Platelets as a prognostic marker for sepsis
A cohort study from the MIMIC-III database

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Abstract

During sepsis, platelets dysfunction contributes to organ dysfunction. Studies on platelets dysfunction in the long-term prognosis of sepsis are lacking. The aim of this study was to assess the role of platelets in the long-term prognosis of sepsis patients.

A total of 4576 sepsis patients were extracted from MIMIC III Database. Survival was analyzed by the Kaplan-Meier method. Univariate and multivariate cox analyses were performed to identify prognostic factors. Significant prognostic factors were combined to build a nomogram to predict 1 year overall survival (OS). The discriminative ability and predictive accuracy of the nomogram were evaluated using the receiver operating characteristic curve (ROC) analysis and calibration curves used for sepsis.

The more abnormal the platelet level, the worse prognosis of patients. After final regression analysis, age, blood urea nitrogen, platelets, international normalized ratio, partial thromboplastin time, potassium, hemoglobin, white blood cell count, organ failures were found to be independent predictors of 1 year OS of sepsis patient and were entered into a nomogram. The nomogram showed a robust discrimination, with an area under the receiver operating characteristic curve of 0.752. The calibration curves for the probability of the prognosis of sepsis patients showed optimal agreement between the probability as predicted by the nomogram and the actual probability.

Platelet was an independent prognostic predictor of 1 year OS for patients with sepsis. Platelet-related nomogram that can predict the 1 year OS of sepsis patients. It revealed optimal discrimination and calibration, indicating that the nomogram may have clinical utility.

Abbreviations: BUN = blood urea nitrogen, Cr = creatinine, DBP = diastolic blood pressure, GCS = Glasgow coma scale, HR = Heart rate, ICD-9 = International Classification of Diseases, Ninth Revision, ICU = intensive care unit, INR = international normalized ratio, MIMIC-III = Medical Information Mart for Intensive Care III, OR = Odds ratio, OS = overall survival, PT = prothrombin time, PTT = partial thromboplastin time, ROC = the area under the receiver operating characteristic, RR = respiratory rate, SAPSII = patients' simplified acute physiology score, SBP = systolic blood pressure, SOFA = sequential organ failure assessment, T = temperature, WBC = white blood cell count.

Keywords: nomogram, platelets, prognosis prediction, sepsis

1. Introduction

Sepsis is one of the leading causes of death worldwide and on average, $16.7 billion US dollars are spent to care for the severely septic patient each year, with costs projected to rise by 1.5% per year. Sepsis incidence rates are up to 535 cases per 100,000 person-years and rising.[1] It was reported remains high death rates among hospitalized patients range between 30% and 45%.[2,3] In 2017, an estimated 48.9 million (95% uncertainty interval 38.9–62.9) incident cases of sepsis were

recorded worldwide and 11.0 million (10.1–12.0) sepsis-related deaths were reported, representing 19.7% (18.2–21.4) of all global deaths.[4] In sepsis patients, hospital-acquired infection is one of the common problems and difficulties faced by hospitals in all countries around the world, the related results show that 43% of the participants in this study had poor knowledge, 42% had average practice, and 37% had a moderate attitude about hospital infection, increasing the awareness of on the prevention and control of HAI is very important for reducing the incidence of sepsis and the mortality of patients.[5]

Sepsis is defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection".[6] This exaggerated response can lead to multi-organ failure (MOF), shock, and death. According to the new definition of sepsis. Dysbalanced immune response and activation of the coagulation system during sepsis are fundamental events leading to sepsis complications and organ failure.[7] The severity of organ dysfunction has a prognostic value, and in clinical practice is usually classified according to the Sequential Organ Failure Assessment (SOFA) score,[8] platelet is an important role in the SOFA score representing hematological function, hematological failure is common in patients with septic shock.[9] Platelets catalyze the development of hyperinflammation, disseminated intravascular coagulation and microthrombosis, and subsequently contribute to multiple organ failure.[10] Inappropriate accumulation and activity of platelets are key events in the development of sepsis-related complications such as acute lung injury and acute kidney injury.[11]

Platelets dysfunction was an independent risk factor for the prognosis of patients with sepsis has been confirmed by study,[12,13] but there is still a lack of large cohort studies and in the long-term prognosis of sepsis. This study is the first by a large clinical database to study the long-term prognosis of platelet dysfunction in patients with sepsis through the establishment of a nomogram.

Therefore, the main objective of the present study by a large clinical database is to evaluate the impact of sepsis on the 1 year OS of patients and then develop a predictive nomogram to individually predict the probability of 1 year OS in sepsis patients. Further evaluation the discriminative ability and predictive accuracy of the nomogram using ROC analysis and calibration curves.

2. Materials and methods

2.1. Database

Data from the MIMIC (Medical Information Mart for Intensive Care) Critical Care Database were used for conducting this study.[14] Patients admitted to the ICU(intensive care unit)of Beth Israel Deaconess Medical Center from 2001–2012 were enrolled.[14] The raw data were extracted using structure query language (SQL) with Navicat and further processed with R software. A blood platelets level ≥ 100 (×109/L) and ≤300 (×109/L) was defined as platelet normal value in the MIMIC -III Database. The MIMIC III database (version 1.4) is publically available from https://mimic.physionet.org/. The MIMIC III database (version 1.4) is publically available from https://mimic.physionet.org/. Any researcher who adheres to the data use requirements is permitted access to the database.

2.2. Patient population

Inclusion criteria were as follows:

(1) sepsis;
(2) ≥18 and ≤89 years-old;
(3) admission time >24 hours in the ICU.

Exclusion criteria:

(1) patients with SOFA <2;
(2) patients having no vital signs or record contains blood platelet levels were also excluded.

Sepsis was identified based on Martin criteria, a widely used method for identifying sepsis in electronic health record database. The Martin criteria defined sepsis following ICD-9-CM codes referring infection and organ failure (Supplementary materials 1, http://links.lww.com/MD/F149).[15] According to the definition of sepsis 3.0, based on sepsis diagnostic criteria of Martin criteria, we selected sepsis patients with SOFA ≥ 2 as our study inclusion patients.

2.3. Data extraction and management

R statistical software (R Foundation for Statistical Computing, Vienna, Austria) was used to retrieve patient information from the MIMIC III Database. The following basic patient data were collected from each patient: age, sex, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), and temperature (T). The following biochemical test results were also collected from each patient: partial thromboplastin time (PTT), international normalized ratio (INR), prothrombin time (PT), white blood cell count (WBC), hemoglobin, platelet, blood urea nitrogen (BUN) and creatinine (Cr). Patients' simplified acute physiology score (SAPSII), sequential organ failure assessment (SOFA), Glasgow coma scale (GCS) were also recorded. The maximum and minimum values of sodium, potassium and glu were retrieved during the first 24 hours of each patient's ICU's stay. The worst scores and laboratory parameters as well as the mean value of vital signs during the first 24 hours of ICU admission were used in this study.

2.4. Statistical analysis

Data distribution was tested using the Shapiro-Wilk test. Patient characteristics were described using median (interquartile range [IQR]), or frequency and percentage, as appropriate. A non-parametric test (Mann-Whitney U test or Kruskal-Wallis test) was applied for data with non-normal distribution or heterogeneity of variances. Categorical data were compared using the Pearson Chi-squared test, Kaplan-Meier curves were analyzed using log-rank tests. The Cox regression model was used to analyze the independent effects of various parameters on mortality. Based on the results from the final regression analysis, a nomogram for mortality probability was constructed. The performance of the nomogram was assessed by discrimination and calibration. The discriminative ability of the model was determined by the area under the receiver operating characteristic curve, which ranged from 0.5 (no discrimination) to 1 (perfect discrimination). The calibration of the prediction model was performed by a visual calibration plot comparing the predicted and actual probability of prognosis of sepsis patients. The nomogram was subjected to 1000 bootstrap resamples for-
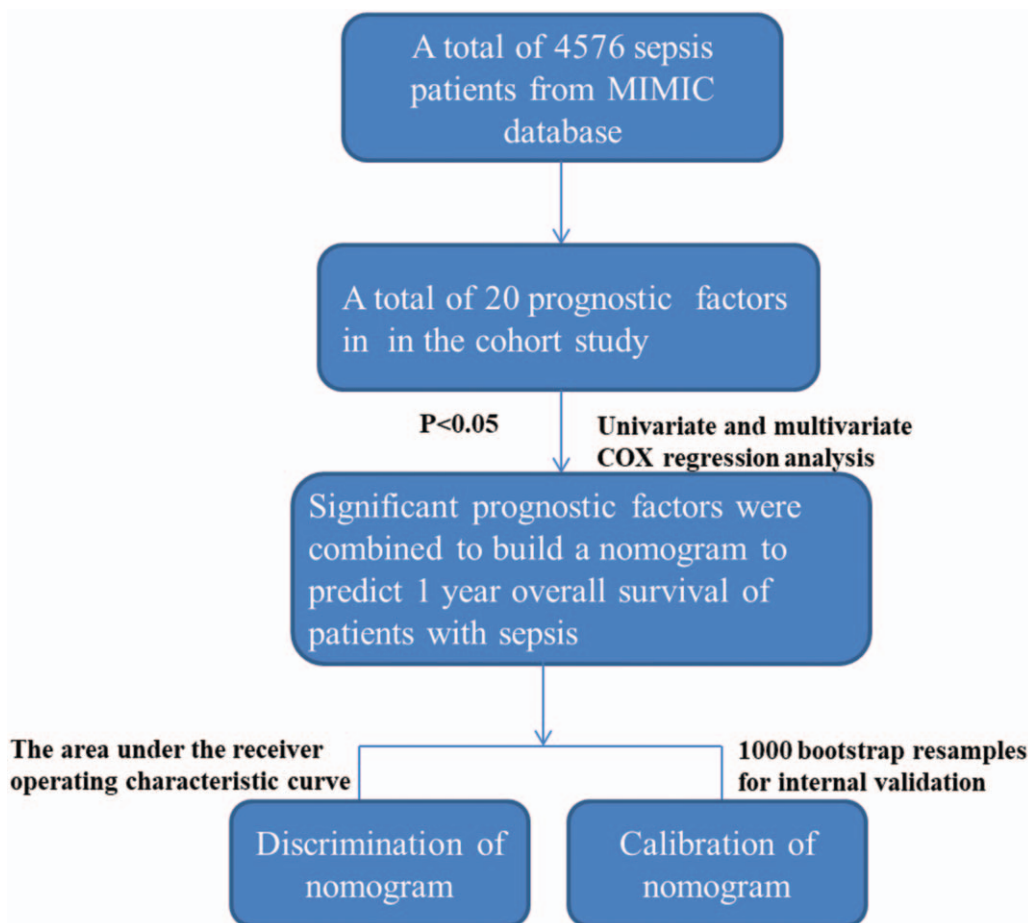
Figure 1. A flow chart of research methodology.

internal validation to assess their predictive accuracies. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed with and R software (version 3.4.3) (Fig. 1).

3. Results

3.1. Baseline patient characteristics and outcomes

A total of 4576 patients fulfilled the definition of sepsis 3.0 in the MIMIC-III database. Patients were divided into either a thrombocytopenia group (Platelet $< 100 \times 10^9$/L) (n = 1117), normal platelets group ($100 \leq$ platelet $\leq 300 \times 10^9$/L)(n = 2686), thrombocytosis group (Platelet $> 300 \times 10^9$/L)(n = 773). Variables with missing data are relatively common in the MIMIC III database. The percentage of missing values for lactate (19.0%), albumin (40.7%), pH(22.8%), SpO$_2$ (27.2%) were significant, which were excluded from this study. The percentage of missing values of PTT (7.9%), INR (7.3%), PT (7.3%) were <10%, and the other variables included were <1%. We replaced any missing values of the included variables with their mean values. The detailed process of data extraction is shown in Figure 2 (Supplementary Material 2, http://links.lww.com/MD/F150).

The baseline patient characteristics and outcomes for the patients are summarized in Table 1. Differences in age, HR, SBP, RR, T, Cr, BUN, glucose, hemoglobin, platelets, INR, PT, PTT,

WBC, potassium_max, sodium_min and sodium_max between the 3 groups were statistically significant. The incidence of mechanical ventilation, renal replacement therapy, norepinephrine, epinephrine, organ failures (renal, hepatic, cardiovascular, respiratory, hematologic) (Supplementary Material 3, http://links.lww.com/MD/F151) and the score of SAPSII, SOFA were significantly higher in patients with thrombocytopenia group more than in patients with other two groups. Besides, hospital mortality and 1 year mortality in thrombocytopenia group and thrombocytosis group up to (44.9%, 62.5%)and(28.3%, 51.4%) were higher in patients with normal platelet group.

3.2. Platelet was an independent prognostic predictor

Survival analysis was conducted to explore the impact of platelet on prognosis. Patients in the normal platelet group had better long-term survival rates (Fig. 3). Furthermore, we performed univariate analysis of the base-line variables, laboratory tests and organ failure. Age, sex, Cr, BUN, glucose, hemoglobin, platelets, PTT, INR, PT, WBC, sodium, potassium, and organ failure were analyzed in the univariate analysis, and the factors significantly correlated with overall survival were adjusted for in the multivariate analysis. According to our results, age, BUN, hemoglobin, platelets, PTT, INR, WBC, potassium_min, renal failure, hepatic failure, cardiovascular failure, respiratory failure
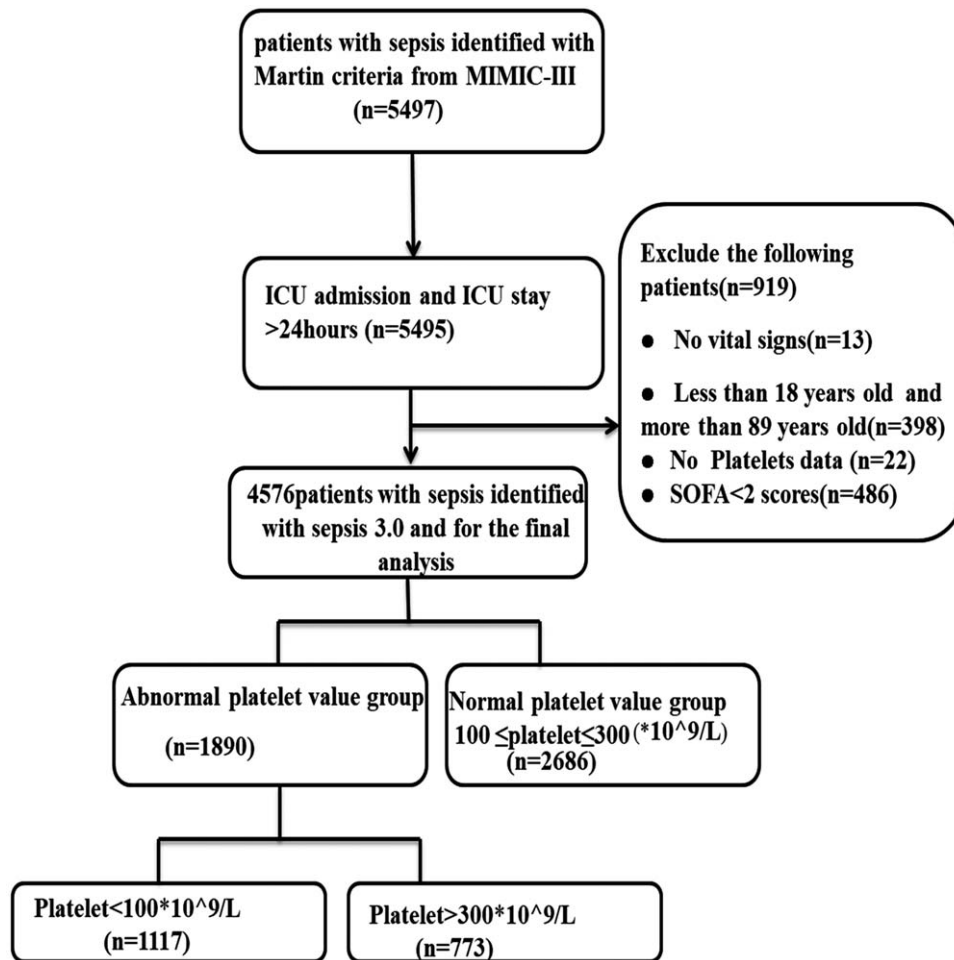
Figure 2. Flow chart of patient selection. MIMIC-III, Medical Information Mart for Intensive Care I.

remained independent prognostic factors for sepsis patients ($P < .01$ or $P < .05$) (Table 2).

3.3. Development of the prognostic scoring model

The prognostic nomogram included all the significant independent factors of the Cox proportional hazards regression model in the training cohort. It established scoring criteria according to the hazard ratio (HR) values of all prognostic factors and gave a score for each level of prognostic factors. By adding up the scores associated with each variable, and projecting total scores to the bottom scale, probabilities can be estimated for 1 year OS. With the aid of a nomogram, it was possible to effectively predict prognoses according to individual patient characteristics. The prognostic nomogram for 1 year OS is shown in Figure 4.

3.4. Validation of the nomogram

Validation of the nomogram was performed using bootstrap analyses with 1000 resamples, processed internally. Analysis of the internal validation cohort for nomogram-based predictions of OS. These findings indicate that the nomogram model was reasonably accurate. The internal calibration curves demonstrat-

ed good agreement between the predicted and observed values for 1 OS in both the training and validation cohorts (Fig. 5).

3.5. Discrimination of the nomogram

Internal validations were conducted on the nomogram. Consequently, internal validation of the training set revealed that the area under the receiver operating characteristic curve of the nomogram in OS prediction was 0.752 (95% CI, 0.738–0.766) (Fig. 6).

4. Discussion

In this study, we found that in the group with abnormal platelet level, especially in the group with thrombocytopenia, the higher the incidence of respiratory, circulatory, renal and liver, coagulation system failure, the higher the use of vasoactive drugs, the higher the incidence of renal replacement therapy and mechanical ventilation, high mortality, and the worse the prognosis. There was a correlation between abnormal platelet level with long-term prognosis. After Cox regression univariate and multivariate analysis, thrombocytosis and thrombocytopenia were found to be independent risk factors for the 1 year OS of patients with sepsis. Based on the platelet value, a model was

Table 1

Baseline characteristics, vitalsigns, laboratory parameters and outcomes of patients.

	Thrombocytosis group n = 773	Normal platelets group n = 2686	Thrombocytopenia group n = 1117	P
Baseline variables				
Age	56.9 (68.7–78.1)	56.4 (68.2–79.0)	50.7 (61.6–73.3)	<.001
Sex (%)				
Female	347 (44.9)	1102 (41.0)	466 (41.7)	.158
Male	426 (55.1)	1584 (59.0)	651 (58.3)	
Ethnicity (%)				
White	563 (72.8)	1914 (71.2)	777 (69.6)	.265
Black	62 (8.0)	255 (9.5)	91 (8.1)	
Asian	16 (2.1)	64 (2.4)	33 (3.0)	
Others	132 (17.1)	453 (16.9)	216 (19.3)	
Admission type (%)				
Emergency	715 (92.5)	2468 (91.9)	1018 (91.1)	.350
Elective	23 (3.0)	68 (2.5)	40 (3.6)	
Urgent	35 (4.5)	150 (5.6)	59 (5.3)	
Vital signs				
HR	79.6 (90.5–102.7)	78.6 (89.6–102.6)	82 (94.3–106.5)	<.001
SBP	101.4 (110–121.1)	101.6 (109.6–121.0)	99.6 (107.6–118.2)	<.001
DBP	50.8 (56.8–63.4)	51.8 (57.2–64.0)	51.6 (57.9–64.4)	.112
MBP	66.6 (72.2–79.8)	67.3 (73.0–80.0)	67.0 (72.8–80.0)	.367
RR	17.6 (20.7–24.1)	17.5 (20.1–23.5)	17.4 (20.8–24.7)	.003
T	36.4 (36.9–37.4)	36.4 (36.9–37.4)	36.3 (36.8–37.3)	<.001
Laboratory parameters				
Cr (mg/dl)	0.8 (1.3–2.3)	1.0 (1.4–2.5)	1.0 (1.5–2.7)	<.001
Glu (mg/dl)	91 (108–135)	89 (108–132)	84 (104–127)	<.001
Hemoglobin (g/dl)	8.4 (9.5–10.7)	8.8 (10.0–11.3)	7.8 (8.9–10.2)	<.001
Platelets (×109 /L)	336 (376–451.5)	138 (177–224.2)	37 (59–78)	<.001
PTT (s)	28.6 (33.9–47.7)	29.8 (36.4–47.7)	33.6 (42.1–59.6)	<.001
INR	1.2 (1.4–2.0)	1.2 (1.5–2.0)	1.4 (1.8–2.4)	<.001
PT (s)	13.8 (15.4–19.0)	14.0 (15.8–19.0)	15.1 (17.7–22.6)	<.001
BUN (mg/dl)	18 (28–49)	19 (30–49.2)	21 (34–55)	<.001
WBC (×109 /L)	13.4 (18.2–25.25)	10.1 (14.6–20.5)	5.5 (10.5–17.4)	<.001
Potassium_min (mmol/L)	3.5 (3.9–4.4)	3.4 (3.8–4.2)	3.3 (3.7–4.1)	.794
Potassium_max (mmol/L)	4.1 (4.5–5.0)	4.0 (4.4–5.0)	3.9 (4.4–4.9)	<.001
Sodium_min (mmol/L)	133 (137–140)	134 (137–140)	133 (137–140)	.001
Sodium_max (mmol/L)	136 (139–142)	137 (140–143)	136 (140–143)	<.001
Score system				
SAPSII	32 (42–53)	32 (42–53)	37 (47–59)	<.001
SOFA	3.0 (5.0–7.0)	4.0 (6.0–8.0)	6 (9.0–12.0)	<.001
GCS	14 (15–15)	13 (15–15)	14 (15–15)	.008
Outcome (%)				
Mechanical ventilation, n (%)	444 (57.4)	1471 (54.8)	691 (61.9)	.135
Renal replacement therapy, n (%)	32 (4.1)	169 (6.3)	159 (14.2)	<.001
Vasopressors, n (%)				
Norepinephrine	319 (41.3)	1158 (43.1)	566 (50.7)	<.001
Dopamine	98 (12.7)	365 (13.6)	154 (13.8)	.762
Epinephrine	19 (2.5)	97 (3.6)	52 (4.7)	.066
Organ failure, n (%)				
Renal	436 (56.4)	1600 (59.6)	743 (66.5)	<.001
Hepatic	35 (4.5)	235 (8.7)	254 (22.7)	.001
Cardiovascular	308 (39.8)	1126 (41.9)	551 (49.3)	<.001
Respiratory	430 (55.6)	1461 (54.4)	699 (62.6)	<.001
Hematologic	53 (6.9)	465 (17.3)	585 (52.4)	<.001
1 OS	397 (51.4)	1178 (43.9)	698 (62.5)	<.001
Hospital mortality	219 (28.3)	699 (26.0)	502 (44.9)	<.001

BUN = blood urea nitrogen, Cr = creatinine, DBP = diastolic blood pressure, GCS = Glasgow coma scale, HR = heart rate, INR = international normalized ratio, OS = overall survival, PT = prothrombin time, PTT = partial thromboplastin time, RR = respiratory rate, SAPSII = Patients' simplified acute physiology score, SBP = systolic blood pressure, SOFA = sequential organ failure assessment, T = temperature, WBC = white blood cell count.

Figure 3. Kaplan–Meier survival curves for patients with normal and abnormal platelet indices were compared and log-rank test were assessed for significance.
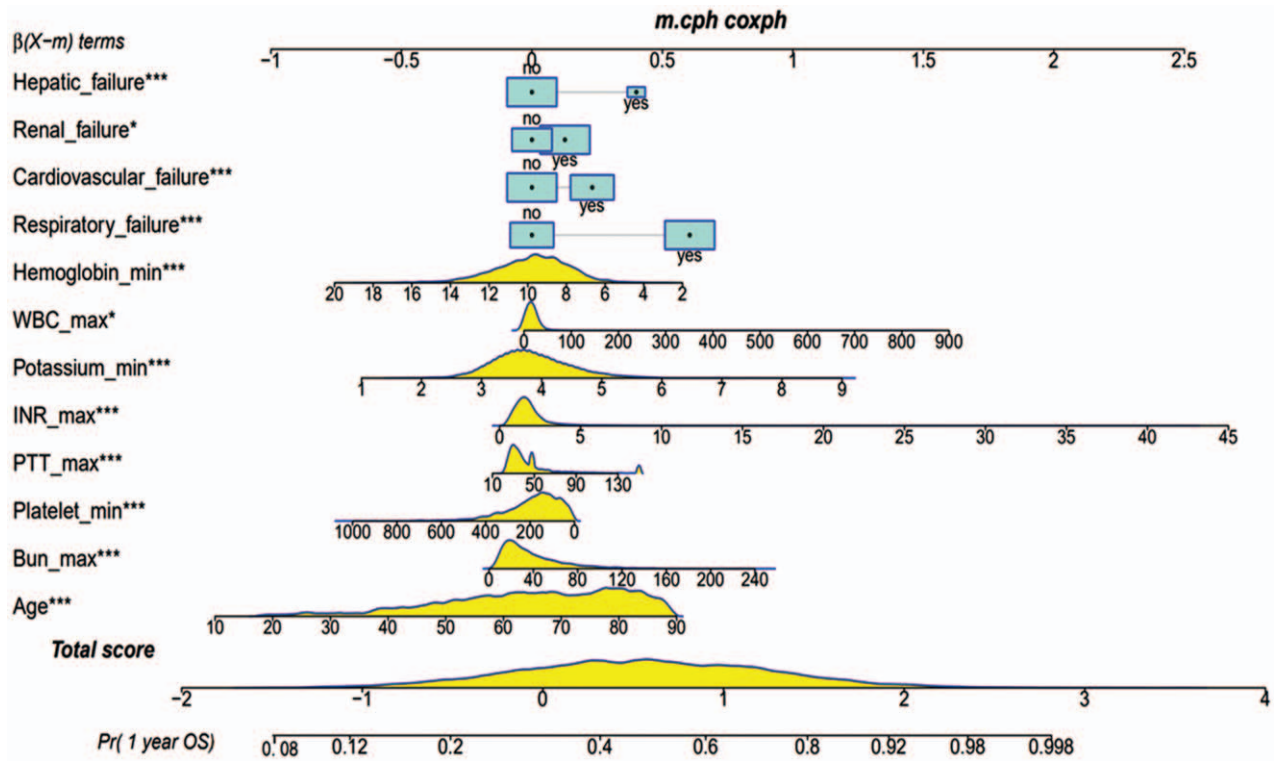
established to predict the 1year OS of patients with sepsis, and the visual nomogram was used to show it, so as to better predict the 1 year OS of patients with sepsis. The results showed that nomogram has good discrimination and calibration ability.

Table 1 shows that HR and RR in the group with thrombocytopenia were significantly higher than those in the group with normal platelet level, the group with thrombocytosis with SBP, SpO$_2$ value were significantly lower than that of the other two groups ($P < .01$ or $P < .05$). The circulation and
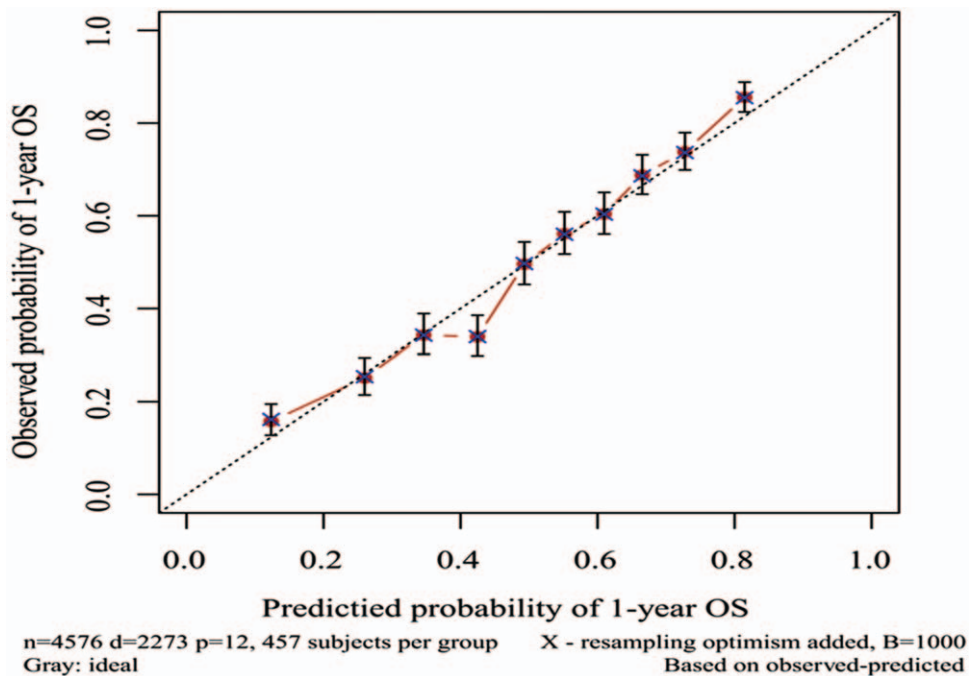
Table 2

Univariate and multivariate analysis of risk factors to 1year OS.

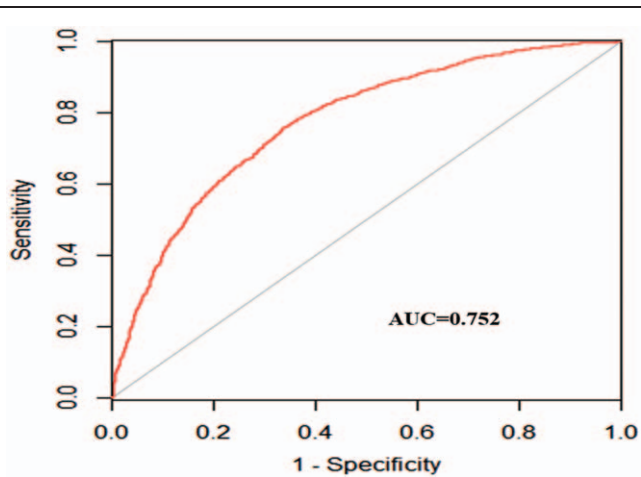|	Univariate analysis				Multivariate analysis			
			95.0% CI				95.0% CI	
	P	OR	Lower	Upper	*P*	OR	Lower	Upper
Age	<.001	1.021	1.018	1.024	<.001	1.024	1.020	1.027
Sex	.599	1.023	0.941	1.111				
Cr(mg/dl)	<.001	1.072	1.054	1.090	.847	0.997	0.970	1.026
BUN(mg/dl)	<.001	1.010	1.009	1.011	<.001	1.004	1.003	1.006
Glu(mg/dl)	.009	1.000	1.000	1.001	.415	1.000	0.999	1.001
Hemoglobin(g/dl)	<.001	0.910	0.890	0.930	<.001	0.947	0.925	0.968
Platelet(X10⁹ /L)								
100–300(reference)		1.000				1.000		
<100	<.001	1.730	1.575	1.900	<.001	1.684	1.517	1.871
>300	.001	1.211	1.081	1.357	.022	1.145	1.019	1.286
INR	<.001	1.097	1.083	1.112	<.001	1.067	1.045	1.089
PTT(s)	<.001	1.007	1.006	1.009	<.001	1.004	1.003	1.005
PT(s)	<.001	1.015	1.012	1.019	.382	0.998	0.994	1.002
WBC(X 10⁹ /L)	<.001	1.002	1.001	1.003	.027	1.002	1.000	1.003
Sodium_min(mmol/L)	.097	0.994	0.986	1.001				
Sodium_max(mmol/L)	.679	0.998	0.991	1.006				
Potassium_min(mmol/L)	<.001	1.396	1.341	1.484	<.001	1.217	1.133	1.309
Potassium_max(mmol/L)	<.001	1.186	1.150	1.222	.146	1.039	0.978	1.095
Organ failure,n(%)								
Renal	<.001	1.746	1.596	1.909	.016	1.135	1.024	1.258
Hepatic	<.001	3.443	2.859	4.418	<.001	1.455	1.285	1.648
Cardiovascular	<.001	1.617	1.489	1.756	<.001	1.251	1.148	1.363
Respiratory	<.001	1.927	1.766	2.103	<.001	1.794	1.639	1.936
Hematologic	<.001	1.312	1.196	1.439	.159	0.928	0.836	1.030

Cr = creatinine, INR = international normalized ratio, OS = overall survival, PT = prothrombin time, PTT = partial thromboplastin time, WBC = white blood cell count.

Figure 4. Nomograms for the prediction of the 1 year OS in patients with sepsis. To use the nomogram, first, the position of each variable on the corresponding axis should be found. Next, a line to the points axis for the number of points should be drawn. Then, the points from all the variables should be added. Finally, a line from the total points axis should be drawn to determine the overall survival probabilities at the lower line of the nomogram. The total points projected to the bottom scale indicate the % probability of the 1-year survival. BUN = blood urea nitrogen, INR = international normalized ratio, OS = overall survival, PTT = partial thromboplastin time.

Figure 5. The calibration curves for the predictions of 1 year OS and the validation, The dashed line represents perfect correspondence between the probabilities predicted by the nomogram (x-axis) and calculated by Kaplan–Meier analysis (y-axis), respectively. OS = overall survival.

Figure 6. Discriminatory accuracy for predicting OS assessed by receiver operator characteristics (ROC) analysis calculating area under the curve (AUC).

respiratory function of patients with thrombocytopenia were poor, the results showed that the incidence of cardiovascular failure, respiratory failure, the use rate of mechanical ventilation and vasoactive drugs in patients with thrombocytopenia were significantly higher than those of the other 2 groups. Thrombocytopenia is associated with respiratory and cardiovascular failure. It is consistent with previous research results.[16,17] Platelet recruitment is mechanism underlying severe lung damage in sepsis, post mortem biopsies of patients who died with acute respiratory distress syndrome(ARDS) have shown excess numbers of platelets and neutrophil deposition in pulmonary vessels.[18] Besides, in a mouse model of ARDS show that increased platelet-derived thromboxane-A2 and P-selectin correlated with increased neutrophil activation.[19] Microparticles (MPs) are small vesicles released from the cell surface of platelets, which function as storage for coagulation factors and cytokines,[20] thrombopoietin (TPO) in platelet-leukocyte interaction and the development of organ damage in sepsis.[21] Incubation of platelet-derived MPs with isolated heart and papillary muscle preparations induces a decrease in myocardial contraction in vitro,[22] Pretreatment with TPO prevents septic serum-induced myocardial contractility depression.[23] With the decrease of platelet level, the coagulation functions of patients get worse. PTT, INR and PT in the group with thrombocytopenia were significantly higher than those in the group with normal platelet level and thrombocytosis. The results of the three groups showed that the incidence of coagulation failure in thrombocytopenia group (52.4%) was significantly higher than that in normal platelet level group (17.3%) and thrombocytopenia group (6.9%). Platelets play a key role in normal hemostasis, stabilizing the clot at endothelial level. During inflammatory states, platelets also act as amplifiers for clotting factor activation and cell recruitment. In particular, platelet-neutrophil aggregates are platforms for thrombi generation and that is the trigger for NET release.[24] The incidence of kidney and liver (56.4%, 4.5%) in thrombocytopenia group was significantly higher than that in the other two groups. Thrombocytopenia may lead to further deterioration of kidney and liver function, acute kidney and hepatic injury are frequent complication of sepsis. Platelets will be arrested and activated on the kidney and liver endothelium activated by circulating deleterious signals. Inflammation-

mediated alteration of endothelial cell glycocalyx can also favor platelet adhesion.[25,26] Besides, leukocyte infiltration in the septic kidney has been widely shown in animal models and septic patient; leukocyte depletion seems to reduce renal injury. P-selectin stored in α-granules of platelets and in endothelial cells is involved in leukocyte recruitment in septic kidney. Blocking P-selectin protects mice from AKI by attenuating neutrophil recruitment into the kidney. [27,28] platelets may be pathophysiological players in sepsis kidney and liver failure.

The scores of SAPSII and SOFA in patients with thrombocytopenia group were significantly higher than those in the other two groups ($P < .01$), the days of hospitalization and 1-year mortality (44.9%, 62.5%) were significantly higher than those in patients with normal platelet level (26.0%, 43.9%) and those in patients with elevated platelet level (28.3%, 51.4%). It seems that the more serious the condition of patients with thrombocytopenia, the worse the prognosis of patient s. However, thrombocytosis was only related to the long-term of sepsis patients. It is consistent with previous research results of Sheng Zhang,[29] their study shows that patients with abnormally low PLT value had higher APACHE II and SOFA scores than those with normally PLT indices, indicating that patients with above-mentioned abnormally PLT indices were likely to have more severe illness. And in our study is that lower platelet count or plateletcrit is associated increased risk of mortality, the result is consistent with several other studies in Zhongheng Zhang and colleagues,[30] which are in support to our findings. These results support the notion that Abnormal platelet value is related to adverse clinical outcomes.

Through univariate and multivariate analysis, it was found that both the thrombocytosis and thrombocytopenia were independent risk factors for the long-term prognosis of sepsis patients (Table 2). The 1-year survival analysis of sepsis patients showed that the prognosis of platelet abnormality group was poor (Fig. 3). Therefore, when establishing platelet related model, the platelet value of all patients should be included to observe the death risk score of patients at different levels. The possible explanation for the link between platelet indices and mortality is inflammatory response, previous studies have shown that IL-18 and IL-35 are negatively correlated with platelets,[31] suggesting that inflammatory factors may be involved in the pathophysiological process of severe sepsis accompanied by thrombocytopenia. It is widely accepted that inflammatory response is significantly associated with adverse clinical outcomes in sepsis patients.

After completing univariate and multivariate analyses, we found that age, BUN, hemoglobin, platelets, PTT, INR, WBC, potassium_min, renal failure, hepatic failure, cardiovascular failure, respiratory failure remained independent prognostic factors were independent prognostic risk factors for sepsis patients and were entered into nomogram, nomogram plays an important role in modern medical decision-making, which is a graphical presentation of statistical prediction models.[32] Therefore, only easily accessible and measurable factors could be considered. Our cohort study shows that the nomogram showed a robust discrimination, with an area under the receiver operating characteristic curve of 0.752 (Fig. 6). The calibration curves for the probability of the prognosis of sepsis patients showed optimal agreement between the probability as predicted by the nomogram and the actual probability (Fig. 5). It revealed optimal discrimination and calibration, indicating that the nomogram may have clinical utility. This model has the potential to assist clinicians in assessing patient 1 year OS.

5. Limitations

There were also some limitations in our study. To begin with, the nomogram establishment was based on retrospective information from the MIMIC dataset, which might cause possible selection bias, our study is retrospective in nature and bears inherent limitations of such study design. The result shows a linkage between abnormal platelet count and mortality, but the causal relationship of them cannot be determined based on the present study. abnormal platelet may be a reflection of the severity of illness rather than the cause of death. Secondly, certain critical clinic indicators related to prognosis, such as lactate and albumin information were excluded, because there were some patients missing many certain values. Thirdly, our study only included data available online and more external validation is still required.

6. Conclusion

In conclusion, our study shows that patients with thrombocytopenia had a higher SAPSII, SOFA score, the incidence of mechanical ventilation and renal replacement therapy, organ failures and mortality. Our study once again confirms the results of previous studies that the less platelets level, the more severe the disease and the worse the prognosis that patients with normal platelets. Besides, new findings from our study that thrombocytopenia and thrombocytosis were both independent risk factors for the long-term prognosis of sepsis patients and for the first time to construct a long-term prognosis nomogram for sepsis. The proposed nomogram was easily used clinical tools that facilitate the popularization of patient counseling and personalized treatment. However, it is necessary to further mine the unknown prognostic factors to optimize the nomogram, and more external validation is still required.

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References

[1] Walkey AJ, Lagu T, Lindenauer PK. Trends in sepsis and infection sources in the United States. A population-based study. Ann Am Thorac Soc 2015;12:216–20.

[2] Reinhart K, Daniels R, Kissoon N, et al. Recognizing sepsis as a global health priority — A WHO resolution[J]. N Engl J Med 2017;377:414–7.

[3] Fleischmann C, Scherag A, Adhikari NKJ, et al. Assessment of global incidence and mortality of hospital-treated sepsis. Current Estimates and Limitations[. Am J Respir Crit Care Med 2016;193:259–72.

[4] Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet 2020;395:200–11.

[5] Sarani H, Balouchi A, Masinaeinezhad N, et al. Knowledge, Attitude and practice of nurses about standard precautions for hospital-acquired infection in teaching hospitals affiliated to Zabol University of medical sciences (2014). Glob J Health Sci 2016;8:

[6] Singer M, Deutschman CS, Seymour CW, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801–10.

[7] Huang M, Cai S, Su J. The pathogenesis of sepsis and potential therapeutic targets. Int J Mol Sci 2019;20:5376.

[8] Vincent J. The SOFA (sepsis-related organ failure assessment) score to describe organ dysfunction/failure 1996;22:707–10.

[9] Bone RC, Francis PB, Pierce AK. Intravascular coagulation associated with the adult respiratory distress syndrome. Am J Med 1976;61:585–9.

[10] Opneja A, Kapoor S, Stavrou EX. Contribution of platelets, the coagulation and fibrinolytic systems to cutaneous wound healing. Thromb Res 2019;179:56–63.

[11] Greco E, Lupia E, Bosco O, et al. Platelets and multi-organ failure in sepsis[. Int J Mol Sci 2017;18:

[12] Zhou Z, Feng T, Xie Y, et al. The effect of recombinant human thrombopoietin (rhTPO) on sepsis patients with acute severe thrombocytopenia: a study protocol for a multicentre randomised controlled trial (RESCUE trial). BMC Infect Dis 2019;19:780.

[13] Wu Q, Ren J, Wu X, et al. Recombinant human thrombopoietin improves platelet counts and reduces platelet transfusion possibility among patients with severe sepsis and thrombocytopenia: a prospective study 2014;29:362–6.

[14] Johnson AE, Pollard TJ, Shen L, et al. MIMIC-III, a freely accessible critical care database. Sci Data 2016;3:160035.

[15] Martin GS, Mannino DM, Eaton S, et al. The epidemiology of sepsis in the United States from 1979 through 2000[J]. N Engl J Med 2003;348:1546–54.

[16] Zhang Z, Ni H. Prediction model for critically ill patients with acute respiratory distress syndrome. PLoS One 2015;10:e0120641.

[17] Chou CH, Fu TC, Tsai HH, et al. High-intensity interval training enhances mitochondrial bioenergetics of platelets in patients with heart failure. Int J Cardiol 2019;274:214–20.

[18] Katz JN, Kolappa KP, Becker RC. Beyond thrombosis: the versatile platelet in critical illness. Chest 2011;139:658–68.

[19] Zarbock A, Singbartl K, Ley K. Complete reversal of acid-induced acute lung injury by blocking of platelet-neutrophil aggregation. J Clin Invest 2006;116:3211–9.

[20] Burnier L, Fontana P, Kwak BR, et al. Cell-derived microparticles in haemostasis and vascular medicine. Thromb Haemost 2009;101:439–51.

[21] Lupia E, Goffi A, Bosco O, et al. Thrombopoietin as biomarker and mediator of cardiovascular damage in critical diseases. Mediat Inflamm 2012;2012:390892–1390892.

[22] Azevedo LC, Janiszewski M, Pontieri V, et al. Platelet-derived exosomes from septic shock patients induce myocardial dysfunction. Crit Care 2007;11:R120.

[23] Lupia E, Spatola T, Cuccurullo A, et al. Thrombopoietin modulates cardiac contractility in vitro and contributes to myocardial depressing activity of septic shock serum. Basic Res Cardiol 2010;105:609–20.

[24] Ammollo CT, Semeraro F, Xu J, et al. Extracellular histones increase plasma thrombin generation by impairing thrombomodulin-dependent protein C activation. J Thromb Haemost 2011;9:1795–803.

[25] Schouten M, Wiersinga WJ, Levi M, et al. Inflammation, endothelium, and coagulation in sepsis. J Leukoc Biol 2008;83:536–45.

[26] Doi K, Rabb H. Impact of acute kidney injury on distant organ function: recent findings and potential therapeutic targets. Kidney Int 2016;89:555–64.

[27] Singbartl K, Forlow SB, Ley K. Platelet, but not endothelial, P-selectin is critical for neutrophil-mediated acute postischemic renal failure. FASEB J 2001;15:2337–44.

[28] Cho J, Kim H, Song J, et al. Platelet storage induces accelerated desialylation of platelets and increases hepatic thrombopoietin production. J Transl Med 2018;16:199.

[29] Zhang S, Cui Y, Diao M, et al. Use of platelet indices for determining illness severity and predicting prognosis in critically ill patients 2015;128:2012–8.

[30] Zhang Z, Xu X, Ni H, et al. Platelet indices are novel predictors of hospital mortality in intensive care unit patients[J] 2014;29:885.e881–6.

[31] Zhu M, Rong X, Li M, et al. IL-18 and IL-35 in the serum of patients with sepsis thrombocytopenia and the clinical significance. Exp Ther Med 2020;19:1251–8.

[32] Balachandran VP, Gonen M, Smith JJ, et al. Nomograms in oncology: more than meets the eye. Lancet Oncol 2015;16: