)
Mechanical ventilation	1974 (42.0)	881 (43.7)
Vital signs		
MAP (mmHg)	75.0 (9.7)	74.7 (9.7)
Heart rate (bpm)	88.7 (16.1)	87.9 (16.4)
Temperature (°C)	36.9 (0.6)	37.0 (0.6)
Respiratory rate (bpm)	20.3 (4.1)	20.3 (4.3)
Laboratory data		
WBC ($*10^9$/L)	11.7 [8.1, 16.4]	11.8 [7.7, 16.3]
PLT ($*10^9$/L)	168.5 [113.7, 238.0]	164.2 [111.8, 238.0]
Hemoglobin (g/L)	9.96 (1.84)	9.99 (1.84)
NLR	9.14 [5.15, 17.20]	9.06 [4.98, 17.77]
LMR	1.94 [1.08, 3.35]	1.92 [1.05, 3.38]
MCV (%)	91.47 (7.46)	91.26 (7.53)
RDW (%)	15.79 (2.49)	15.74 (2.52)
pH	7.37 (0.08)	7.36 (0.08)
PaO_2/FiO_2 (mmHg)	240.5 [177.1, 317.2]	232.6 [172.3, 310.6]
Lactate level (mmol/L)	2.35 (1.87)	2.32 (1.88)
Outcome		
In-hospital mortality, n (%)	672 (14.3)	296 (14.7)
Length of ICU stay	3.1 [2.0, 6.0]	3.1 [1.9, 6.0]
Length of hospital stay	9.0 [6.0, 16.0]	9.0 [6.0, 16.0]

SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; MAP, Mean Arterial Pressure; WBC, White Blood Cell count; PLT, Platelet; NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocytes to Monocytes Ratio; MCV, Mean Corpuscular Volume; RDW, Red cell Distribution Width.

ratios (ORs) of 1.12 (95% CI: 1.07-1.16), 1.15 (95% CI: 1.12-1.18), 1.01 (95% CI: 1.01-1.02), 1.03 (95% CI: 1.00-1.05), 1.03 (95% CI: 1.02-1.04), and 1.15 (95% CI: 1.12-1.18), respectively (all *P* values <0.05) (**Table 2**). The Akaike information criterion result for the model was 3531.98. The Cox & Snell R Square and Nagelkerke R Square was 0.125 and 0.206, respectively.

A nomogram was constructed using the risk factors identified by multivariate analysis (**Figure 2**). To generate the nomogram, each independent prognostic parameter was assigned a weighted score based on a point scale. The total score was calculated as follows: (3.566 * SOFA-7.133) + (4.524 * CCI) + (0.569 * NLR) + (0.913 * LMR) + (0.852 * MCV-51.118) + (4.545 * RDW-45.455).

Table 2. Univariable model and full multivariable model for the relationship between risk factors and in-hospital mortality in primary cohort

	Univariable model			Full multivariable model		
	OR	95% CI	*P* value	OR	95% CI	*P* value
SOFA	1.18	1.13-1.22	<0.001	1.12	1.07-1.16	<0.001
CCI	1.19	1.16-1.23	<0.001	1.15	1.12-1.18	<0.001
NLR	1.02	1.01-1.02	<0.001	1.01	1.01-1.02	<0.001
LMR	0.99	0.96-1.01	0.24	1.03	1.00-1.05	0.023
MCV	1.04	1.02-1.05	<0.001	1.03	1.02-1.04	<0.001
RDW	1.21	1.17-1.24	<0.001	1.15	1.12-1.18	<0.001

SOFA, Sequential Organ Failure Assessment; CCI: Charlson Comorbidity Index; NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocytes to Monocytes Ratio; MCV, Mean Corpuscular Volume; RDW, Red cell Distribution Width.

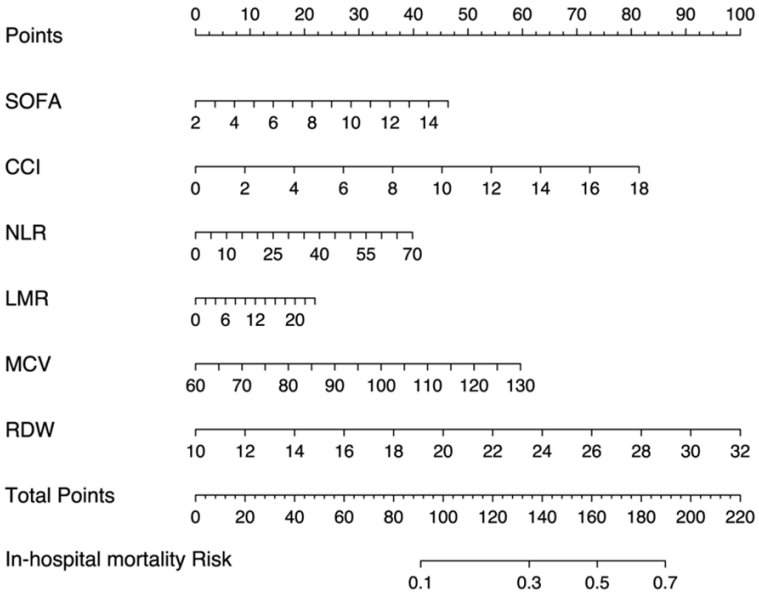

Figure 2. Nomogram predicting in-hospital mortality in septic patients. SOFA, Sequential Organ Failure Assessment; CCI, Charlson Comorbidity Index; NLR, Neutrophil-to-Lymphocyte Ratio; LMR, Lymphocyte to Monocyte Ratio; MCV, Mean Corpuscular Volume; RDW, Red Cell distribution Width.

Nomogram model validation

The calibration plot (**Figure 3**) indicated an adequate nomogram fit for outcome prediction in both cohorts (i.e., primary and validation). ROC curve analysis for outcome discriminatory ability (**Figure 4**) revealed an AUC of 0.724 (95% CI: 0.705-0.743) for the nomogram, which was better than SOFA alone (0.585, 95% CI: 0.562-0.609; P<0.001). The AUC of the nomogram model was 0.745 (95% CI: 0.678-0.765) in bootstrapping validation. The result for the validation cohort was similar. The AUC of the nomogram model or SOFA did not differ significantly between the primary cohort and the validation cohort (P=0.47 for nomogram model, P=0.32 for SOFA). The DCA curve (**Figure 5**) indicated that a better net benefit was gained using the nomogram than the SOFA score; the threshold probabilities were 0-0.3 vs. 0-0.28, respectively, for the primary cohort and 0-0.31 vs. 0-0.17, respectively, for the validation cohort.

The results of the reclassification statistics analysis indicated an improved classification ability of the nomogram model, compared with the original SOFA score. The nomogram resulted in an additive NRI of 20.5% (95% CI: 16.2%-24.7%; P<0.001), and an IDI of 6.0% (95% CI: 5.1%-6.8%; P<0.001) in the primary cohort. It resulted in an additive NRI of 28.5% (95% CI: 21.9%-35.1%; P<0.001), and an IDI of 8.1% (95% CI: 6.6%-9.7%; P<0.001) in the validation cohort.

Classification of patients with sepsis based on risk score

The risk score was 95.1 (79.8-113.4) in the primary cohort. Patients were classified into four groups by total points (very low risk: <79.8, low risk: 79.9-95.1, medium risk: 95.2-113.4, high risk: ≥13.5). Multivariate logistic regression showed that compared to patients with very low risk, the patients with low risk, medium risk, and high risk were associated with

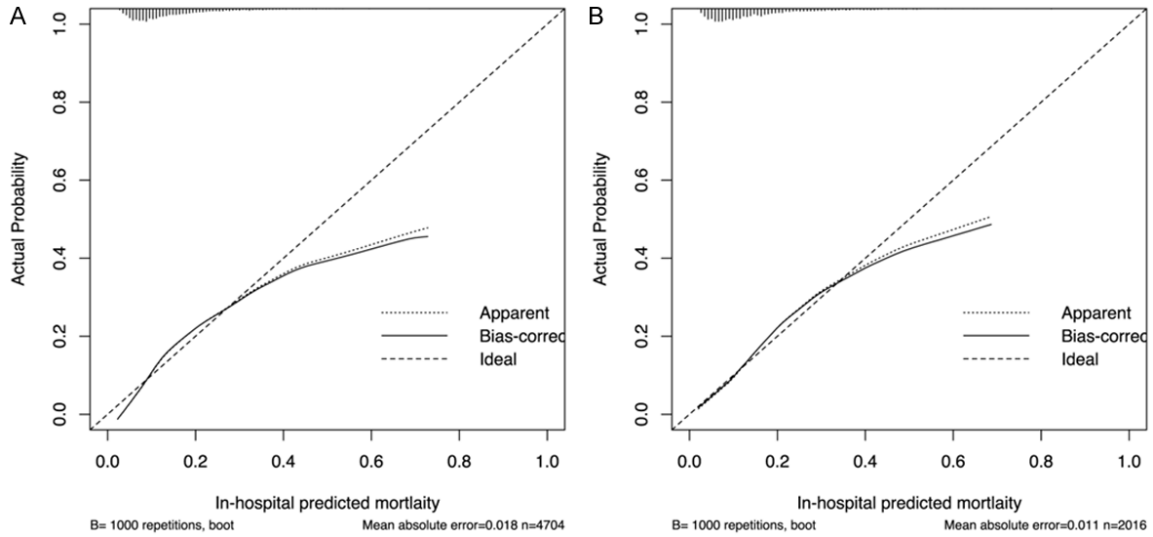

Figure 3. Calibration curves for predicting the outcome of septic patients in the emergency department in the primary cohort (A), validation cohort (B).

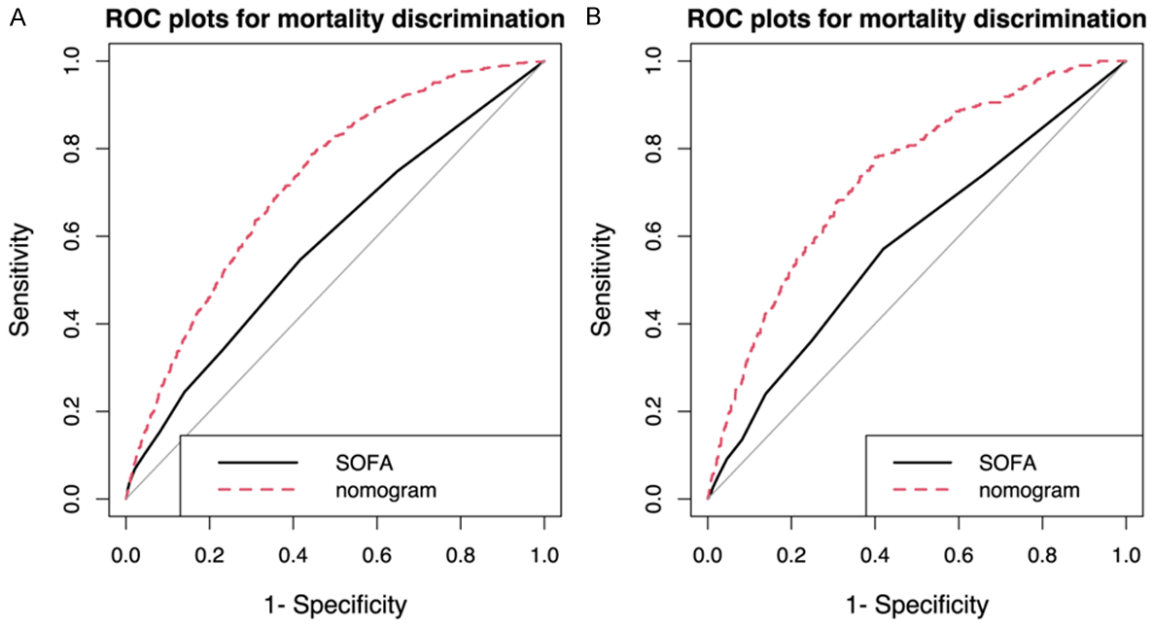

Figure 4. Receiver operating characteristic curve analysis and comparison of the AUCs for the nomogram and SOFA score in the primary cohort (A), validation cohort (B). AUC: Area Under the Curve; SOFA: Sequential Organ Failure Assessment.

increased in-hospital mortality, with adjusted ORs of 1.75 (95% CI: 1.07-2.90), 3.68 (95% CI: 2.25-6.17), and 5.85 (95% CI: 3.32-10.48), respectively (all *P* values <0.05).

Discussion

The results of this study suggested that a new SOFA score modified using CCI, RDW, NLR, LMR, and MCV through a nomogram had better performance for prediction and risk stratification for septic patients.

Because it is simple to use and includes graded assessment of organ failure, the SOFA score is the most widely used scoring system for patients with sepsis. As the definition and clinical management of sepsis have changed over

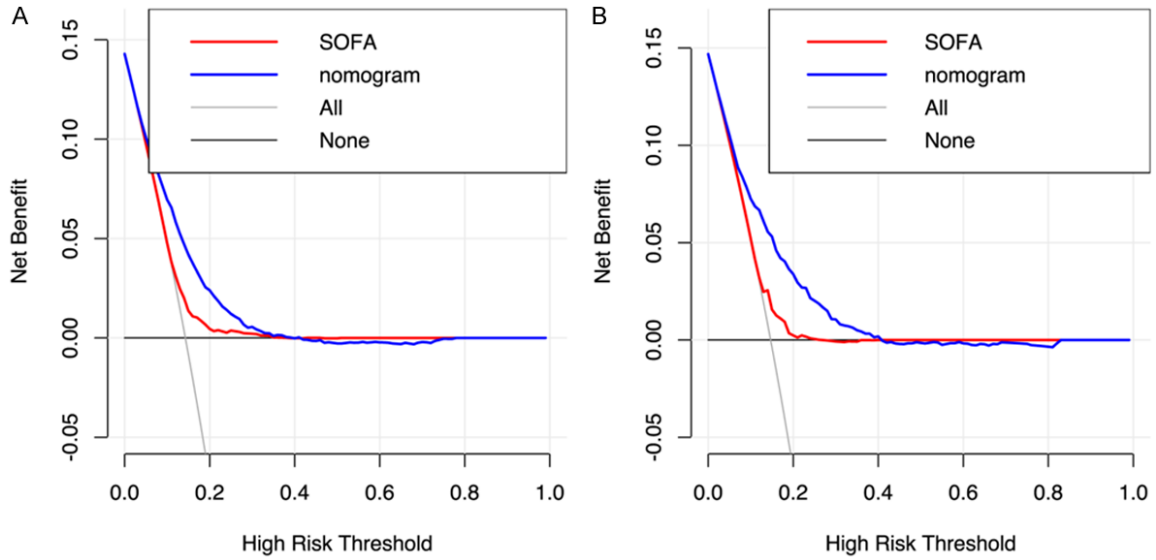

Figure 5. Decision curves for the primary cohort (A), and validation cohort (B) implicating the net benefit with respect to the use of the nomogram for predicting mortality of septic patients. SOFA: Sequential Organ Failure Assessment.

time, the priority for sepsis management has become not just addressing organ failure but also the severity of organ failure and the exaggerated inflammatory response [11]. Because of these changes, there was an inevitable decline in the existing SOFA score performance and the model has been updated over time. Glasgow Coma Scale (GCS) is not available for use or is not applied consistently at some healthcare facilities, thus Vasilevskis et al. [12] proposed a modified SOFA score that uses the Richmond Agitation-Sedation Scale (RASS) instead of the GCS. They found that compared to a GCS-based SOFA score (0.799), a Mean RASS-based SOFA score can achieve an AUC of 0.814 for prediction of ICU mortality. A modified cardiovascular component of the SOFA score was developed and validated by Yadav et al. [13]. All clinically-used vasoactive agents are accounted for by this modification. A shock index is used as a mean arterial pressure substitute, and serum lactate serves as a shock state biomarker. They found that ROC curves used to predict ICU mortality, hospital mortality, and 28-day mortality are significantly higher for the modified cardiovascular component of the SOFA score than for the original cardiovascular component of the SOFA score. In this study, we constructed a new SOFA score by modifying the assessment of inflammation-based markers, including RDW, NLR, and MCV through a nomogram. The AUC of the nomogram to predict 28-day mortality of septic patients was as high as 0.704, compared to the SOFA score alone ($P<0.001$).

In critically ill patients, RDW can be independently associated with all-cause mortality risk [14-16]. RDW can provide additional prognostic value beyond that of severity scores, including the APACHE II and SOFA scores [17, 18]. Consistent with these findings, the results of this study suggested that RDW was an important independent risk factor for 28-day mortality in septic patients admitted to the ICU. RDW can be affected by factors including anemia, ischemia, renal function, and inflammatory responses. Sepsis-associated inflammatory responses can result in inadequate erythropoiesis, altered iron metabolism, and inhibition of erythrocyte maturation. Immature red blood cells are then released into the circulation to result in an elevated RDW, which may partially represent the inflammation state of patients with sepsis [19]. On the other hand, reactive erythropoiesis participates in compensation for acute stress and the resulting tissue hypoxia. How well this process is carried out might be determined by genetic factors. The level of response may also reflect the extent of physiologic reserves available to the patient, and explain why RDW is independent of organ dysfunction severity during sepsis.

Sepsis pathophysiology includes unregulated inflammation; the inflammatory response in-

cludes neutrophils, lymphocytes, and red blood cells. Changes in NLR, LMR, and MCV indicate the presence of inflammatory response or immune status imbalances, or imbalances in both. Hence, NLR, LMR, and MCV are used over time as inflammation-based markers for patients who are critically ill, have cardiovascular disease, or have tumors [20, 21]. Patients with increased NLR, LMR, or MCV values have poorer outcomes. Lu et al. found a significant relatively shorter overall survival time to be associated with nasopharyngeal carcinoma and an NLR ≥2.28. Cox regression analysis found that compared to quintile 3 (8.6 (7.1-9.9)), quintile 1 (0.2 (0.1-0.7)) and quintile 5 (31 (24.6-46.8)) NLR values are significant risk factors for prediction of 28-day mortality in critically ill patients with sepsis [8]. In this study, we found that an NLR ≥12.8 and an MCV ≥93.3 in the initial blood sample collected after ICU admission had significant associations with increased in-hospital mortality.

The predictive performance of the SOFA score for in-hospital mortality was relatively low, compared to previous research [6, 22]. This may be because of different environments to calculate SOFA scores in the MIMIC IV database. There are many missing values in MIMIC IV regarding the parameters to calculate SOFA scores, especially the bilirubin, and all missing values were transformed to 0 when calculating the SOFA score, which could affect the predictive value of the SOFA score [23].

This study was the first to construct and use a nomogram model to examine prognostic accuracy and validity of combining the SOFA score with inflammation-based markers, including CCI, RDW, NLR, LMR, and MCV in patients with sepsis in the ICU. We also proposed a new risk stratification strategy for septic patients based on risk score.

This study had some limitations. First, we performed a retrospective analysis using data from an online database. Missing and outlier data were common and may have increased the study bias. Well-designed prospective studies are required to further evaluate our nomogram. Second, we only used admission SOFA scores to construct the nomogram. An evaluation over time could be more informative and aid in treatment adjustment decisions. Third, we evaluated the prediction performance only for in-hospital mortality. Prediction of shorter- or longer-term mortality and other outcomes (e.g., length of ICU stay, hospitalization costs, and quality of life) could also be evaluated in future studies.

Conclusions

Compared to use of the SOFA score alone, a nomogram model based on SOFA score, CCI, RDW, NLR, LMR, and MCV values provided more accurate death prediction and risk stratification for patients with sepsis in the ICU.

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Disclosure of conflict of interest

None.

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