Development and Validation of a Prognostic Nomogram to Predict 30-Day Mortality Risk in Patients with Sepsis-Induced Cardiorenal Syndrome

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\textbf{Abstract}

\textbf{Introduction:} Sepsis-induced cardiorenal syndrome (sepsis-induced CRS) is a devastating medical condition that is frequently associated with a high fatality rate. In this study, we aimed to develop an individualized nomogram that may help clinicians assess 30-day mortality risk in patients diagnosed with sepsis-induced CRS. \textbf{Methods:} A total of 340 patients with sepsis-induced CRS admitted from January 2015 to May 2019 in Shanghai Tongji Hospital were used as a training cohort to develop a nomogram prognostic model. The model was constructed using multivariable logistic analyses and was then externally validated by an independent cohort of 103 patients diagnosed with sepsis-induced CRS from June 2019 to December 2020. The prognostic ability of the nomogram was assessed through discrimination, calibration, and accuracy. \textbf{Results:} Five prognostic factors were determined and included in the nomogram: age, Sequential (sepsis-related) Organ Failure Assessment (SOFA) score, vasopressors, baseline serum creatinine, and the rate of change in myoglobin. Our prognostic nomogram showed well-fitted calibration curves and yielded strong discrimination power with the area under the curve of 0.879 and 0.912 in model development and validation, respectively. In addition, the nomogram prognostic model exhibited an evidently higher predictive accuracy than the SOFA score. \textbf{Conclusions:} We developed a prognostic nomogram model for patients with sepsis-induced CRS and externally validated the model in another independent cohort. The nomogram exhibited greater strength in predicting 30-day mortality risk than the SOFA score, which may help clinicians estimate short-term prognosis and modulate therapeutic strategies.

\textbf{Keywords}

Sepsis · Cardiorenal syndrome · Prognosis · Nomogram

\section*{Introduction}

Cardiorenal syndrome (CRS) has been described as a broad range of serious multi-organ diseases involving the heart and kidneys [1]. Owing to the complex interconnection between these two organs, an acute or chronic dysfunction of the heart or kidney could result in the acute or chronic injury of the other organ [2]. CRS is generally classified into five types [3]; CRS type 1–4 concerns acute or chronic CRS or reno-cardiac syndromes, and
Sepsis is a systemic inflammatory disorder resulting from the deranged reaction of the body to infection. Despite the improvements that have been made in treatment and prognosis, sepsis remains a critical clinical condition with high risk of morbidity and fatality [5], demanding continued research. In 2006, the Third International Consensus Definitions Task Force (Sepsis 3.0) highly recommended the application of the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score to evaluate organ dysfunction in septic patients, and it also reported that in-hospital mortality rate would at least reach 10% if the patient had an elevation in SOFA score ≥2 points [6]. In addition, other studies have shown that the incidence rate of multi-organ injury in septic patients can reach 40–60% [4], and the 90-day [7], 1-year [7], 3.5-year [8], and 5-year mortality [8] rates for those who developed severe sepsis and survived hospitalization were 28%, 44%, 53%, and 61%, respectively. Acute kidney injury (AKI) and acute cardiovascular dysfunction are often observed in patients with sepsis and septic shock. The clinical picture of concomitant acute cardiac and renal injury (or dysfunction) secondary to sepsis is currently referred to as “CRS type 5 in sepsis” [9, 10] or “sepsis-induced CRS” [11, 12].

Previous studies revealed that patients with sepsis-induced CRS tend to have a worse clinical manifestation and prognosis than those without AKI or cardiac insult [9]. To date, some studies have focused on predicting prognosis in sepsis-induced AKI [13–15], sepsis-associated encephalopathy [16], and sepsis-induced coagulopathy [17], and some have reported greater prognostic ability for septic AKI or critically ill surgical patients when using a combination of SOFA score and other biomarkers [14, 18]. However, research concerning the prognosis in patients with sepsis-induced CRS is sporadic. Individualized evaluation of clinical outcomes for patients in the early phase of sepsis-induced CRS is vital because it can promote well-timed medical intervention and active nursing strategies and may improve clinical outcomes. Therefore, the specific aim of our study was (1) to explore the independent risk factors affecting the short-term prognosis in patients diagnosed with sepsis-induced CRS and (2) to develop and validate a prognostic model to estimate 30-day mortality risk in such patients. To our knowledge, there is by far no research reporting the use of the nomogram for risk prediction of 30-day mortality in sepsis-induced CRS.

### Materials and Methods

#### Data Source and Study Design

This was an observational study that retrieved the clinical data of patients diagnosed with sepsis during hospitalization in Shanghai Tongji Hospital from 1 January 2015 through to 31 December 2020. The inclusion criteria were as follows: (1) age >18 years; (2) meeting the consensus of sepsis definition issued in 2016 [6]; (3) meeting the diagnostic criteria of AKI issued by the 2012 Kidney Disease Improving Global Outcomes (KDIGO) guidelines [19]; (4) acute cardiovascular injury occurring during hospitalization. We excluded patients with (1) hospital stay ≤48 h; (2) acute cardiac or renal injury with nonseptic causes such as autoimmune disease and surgery; (3) active malignant tumors; (4) mental disorders; (5) pregnancy; and (6) missing values in clinical data. The eligible patients hospitalized between 1 January 2015 and 31 May 2019 were assigned to the training cohort, and patients admitted between 1 June 2019 and 31 December 2020 were assigned to the validation cohort. All patients enrolled were complete cases with no missing data. The report of this study complied with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines [20] (shown in online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000524483).

#### Data Collection

In order to select prognostic factors for model development, we collected the following clinical data in training cohort: (1) basic characteristics, including age, sex, department, infection site, blood culture, preexisting disease, medication history; the “infection site” recorded the site of infection identified by clinicians; the “medication history” recorded the prescription 3 months prior to hospitalization from both outpatient and inpatient medical records; (2) quick SOFA (qSOFA) score and SOFA score that were calculated and recorded by clinicians on the first day of the diagnosis of sepsis-induced CRS; (3) in-hospital treatment, including mechanical ventilation and vasopressor use, such as dopamine, norepinephrine, and epinephrine; (4) laboratory variables which were tested on the first and the third day of diagnosis by Clinical Laboratory of Shanghai Tongji Hospital, including cardiac troponin I (cTnI), myoglobin (MYO), serum creatinine (SCr), C-reactive protein (CRP), and procalcitonin (PCT); (5) baseline SCr: this variable was measured in accordance with the varying conditions of the patients in the following order – (A) SCr value from the most recent examination before hospitalization (within 12 months); (B) the nadir creatinine value measured during the first 3 days of hospitalization; and (C) the baseline SCr inversely deduced using the back-estimation formula according to the population’s average glomerular filtration rate of 75 mL/(min·1.73 m²) [21]. Data collection for the validation cohort was started after developing the nomogram. Therefore, based on the results of the training cohort, we recorded the clinical data in the validation cohort, including basic characteristics (age, sex, department, infection site, and preexisting disease), qSOFA score, SOFA score, in-hospital treatment, and laboratory variables (baseline SCr and MYO). All patients were followed up for at least a month after hospital discharge, and as the outcome of our study, deaths were confirmed according to medical records or telephone follow-ups. Additionally, the testing and recording of the predictor variables occurred before recording the outcome.
and the data of predictors and outcomes were collected by different researchers. Therefore, the assessment of predictors was blind to the outcome.

**Sepsis-Induced CRS**

According to the sepsis-3 definition published in 2016, sepsis is diagnosed based on evidence of acute infection and newly developed organ dysfunction. Organ dysfunction was demonstrated by an increase of at least two points in the SOFA score. Sepsis can also be rapidly recognized using the qSOFA score [6]. In this study, we confirmed sepsis by both admission diagnoses made by clinicians and SOFA (or qSOFA) scores calculated by researchers.

Acute CRS was confirmed by the biomarker-based definition. We combined the use of elevated serum cTnI, B-type natriuretic peptide (BNP), N-terminal pro-BNP (NT-proBNP), and the KDIGO definition of AKI. AKI is defined by (1) elevated SCR ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h, or (2) elevated SCR ≥1.5 times of baseline SCR within 7 days, or (3) urine volume <0.5 mL/(kg/h) for 6 h. Acute cardiac injury in CRS [22] is indicated by at least one of the following changes within 48 h: (1) increase in BNP ≥100 pg/mL; (2) increase in NT-proBNP ≥300 pg/mL; and (3) increase in cTnI ≥0.03 ng/mL.

**Statistical Analysis**

The baseline characteristics are presented as percentages for categorical data and as medians with interquartile ranges for continuous data. Restricted cubic spline was used to evaluate the linear relationship between the potential variables and the outcome, and continuous variables that showed a nonlinear relationship with the 30-day mortality risk in the restricted cubic spine, such as SCr and cTnI, were converted to categorical variables. The tolerance indices and variance inflation factor (VIF) were used to test the multicollinearity between the predictors. If tolerance <0.1 or VIF > 10, it indicates a serious multicollinearity problem between the variables [23], and normally one of the two variables that have close linear intercorrelation would be removed. The rate of change in MYO was calculated using data collected from the first and third days of diagnosis. The rate of change in cTnI and baseline SCr was not included in the logistic regression analysis as the denominator of cTnI could be 0, and there exists a large collinearity (VIF > 10) between the rate of change in SCr and the SCr level on the first and third days. In the training cohort, the potential prognostic variables of $p < 0.10$ in univariate logistic analysis were included in the multivariable analysis. Multivariable logistic regression analysis was used to identify the independent risk factors for the 30-day mortality rate and to develop a nomogram predictive model. Bootstrap resampling methods were carried out for both internal and external validation of the model. In model validation, the predictive ability of the nomogram model was assessed by discrimination, calibration, and accuracy. Model discrimination ability was evaluated using the area under the receiver operating characteristic curve (AUC), while the calibration ability was assessed by the Hosmer-Lemeshow test and the calibration curve. The model accuracy was determined by the Brier score (the closer the Brier score is
Table 1. Patients’ demographic features and clinical characteristics in training cohort

| Variables                        | Survivors (n = 226) | Non-survivors (n = 114) | Z/χ²  | p value |
|----------------------------------|---------------------|-------------------------|-------|---------|
| Age                              | 81.00 (68.00–87.00) | 83.00 (72.75–88.00)    | −2.358| 0.018   |
| Male, n (%)                       | 118 (52.2)          | 67 (58.8)               | 1.314 | 0.252   |
| Department, n (%)                 |                     |                         |       |         |
| ICU                              | 74 (32.7)           | 36 (31.6)               |       |         |
| Emergency department             | 95 (42.0)           | 30 (26.3)               | 12.935| 0.005   |
| Medical ward                     | 41 (18.1)           | 38 (33.3)               |       |         |
| Surgical ward                    | 16 (7.1)            | 10 (8.8)                |       |         |
| Infection site, n (%)            |                     |                         |       |         |
| Respiratory system               | 111 (49.1)          | 82 (71.9)               | 17.882| <0.001  |
| Digestive system                 | 50 (22.1)           | 15 (13.2)               |       |         |
| Urinary system                   | 47 (20.8)           | 9 (7.9)                 |       |         |
| Other                            | 18 (8.0)            | 0 (7.0)                 |       |         |
| Blood culture, n (%)             |                     |                         |       |         |
| Negative                         | 117 (51.8)          | 61 (53.5)               | 6.432 | 0.169   |
| Gram, positive                   | 14 (6.2)            | 9 (7.9)                 |       |         |
| Gram, negative                   | 31 (13.7)           | 23 (20.2)               |       |         |
| Fungus                           | 17 (7.5)            | 3 (2.6)                 |       |         |
| Polymicrobial infection, n (%)   | 47 (20.8)           | 18 (15.8)               |       |         |
| SBP, mm Hg                       | 120.00 (101.75–140.00) | 120.00 (101.75–140.00) | −0.237| 0.812   |
| DBP, mm Hg                       | 70.00 (60.00–80.00) | 69.5 (58.50–80.00)      | −0.770| 0.441   |
| HR                               | 85.00 (80.00–100.00) | 86.00 (80.00–105.00)    | −0.438| 0.661   |
| T, °C                            | 37.00 (36.50–37.93) | 37.00 (36.50–37.30)     | −1.874| 0.061   |
| Preexisting disease, n (%)       |                     |                         |       |         |
| Diabetes                         | 73 (32.3)           | 38 (33.3)               | 0.037 | 0.848   |
| Hypertension                     | 149 (65.9)          | 67 (58.8)               | 1.675 | 0.196   |
| CAD                              | 75 (33.2)           | 39 (34.2)               | 0.036 | 0.850   |
| Stroke                           | 77 (34.1)           | 39 (34.2)               | 0.001 | 0.980   |
| CKD                              | 38 (16.8)           | 16 (14.0)               | 0.438 | 0.508   |
| History of tumor, n (%)          | 21 (9.3)            | 8 (7.0)                 | 0.502 | 0.478   |
| History of smoking, n (%)        | 41 (18.1)           | 29 (25.4)               | 2.468 | 0.116   |
| Medication history, n (%)        |                     |                         |       |         |
| Diuretics                        | 83 (36.7)           | 56 (49.1)               | 4.819 | 0.028   |
| CCB                              | 75 (33.2)           | 33 (28.9)               | 0.628 | 0.428   |
| ACEI                             | 21 (9.3)            | 7 (6.1)                 | 0.996 | 0.318   |
| ARB                              | 63 (27.9)           | 29 (25.4)               | 0.228 | 0.633   |
| β-Blocker                        | 53 (23.5)           | 22 (19.3)               | 0.760 | 0.383   |
| Statin                           | 58 (25.7)           | 24 (21.1)               | 0.880 | 0.348   |
| Nitrate ester                    | 45 (19.9)           | 26 (22.8)               | 0.385 | 0.353   |
| Digoxin                          | 18 (8.0)            | 16 (14.0)               | 3.103 | 0.078   |
| Antiplatelet drug                | 77 (34.1)           | 34 (29.8)               | 0.621 | 0.431   |
| Warfarin                         | 47 (20.8)           | 17 (14.9)               | 1.717 | 0.190   |
| In-hospital treatment, n (%)     |                     |                         |       |         |
| Mechanical ventilation           | 42 (18.6)           | 50 (43.9)               | 24.528| <0.001  |
| In-hospital treatment            | 94 (41.6)           | 95 (83.3)               | 53.477| <0.001  |
| qSOFA, n (%)                     |                     |                         |       |         |
| ≤2                               | 162 (71.7)          | 80 (70.2)               | 0.084 | 0.772   |
| >2                               | 64 (28.3)           | 34 (29.8)               |       |         |
| Total SOFA                       | 5.00 (3.00–8.00)    | 11.00 (8.00–13.00)      | −9.586| <0.001  |
| Respiratory system               | 0.00 (0.00–3.00)    | 3.00 (1.75–3.00)        | −7.197| <0.001  |
| Nervous system                   | 0.00 (0.00–1.00)    | 2.00 (1.00–3.00)        | −9.718| <0.001  |
| Cardiovascular system            | 0.00 (0.00–1.00)    | 3.00 (1.00–3.00)        | −8.134| <0.001  |
| Liver                            | 0.00 (0.00–1.00)    | 0.00 (0.00–1.00)        | −1.871| 0.061   |
| Coagulation                      | 1.00 (0.00–2.00)    | 1.00 (0.00–2.00)        | −0.314| 0.753   |
| Kidneys                          | 2.00 (1.00–2.00)    | 2.00 (2.00–3.00)        | −3.474| <0.001  |
to 0, the better the accuracy of the model). IBM SPSS Statistics 22.0 and R software (R 4.0.2) were used for statistical analysis. Two-tailed \( p < 0.05 \) was considered of statistical significance.

The rate of change in MYO, \( \% = 100\% \times \frac{\text{MYO}_{\text{Day} 3} - \text{MYO}_{\text{Day} 1}}{\text{MYO}_{\text{Day} 1}} \).

### Results

#### Clinical Characteristics

As shown in Figure 1, a total of 1,541 patients diagnosed with sepsis at Shanghai Tongji Hospital between 1 January 2015 and 31 December 2020 were screened, and 642 of them had concomitant acute cardiac and kidney injury secondary to sepsis during hospitalization. According to the exclusion criteria, 199 patients were excluded from the study. Finally, 443 patients diagnosed with sepsis-induced CRS were enrolled in the study and were divided into the training cohort (\( n = 340 \)) and validation cohort (\( n = 103 \)). In the training cohort, the median age was 77.02 ± 14.02 years. Sepsis-induced CRS was most frequently observed and diagnosed in the emergency department (36.8%), followed by in the intensive care unit (ICU) (32.4%), medical ward (23.2%), and surgical ward (7.6%). More than half (56.8%) of the patients had respiratory system infection, 19% had digestive system infection, and 16% had urinary system infection. After 30 days of follow-up, 114 deaths were confirmed. The clinical profiles and characteristics of the training cohort are presented in Table 1. Of the 103 patients in the validation cohort, 35.0% (36 patients) died within 30 days. The baseline SCr in the validation cohort was lower than that in the training cohort. Most of the baseline characteristics showed no statistical differences and were comparable in both the training and validation cohorts (Table 2).

#### Development of the Nomogram

The prognostic factors were assessed by univariate and multivariable logistic regression (shown in Table 3),...
which determined five independent predictors for short-term mortality in sepsis-induced CRS patients: age (OR = 1.06, 95% CI: 1.03–1.09), SOFA (OR = 1.37, 95% CI: 1.26–1.50), vasopressors (OR = 2.46, 95% CI: 1.23–5.04), baseline SCr (OR = 1.00, 95% CI: 1.00–1.01), and the rate of change in MYO (OR = 1.55, 95% CI: 1.23–2.04). A prognostic model incorporating these five independent risk factors was developed and visualized as a nomogram (shown in Fig. 2). The β-coefficients of the prognostic models developed in the training cohort are shown in Table 4. The application methods for the nomogram are described as follows. First, we drew an ascending line from the variable axis to the "Points" axis to obtain the points for each risk factor. Then, the scores of all variables were combined to obtain the total number of points. Finally, we drew a downward perpendicular line from the “Total Points” axis to the “Risk” axis. The corresponding number was then presented as the estimated 30-day mortality risk.
Table 3. Univariate and multivariable analyses for prognostic factors

| Variables                  | Category          | Univariate analysis | Multivariable analysis |
|----------------------------|-------------------|---------------------|------------------------|
|                            |                   | OR [95% CI]         | p value                | OR [95% CI]         | p value                |
| Age                        | Per year          | 1.03 [1.01–1.05]    | 0.006                  | 1.06 [1.03–1.09]    | <0.001                 |
| Sex                        | Female            | 1                   | 0.252                  |                       |                        |
|                            | Male              | 1.31 [0.83–2.06]    |                       |                       |                        |
| SBP                        | Per mm Hg         | 1.00 [0.99–1.01]    | 0.600                  |                       |                        |
| DBP                        | Per mm Hg         | 0.99 [0.98–1.01]    | 0.453                  |                       |                        |
| HR                         | Per minute        | 1.00 [0.99–1.02]    | 0.543                  |                       |                        |
| T, °C                      | Per degrees Celsius | 0.94 [0.85–1.05] | 0.282                  |                       |                        |
| Blood culture              | Negative          | 1                   | 0.192                  |                       |                        |
|                            | Gram positive     | 1.23 [0.51–3.01]    | 0.646                  |                       |                        |
|                            | Gram negative     | 1.42 [0.76–2.65]    | 0.266                  |                       |                        |
|                            | Fungus            | 0.34 [0.10–1.20]    | 0.093                  |                       |                        |
|                            | Multi-bacterial   | 0.74 [0.40–1.37]    | 0.334                  |                       |                        |
| Basic disease              |                   |                      |                        |                       |                        |
| Diabetes                   | No                | 1                   |                       |                       |                        |
|                            | Yes               | 1.05 [0.65–1.69]    | 0.848                  |                       |                        |
| Hypertension               | No                | 1                   |                       |                       |                        |
|                            | Yes               | 0.74 [0.46–1.17]    | 0.737                  |                       |                        |
| CAD                        | No                | 1                   |                       |                       |                        |
|                            | Yes               | 1.05 [0.65–1.69]    | 0.850                  |                       |                        |
| Stroke                     | No                | 1                   |                       |                       |                        |
|                            | Yes               | 1.01 [0.63–1.62]    | 0.980                  |                       |                        |
| CKD                        | No                | 1                   |                       |                       |                        |
|                            | Yes               | 0.81 [0.42–1.52]    | 0.509                  |                       |                        |
| History of tumor           | No                | 1                   |                       |                       |                        |
|                            | Yes               | 0.74 [0.32–1.72]    | 0.480                  |                       |                        |
| History of smoking         | No                | 1                   |                       |                       |                        |
|                            | Yes               | 1.54 [0.90–2.64]    | 0.118                  |                       |                        |
| Medication history         |                   |                      |                        |                       |                        |
| Diuretics                  | No                | 1                   |                       |                       |                        |
|                            | Yes               | 1.66 [1.05–2.63]    | 0.029                  | 1.40 [0.75–2.64]    | 0.295                  |
| CCB                        | No                | 1                   |                       |                       |                        |
|                            | Yes               | 0.82 [0.50–1.34]    | 0.428                  |                       |                        |
| ACEI                       | No                | 1                   |                       |                       |                        |
|                            | Yes               | 0.64 [0.26–1.55]    | 0.322                  |                       |                        |
| ARB                        | No                | 1                   |                       |                       |                        |
|                            | Yes               | 0.88 [0.53–1.47]    | 0.633                  |                       |                        |
| β-Blocker                  | No                | 1                   |                       |                       |                        |
|                            | Yes               | 0.78 [0.45–1.36]    | 0.384                  |                       |                        |
| Statin                     | No                | 1                   |                       |                       |                        |
|                            | Yes               | 0.77 [0.45–1.33]    | 0.349                  |                       |                        |
| Nitrate ester              | No                | 1                   |                       |                       |                        |
|                            | Yes               | 1.19 [0.69–2.05]    | 0.535                  |                       |                        |
| Antiplatelet drug          | No                | 1                   |                       |                       |                        |
|                            | Yes               | 0.82 [0.51–1.34]    | 0.431                  |                       |                        |
| Warfarin                   | No                | 1                   |                       |                       |                        |
|                            | Yes               | 0.67 [0.36–1.23]    | 0.192                  |                       |                        |
| In-hospital treatment      |                   |                      |                        |                       |                        |
| Mechanical ventilation     | No                | 1                   |                       |                       |                        |
|                            | Yes               | 3.42 [2.08, 5.64]   | <0.001                 | 1.76 [0.87–3.58]    | 0.114                  |
| Vasopressor                | No                | 1                   |                       |                       |                        |
|                            | Yes               | 0.14 [0.08–0.25]    | <0.001                 | 2.47 [1.21–5.14]    | 0.014                  |
| qSOFA                      | ≤2                | 1                   |                       |                       |                        |
|                            | >2                | 1.08 [0.66–1.77]    | 0.772                  |                       |                        |
| Total SOFA                 |                   | 1.39 [1.29–1.49]    | <0.001                 | 1.33 [1.22–1.47]    | <0.001                  |
Table 3 (continued)

| Variables | Category | Univariate analysis | Multivariable analysis |
|-----------|----------|---------------------|-----------------------|
|           |          | OR [95% CI] | p value | OR [95% CI] | p value |
| Laboratory variables |          |          |          |          |          |
| Baseline SCr, μmol/L |          | 1.00 [1.00–1.01] | 0.002 | 1.00 [1.00–1.01] | 0.028 |
| SCr on day 1, μmol/L |          | 1.00 [1.00–1.00] | 0.074 | 1.00 [0.99–1.00] | 0.763 |
| SCr on day 3, μmol/L | <133     | 1         | 0.052 | 1         |          |
|                      | 133–177  | 0.83 [0.42–1.64] | 0.589 | 0.61 [0.29–1.52] | 0.297 |
|                      | 178–442  | 1.56 [0.92–2.67] | 0.101 | 1.68 [0.83–3.46] | 0.152 |
|                      | >443     | 2.29 [1.05–4.99] | 0.037 | 2.08 [0.72–6.18] | 0.182 |
| MYO on day 1, ng/mL | Per ng/mL | 1.00 [1.00–1.00] | 0.001 | 1.00 [1.00–1.00] | 0.112 |
| The rate of change in MYO, % | Per percentage | 1.50 [1.23–1.84] | <0.001 | 1.61 [1.26–2.14] | <0.001 |
| cTnI on day 1, ng/mL | <0.03     | 1         | 0.246 |          |          |
|                      | 0.03–0.5  | 1.04 [0.50–2.15] | 0.919 |          |          |
|                      | >0.5      | 0.64 [0.27–1.48] | 0.295 |          |          |
| cTnI on day 3, ng/mL | <0.03     | 1         | 0.766 |          |          |
|                      | 0.03–0.5  | 0.91 [0.49–1.67] | 0.750 |          |          |
|                      | >0.5      | 1.12 [0.53–2.34] | 0.765 |          |          |
| CRP on day 1, mg/L  |          | 1.00 [0.99–1.00] | 0.774 |          |          |
| CRP on day 3, mg/L  |          | 1.00 [0.99–1.01] | 0.059 |          |          |
| PCT on day 1, mg/L  |          | 0.99 [0.99–1.00] | 0.345 |          |          |
| PCT on day 3, mg/L  |          | 0.99 [0.99–1.01] | 0.884 |          |          |

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; T, temperature; CAD, coronary artery disease; CKD, chronic kidney disease; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; SCr, serum creatinine; SOFA, Sequential (Sepsis-related) Organ Failure Assessment; qSOFA, quick SOFA; MYO, myoglobin; cTnl, cardiac troponin I; CRP, C-reactive protein; PCT, procalcitonin.

Fig. 2. Nomogram for predicting 30-day mortality risk in patients with sepsis-induced CRS.
Validation of the Nomogram

In internal validation, the prognostic nomogram yielded an AUC of 0.879 (95% CI: 0.840–0.917) (shown in Fig. 3a), and after 500 times of bootstrap resampling methods, the model showed low optimism with a bias-corrected AUC of 0.872, which demonstrated good discrimination of the prognostic model. The p value of the Hosmer-Lemeshow test was 0.146, and the calibration curve shown in Figure 3c showed high consistency between the predicted and actual probabilities, which reflected good calibration ability. In addition, the prognostic model showed good accuracy and robustness with the Brier score and internally validated Brier score of 0.131 and 0.136, respectively. In the external validation, we applied the prognostic model to the validation cohort, and the model achieved an AUC of 0.912 (95% CI: 0.860–0.965) (shown in Fig. 3b), suggesting that the prognostic model had strong discrimination power. When SOFA or the rate of change in MYO was solely used to predict 30-day outcomes, they achieved an AUC of 0.855 (95% CI: 0.784–0.987) and 0.774 (95% CI: 0.678–0.871), respectively. The DeLong test was used for comparison of AUC between the SOFA score and the nomogram, which showed that the prognostic nomogram had an evidently higher discrimination ability than the SOFA score (Z = −2.033, p = 0.042). The calibration curves (shown in Fig. 3d) and the Hosmer-Lemeshow test (p = 0.843) showed that the model had excellent concordance performance. A brier score of 0.117 reflects the accuracy of the model. In addition, decision curve analysis revealed that the nomogram yielded higher net benefits in predicting 30-day mortality risk than did the SOFA score (shown in Fig. 4).

Discussion

In the training cohort of 340 patients diagnosed with sepsis-induced CRS, five prognostic factors were identified by multivariable logistic regression and a simple-to-use nomogram was developed for predicting 30-day mortality risk. Furthermore, the nomogram predictive model went through external validation in an independent cohort of 103 patients using metrics such as AUC, calibration curves, and Brier score. Our nomogram encompasses five clinical variables: age, vasopressor use, the rate of change in MYO, baseline SCr, and the SOFA score. It is widely known that the SOFA was highly recommended by Sepsis 3.0, as the standard for clinical diagnosis of septic patients. However, there is limited evidence on the prognostic value of the SOFA in sepsis-induced CRS, and the SOFA alone may be insufficient to predict outcomes in such patients. Therefore, we included not only the SOFA, but also other potential factors for the evaluation of independent prognostic predictors, and the results showed that the combined use of the above factors yielded significantly higher discrimination power and greater net benefits when predicting 30-day outcomes, compared to the SOFA score alone.

The discovery of the five prognostic factors for sepsis-induced CRS may be one of the most appealing parts of our study. Notably, in our study, the serum MYO level was identified as an important prognostic factor. MYO is a heme protein expressed in cardiomyocytes and skeletal muscle cells [24]. Recent studies have revealed a strong correlation between an increase in serum MYO and a higher mortality rate in patients with sepsis and septic shock [25, 26]. In the setting of sepsis, MYO is first released from the damaged cardiac and muscle cells, accumulates in the bloodstream, and is then deposited in the kidney tissue, exacerbating kidney injury, and causing
oxidative damage and lipid peroxidation [25]. Therefore, the continuous rise in serum MYO could not only reflect the severity of sepsis but may also be involved in organ crosstalk between the heart and kidney, which is worthy of further investigation. In the present study, external validation verified that an increase in MYO within 3 days of diagnosis strongly portends a worse short-term outcome. Based on what we know so far, our study is the first to report a correlation between the serum MYO and the prognosis of sepsis-induced CRS.

Fig. 3. ROC curve and calibration curve. a The ROC curve of nomogram in training cohort. b Comparison of the ROC curves between the nomogram, SOFA, and rate of change in MYO in the validation cohort. c The calibration curve of the nomogram in training cohort. d The calibration curve archived in validation cohort. ROC, receiver operating characteristic.
Baseline SCr was another useful prognostic predictor in our study. Previous studies reported that chronic kidney disease (CKD) is a significant amplifier in the development of AKI and sepsis-related multi-organ dysfunction [27], and AKI on CKD usually portends poor prognosis in septic patients [28]. While high-baseline SCr is closely related to poor prognosis, critical patients with low-baseline SCr are also inclined to have a high mortality rate because of their malnutrition state and weakened ability to fight illness [29]. Currently, there is no consensus regarding the influence of baseline creatinine levels on the prognosis of critically ill patients. The present study revealed that an increase in baseline SCr was accompanied by an elevated risk of short-term mortality in patients with sepsis-induced CRS, and in both the training and validation processes, baseline SCr demonstrated good prognostic value.

Interestingly, vasopressors are recommended in the treatment of septic shock for their rapid and conspicuous effect on blood pressure; however, different dosages and timing of vasopressor use may lead to diverse clinical outcomes. Although early use of vasopressors was advised along with early goal-directed therapy for septic shock by River et al. [30], subsequent studies have denied their effect on improving clinical outcomes [31, 32]. Our study showed that 30-day mortality was generally higher in patients who received vasopressors. The appropriate dosage and optimal timing of vasopressor use are questions that require further research, especially for elderly and critical patients.

Like the vasopressors, mechanical ventilation can also be a double-edged sword and present a great challenge in clinical practice. It has important functions in providing adequate oxygenation [33], but it can also cause ventilatory-induced lung injury [34]. In this retrospective study, it is difficult to obtain all the detailed information in mechanical ventilation. We think that the reasons why the mechanical ventilation in our study did not exhibit the same level of statistical significance as MYO may be as follows: (1) the mechanical ventilation was not classified in detail and was treated as a dichotomous variable, while MYO was treated as a continuous variable; (2) our study mainly focused on the sepsis-induced AKI and cardiac injury. Therefore, factors concerning the sepsis-induced lung injury were less attended to, and this may cause certain bias in the data collection and statistical analysis.

Inflammatory indicators such as the CRP and PCT were widely used to evaluate body’s infection in clinical practice and were also recommended in the diagnosis of sepsis. However, the prognostic value of the CRP and PCT remained controversial. Some studies reported a minor correlation between the CRP and the development of sepsis [35]. As for PCT, some researches denied its ability in predicting clinical outcome in septic patients [36, 37]. In our study, both the CRP and PCT did not show strong prognostic value, which may be due to the reason that they were less sensitive in evaluating organ dysfunction than the SOFA score and serum MYO level.

There are some limitations to the present study. First, although the nomogram-illustrated model underwent
external validation, data were retrospectively collected from the same institution. Hence, the nomogram developed in the present study requires further multicenter external validation before clinical application. Second, we recognized that apart from traditional serum biomarkers such as cTnI, BNP, and NT-proBNP, echocardiography [38] is another suitable diagnostic method for sepsis-associated cardiomyopathy. However, in this retrospective study, we found that the detection rate of echocardiography is apparently low, and it may be associated with the inconvenience of critically ill patients leaving the ward and the lack of utilization in bedside echocardiography outside the ICU and cardiology ward. Therefore, we recommend the inclusion of echocardiography in future prospective clinical studies of sepsis-induced CRS, and we would promote the use of bedside ultrasound machines in clinical practice.

In conclusion, the present study constructed and externally validated an easy-to-use nomogram for predicting 30-day mortality in patients with sepsis-induced CRS. Our nomogram encompasses five clinical variables: age, SOFA, vasopressor use, the rate of change in MYO, and baseline SCr. The nomogram-illustrated model showed higher strengths and advantages in predicting 30-day prognosis than the SOFA score. Early prediction of prognosis in patients with sepsis-induced CRS may help clinicians evaluate disease severity and adjust clinical treatment.

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