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Development of a Prognostic Model for Hospital Mortality in Patients with Systemic Lupus Erythematosus Admitted to the Intensive Care Unit

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Abstract

Objectives: This study aimed to develop a prognostic model to predict mortality among SLE patients in ICU.

Methods: In this retrospective cohort study, we extracted SLE patients from the MIMIC-IV database. Multivariate Cox regression based on the Akaike information criterion and P value was used to establish the prognostic model. Internal validation was performed by a bootstrap resampling approach with 100 replications. The discrimination and calibration of the model were evaluated by Harrell's concordance index and calibration plot. Decision curve analysis was performed to evaluate its clinical application.

Results: A total of 301 patients were finally included in the study. 276 (91.7%) patients were in the survivor group and 25 (8.3%) patients were in the non-survivor group. Multivariate Cox regression analysis included Peripheral vascular disease (adjusted HR 8.47 [2.57-27.98]，p<0.001), Peptic ulcer disease (adjusted HR 3.79 [1.01-14.14]，p=0.048), Metastatic solid tumor (adjusted HR 16.80 [3.95-71.90]，p<0.001), GCS motor upon ICU admission (adjusted HR 0.79 [0.65-0.98]，p=0.028), lowest SBP (adjusted HR 0.95 [0.93-0.97], p<0.001) and lowest AG (adjusted HR 1.18 [1.09-1.29]，p<0.001) to construct the model. The adjusted C-index was 0.805 and the calibration plot revealed that the predicted outcome was in agreement with the actual observations. The Kaplan–Meier survival curves revealed a significantly lower survival probability in the high-risk group than in the low-risk group (P < 0.0001). DCA showed that the model was clinically useful.

Conclusion: The prognostic model could help clinicians to stratify SLE patients and provide appropriate care.

Keywords: clinical prognostic model, cox regression analysis, intensive care unit, mortality, systemic lupus erythematosus

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with multi-organ involvement mediated by multiple autoantibodies. Globally, estimates of SLE prevalence in adults range from 30 to 150 per 100, 000, and incidence ranges from 2.2 to 23.1 per 100 000 per year. Despite early diagnosis and immunosuppressive treatment, SLE continues to be associated with mortality. The standardized mortality rate for SLE is estimated at 2.4 to 5.9%.(1) Previously, 5-year survival in patients with SLE was about 50%, whereas the 10-year survival now exceeds 90%. Despite the improvement in the overall survival of SLE patients, it remains the most common rheumatic disease admitted to the ICU, and the survival of SLE patients in the ICU is still poor.(2-4)

Currently, the clinical features and outcomes of patients with SLE admitted to the ICU have been studied(5, 6). Besides, several pre-existing scoring systems have been used in the ICU, such as Acute Physiology and Chronic Health Evaluation II (APACHE II)(7), Simplified Acute Physiology Score II (SAPS II)(8), and Oxford Acute Severity of Illness Score (OASIS). APACHE II score is currently the most widely used and has been widely used in the classification of critically ill patients and prognosis prediction. However, the value of APACHE II in

predicting the outcome of patients with SLE admitted to the ICU is somewhat contradictory(9, 10). A prognostic scoring system specifically for SLE patients does not yet exist. Therefore, the development of an effective prognostic model to predict the mortality of patients with SLE in the ICU is urgently needed.

In this present study, we enrolled a total of 301 SLE patients admitted to the ICU from an online international database-Medical Information Mart for Intensive Care-IV (MIMIC-IV). The epidemiological information, clinical characteristics, severe events in the ICU, and outcomes of patients were collected. Ultimately, we identified six independent prognostic factors and developed and evaluated a simple model to predict the in-ICU mortality of patients with SLE. These results could be useful to stratify patients into different risk groups of in-ICU mortality and provide patients with suitable management.

2. Methods

2.1 Data Source and Study Population

Data in the current study were extracted from the MIMIC-IV database, a comprehensive and high-quality dataset developed by the computational physiology laboratory of Massachusetts Institute; patients admitted to ICUs at Beth Israel Deaconess Medical Center (BIDMC) were included in the MIMIC-IV. The MIMIC-IV database includes desensitization data for over 50,000 critically ill patients at BIDMC between 2008 and 2019. The MIMIC-IV database was used after passing a necessary exam (No. 48831818). Our study participants were patients with SLE and hospitalized in ICUs. Diagnosis of SLE met the 1997 American College of Rheumatology (ACR) criteria for the classification of SLE.(11) 323 adult patients were primarily screened. The exclusion criteria were (i) an age of < 18 years, (ii) length of ICU stay less than 24 hours, and (iii) patients with missing data exceeding 20%. The final 301 patients were included for model development (n = 301) in this study and analysis of only the first admission for patients who were hospitalized multiple times.

2.2 Outcome and Predictors

Patient's data within the first 24 h after ICU admission were extracted from MIMIC-IV and were collected as follows: (1) Epidemiological: age, sex, race, and length of ICU stay; (2) Comorbidities based on Charlson comorbidity index; (3) Vital signs: body temperature, heart rate, respiratory rate, mean blood pressure, and percutaneous oxygen saturation (SPO2); (4) Laboratory parameters: blood routine examination, biochemical profile, coagulation function, arterial blood gases, erythrocyte sedimentation rate, and C-reactive protein; (5) Scoring systems: APACHE II, SAPS II, OASIS and Glasgow Coma Score (GCS); (6) Organ function support and severe events during ICU hospitalization: vasopressors, invasive ventilation, dialysis, FFP transfusion, RBC transfusion and sepsis. The primary outcome was all-cause mortality after admission to ICU. Survival time was defined as the interval between the admission date into the ICU and the date of death or the discharge date out of the ICU.

2.3 Statistical Analysis

Variables with more than 50% missing (PaO2/FiO2, A-aDO2, Lactate dehydrogenase, Albumin, Lactate, Alkaline phosphatase, and Height) are first excluded. Missing data were handled using multiple imputations, where numerical variables were imputed using logistic regression, and categorical variables were imputed using Predicted Mean Matching. In the imputation model, we included all candidate predictor variables, the baseline cumulative hazard, and the outcome indicator. Categorical variables were established as frequencies or percentages, and we used the χ2-test or Fisher's exact test for categorical data comparison. Continuous variables were summarized as the medians and interquartile range. The Mann-Whitney U test tested differences for continuous measurements.

All candidate prognostic factors were used to fit the model with the Least Absolute Shrinkage and Selection Operator (LASSO) to sieve possible related factors with non-zero regression coefficients; otherwise, the factors were regarded as insignificant and excluded from further analysis. Then, a prognostic model was developed by multivariable Cox regression based on the Akaike information criterion (AIC) and statistical significance. The fitted model was diagnosed in terms of linear relationship, multicollinearity, and the proportional hazards assumption. Restricted cubic spline was used for the linear relationship between continuous variables and outcome(12). We assessed the multicollinearity problem by calculating variance inflation factors (VIF). Internal validation was performed by an enhanced bootstrap resampling approach with 100 replications (n=100). Using the original sample, a new sample with the same sample size as the original sample is constructed as the training set by repeated sampling with put-back. Implement the complete model training process in the training set, calculate the differentiation and calibration of the above model during the original model development process, and calculate the optimism valuation with the model performance in the training set, repeat the above process n times to get the optimism valuation of the n model performances, calculate the mean of the optimism valuation of the n model

performances as the optimism valuation adjustments, and the performance of the model in the original data minus the optimism valuation adjustments as the model performance in internal validation. The following indicators were calculated to assess the prognostic model's performance: the Harrell C statistic and time-dependent receiver operating characteristic (ROC) curve to evaluate the model discrimination, and model calibration are described by the calibration plot. Decision curve analysis (DCA) was performed to assess the clinical applicability of the model. Based on the model's predicted 21-day risk of death in the ICU, we further divided the patients into high and low-risk groups and compared the Kaplan-Meier survival curves of the two groups. In addition, we compared the prognostic model with SAPS II, APACHE II, and OASIS in terms of the area under the time-dependent receiver operating characteristic (ROC) curve. All statistical analyses were performed using R, version 4.2.2. Two-sided p-values less than 0.05 were considered statistically significant. In this study, we followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) reporting guidelines and the Prediction model Risk of Bias Assessment Tool (PROBAST). (13, 14)

3. Results

3.1 Demographics and Clinical Characteristics

The general characteristics of these 301 patients are summarized in Table 1. Twenty-five (8.3%) patients were in the non-survivor group and 276 (91.7%) patients were in the survivor group, including 21 and 238 (84.0% VS. 86.0%, P=0.763) female patients respectively. The dead group tended to have a longer length of stay in ICU (median (IQR): 5.4 (1.1, 11.9) days VS. 2.1 (1.2, 3.9) days, P=0.034) and higher APACHE II (median (IQR): 81 (53, 109) VS. 45 (34, 56), P<0.001), SAPS II (median (IQR): 40 (36, 58) VS. 30 (21, 38), P<0.001), and OASIS (median (IQR): 41 (37, 49) VS. 29 (23, 35), P<0.001) scores at ICU admission, than the survived group. The GCS scores at admission to the ICU in the non-survivor and survivor groups were 13.0 (7.0, 14.0) and 14.0 (13.0, 15.0), respectively (P=0.002). A summary of the vital signs and laboratory data of the 301 patients on the first day of ICU admission is shown in Supplementary Table 1. Deceased patients had significantly lower levels of SBP (81 (72, 89) VS. 92 (84, 107), P<0.001) and SPO2 (91.0% (82.0%, 96.0%) VS. 93.0% (91.0%, 96.0%), P=0.035). While, the level of anion gap was significantly higher in non-survivors (15.0 (14.0, 18.0) VS. 13.0 (11.0, 15.0), P=0.001).

Table 1. General characteristics of the 301 patients

	In-hospital deaths (n=251)	Survivors (n=2761)	P
Age	57 (47, 71)	57 (42, 65)	0.380
Sex, female	21 (84%)	238 (86%)	0.763
Race			0.519
White	13(52%)	125(45%)	
Others	12(48%)	151(55%)	
Length of stay before ICU, (hour)	91 (19, 163)	92 (54, 514)	0.561
Length of stay in ICU, (day)	5.4 (1.1, 11.9)	2.1 (1.2, 3.9)	0.034
APACHE II upon ICU admission	81 (53, 109)	45 (34, 56)	<0.001
SAPS II upon ICU admission	40 (36, 58)	30 (21, 38)	<0.001
OASIS upon ICU admission	41 (37, 49)	29 (23, 35)	<0.001
GCS upon ICU admission	13.0 (7.0, 14.0)	14.0 (13.0, 15.0)	0.002
GCS motor	0(0,1)	1(1,1)	<0.001
GCS verbal	1(1,4)	5(4,5)	<0.001
GCS eyes	3(1,3.5)	4(3,4)	<0.001

1 11, Median (IQR); n (%); ICU, Intensive Care Unit; APACHE II, Acute Physiology and Chronic Health Evaluation II; SAPS II, Simplified Acute Physiology Score II; OASIS, Oxford Acute Severity of Illness Score; GCS, Glasgow Coma Score.

The comorbidities of the 301 patients at ICU admission are shown in Table 2. The most common comorbidities of SLE patients were cardiovascular complications, including congestive heart failure, cerebrovascular disease, peripheral vascular disease, and myocardial infarction. There were 5 (20.0%) and 27 (9.8%) patients with peripheral vascular disease, 3 (12.0%) and 12 (4.3%) patients with peptic ulcer disease, and 3 (12.0%) and 11 (4.0%) patients with metastatic solid tumor of the 25 patients and 276 patients, respectively. In terms of

comorbidities, there were no significant differences between the two groups. The severe events of 301 patients during their ICU stay are shown in Table 2. Non-survivors were more likely to be treated with mechanical ventilation (15 (60.0%) VS. 70 (25.0%), P=0.001) and vasoactive drug (19 (76.0%) VS. 66 (24.0%), P<0.001).

Table 2. Comorbidity on ICU admission and severe events in ICU of the 301 patients

	In-hospital deaths (n=25[1])	Survivors (n=276[1])	P
Comorbidity*			
Congestive heart failure	12 (48%)	76 (28%)	0.039
Cerebrovascular disease	7 (28%)	42 (15%)	0.817
Peripheral vascular disease	5 (20%)	27 (9.8%)	0.163
Myocardial infarct	2 (8.0%)	33 (12%)	0.751
Dementia	0 (0%)	4 (1.4%)	1.000
Chronic pulmonary disease	5 (20%)	86 (31%)	0.363
Peptic ulcer disease	3 (12%)	12 (4.3%)	0.118
Diabetes mellitus	1(4%)	58(20%)	0.094
Chronic kidney disease	11 (44%)	114 (41%)	0.834
Renal failure	10 (40%)	107 (39%)	1.000
Liver disease	6 (24%)	33 (12%)	0.113
Malignant cancer	3 (12%)	12 (4.3%)	0.118
Metastatic solid tumor	3 (12%)	11 (4.0%)	0.100
Severe events in ICU			
Mechanical ventilation	15 (60%)	70 (25%)	0.001
Vasoactive agent use	19 (76%)	66 (24%)	<0.001
Dialysis	9 (36%)	71 (26%)	0.343
FFP transfusion	9 (36%)	20 (7.2%)	<0.001
RBC transfusion	11 (44%)	71 (26%)	0.061
Sepsis	19(76%)	145(52.5%)	0.034

1, Median (IQR); n (%); FFP, fresh frozen plasma; RBC, red blood cell; *, by Charlson Comorbidity Index (CCI).

3.2 Development of the Prognostic Model

The LASSO selected 12 variables with non-zero coefficients taking the penalty parameter 0.028860 (**Supplementary figure 1 Variable selection by LASSO**), which included length of ICU stay, Peripheral vascular disease, Peptic ulcer disease, Malignant cancer, Metastatic solid tumor, GCS motor score upon ICU admission, lowest SBP, lowest SPO2, highest PH, lowest PCO2, lowest AG and Eosinophils percentage. With the described variable selection methods, the final multivariable Cox regression model is shown in Table 3, which included Peripheral vascular disease (adjusted HR 8.47 [2.57-27.98]，p<0.001), Peptic ulcer disease (adjusted HR 3.79 [1.01-14.14]，p=0.048), Metastatic solid tumor (adjusted HR 16.80 [3.95-71.90]，p<0.001), GCS motor upon ICU admission (adjusted HR 0.79 [0.65-0.98]，p=0.028), lowest SBP (adjusted HR 0.95 [0.93-0.97], p<0.001) and lowest AG (adjusted HR 1.18 [1.09-1.29]，p<0.001).

Table 3. Prognostic model to predict mortality in ICU

Prognostic factors	**Univariate Analysis**			**Multivariate Analysis**		
	β	**HR (95% CI)**	**P**	**β**	**HR (95% CI)**	**P**
Peripheral vascular disease	1.098	3.00(1.10-8.16)	0.032	2.137	8.47(2.57-27.98)	<0.001
Peptic ulcer disease	1.521	4.58(1.32-15.86)	0.017	1.332	3.79(1.01-14.14)	0.048
Malignant cancer	1.758	5.80(1.61,20.90)	0.007	-	-	-
Metastatic solid tumor	1.838	6.28(1.77-22.32)	0.004	2.824	16.80(3.95-71.90)	<0.001
GCS motor upon ICU admission	-0.263	0.77(0.63,0.93)	0.007	-0.229	0.79(0.65-0.98)	0.028

SBP min	-0.044	0.96(0.93-0.98)	<0.001	-0.050	0.95(0.93-0.97)	<0.001
SPO2 min	-0.036	0.96(0.94-0.99)	0.001	-	-	-
PH max	6.079	436.62(1.49-128057)	0.036	-	-	-
PCO2 min	-0.107	0.90(0.85-0.96)	<0.001	-	-	-
AG min	0.146	1.16(1.06-1.27)	0.002	0.169	1.18(1.09-1.29)	<0.001
E%	0.024	1.02(1.00-1.05)	0.042	-	-	-
GCS, Glasgow Coma Score; SBP, systolic blood pressure; PH, potential of hydrogen; AG, anion gap; E%, eosinophils percentage.						

We diagnosed the fitted multivariate Cox model from 3 aspects: linear relationship, multicollinearity, and the proportional hazards assumption. First, after adjusting the other variables in the model, the two continuous independent variables, the lowest SBP, and lowest AG, satisfy a linear relationship with the predicted outcome, as shown in Supplementary figure 2 (**Supplementary figure 2 Restricted cubic spline for the association between SBP/AG and mortality**). Second, we diagnosed multicollinearity between predictors, and VIF values were 1.30, 1.10, 1.30, 1.28, 1.27, and 1.25, respectively, all less than 2. Finally, the global P value was 0.09, which met the proportional hazards assumption.

We used the model to predict 21-day mortality in patients with SLE in the ICU. Based on the model prediction of 21-day mortality risk, patients were divided into high and low-risk groups (cut-off: 0.026), with 31 patients in the high-risk group and 270 patients in the low-risk group. The Kaplan–Meier curve of the two groups is shown in Figure 1 (**Figure 1 Kaplan–Meier survival curve for mortality according to 21-day mortality risk**). The survival probability of the low-risk group was higher than the high-risk group ($P < 0.0001$ by log-rank test). $P < 0.05$ indicates that our model construction is reasonable.

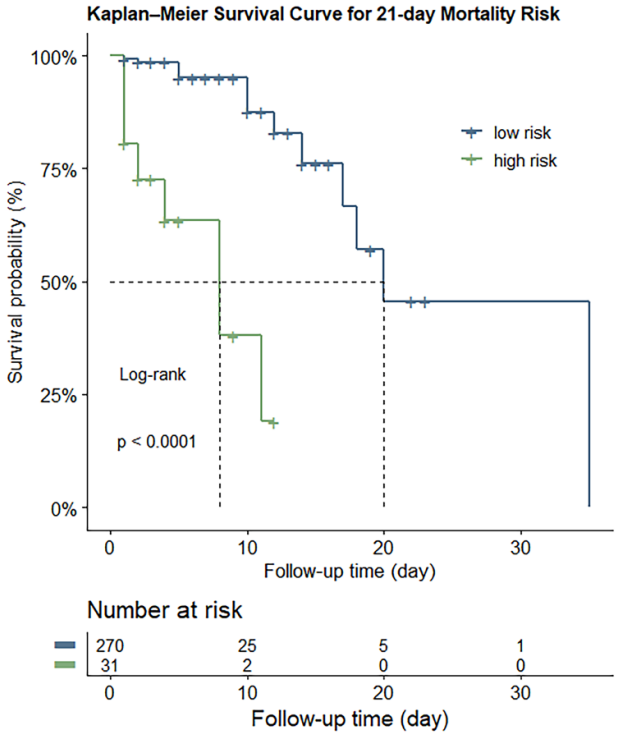

Figure 1. Kaplan–Meier survival curve for mortality according to linear predictor

301 patients were divided into high and low-risk groups (cut-off: 0.026), with 31 patients in the high-risk group and 270 patients in the low-risk group. The survival probability of the low-risk group was higher than the high-risk group at the time point of 21 days ($P < 0.0001$ by log-rank test).

3.3 Performance and Internal Validation of the Prognostic Model

We evaluated the performance of the fitted model in terms of 3 aspects: discrimination, calibration, and clinical utility. The crude C-index of the model was 0.854. The area under the time-dependent ROC curve at the time

points of 3 days, 7 days, and 21-day was 0.860, 0.740, and 0.950, respectively (**Figure 2a Evaluation of the prognostic model in predicting 3-day, 7-day, and 21-day mortality among SLE patients in ICU**), suggesting that the model predicts 3-day, 7-day, and 21-day mortality during ICU hospitalization in SLE patients with good discrimination. We used bootstrap resampling (n=100) for internal validation of the model. The adjusted Harrell's C-index was 0.816. The calibration plot and decision curve analysis (DCA) are shown in Figures 2b and 2c (**Figure 2b and 2c Evaluation of the prognostic model in predicting 21-day mortality among SLE patients in ICU**). The calibration curve revealed that the predicted outcome was in agreement with the actual observations. The DCA indicated that the model has an efficient predictive capability. The ordinate represents the net benefit, and the abscissa is the threshold probability in the DCA curve. The result of DCA demonstrated that the clinical net benefit would be higher using the prognostic model as the predictive tool compared to that using the strategies of screening all patients or screening no one.

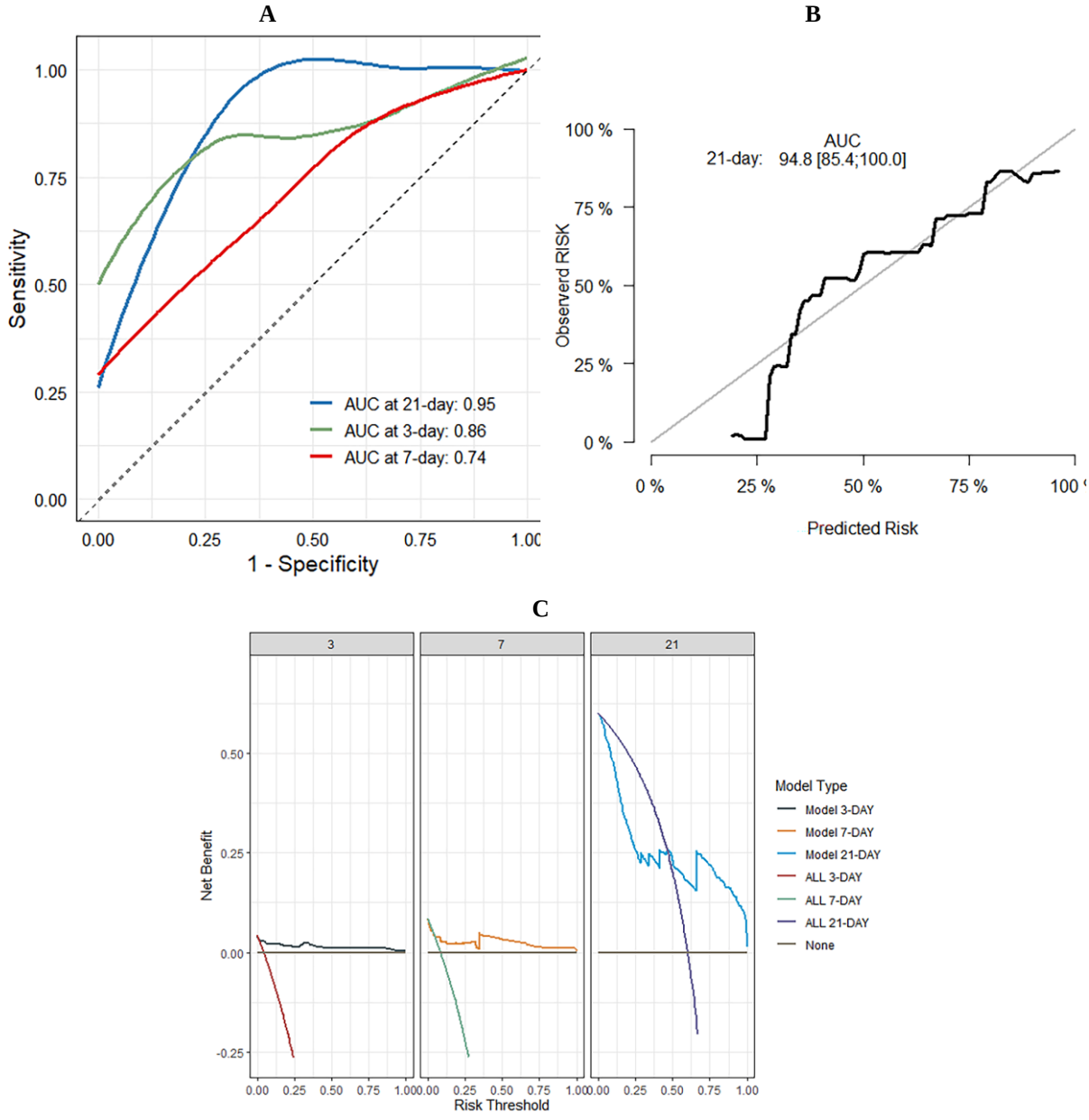

Figure 2. Evaluation of the prognostic model in predicting 3-day, 7-day, and 21-day mortality among SLE patients in ICU

A: the area under the time-dependent ROC curve at the time points of 3-day, 7-day, and 21-day were 0.86, 0.74, and 0.95, respectively. B: Predicted VS. observed overall survival (OS) probability after 100 bootstraps. C: decision curve of the model at the time points of 3-day, 7-day, and 21-day. The x-axis showed the threshold

probability. The y-axis represents the net benefit. The black, yellow, and blue lines indicate the model at 3-day, 7-day, and 21-day, respectively.

3.4 Comparison with the APACHE II, SAPS II, and OASIS

The severity score that has been most associated with the mortality of critically ill patients is APACHE II. Other scores included SAPS II, OASIS, and so on. We compared the predictive performance of the model with APACHE II, SAPS II, and OASIS. The Harrell C-indexes were 0.860, 0.670, 0.750, and 0.700 for the prognostic model, APACHE II, SAPS II, and OASIS, respectively. The time-dependent ROC-AUC at the time points of 21 days was shown in Supplementary figure 3 (**Supplementary figure 3 The time-dependent receiver operating characteristic curve's comparison of the prognostic model with SAPS II, APACHE II, and OASIS**). The time-dependent ROC-AUC of Model, APACHE II, SAPS II, and OASIS in predicting mortality among SLE patients in ICU were 0.95, 0.87, 0.71, and 0.60 at 21 days, respectively. Finally, we also compared their clinical utility, decision curve analysis (DCA) is shown in Figure 3 (**Figure 3 Decision curve analysis's comparison of the prognostic model with SAPS II, APACHE II, and OASIS for survival in ICU**). The decision curves of the fitted model are all above the other three scores, and the clinical benefit is better.

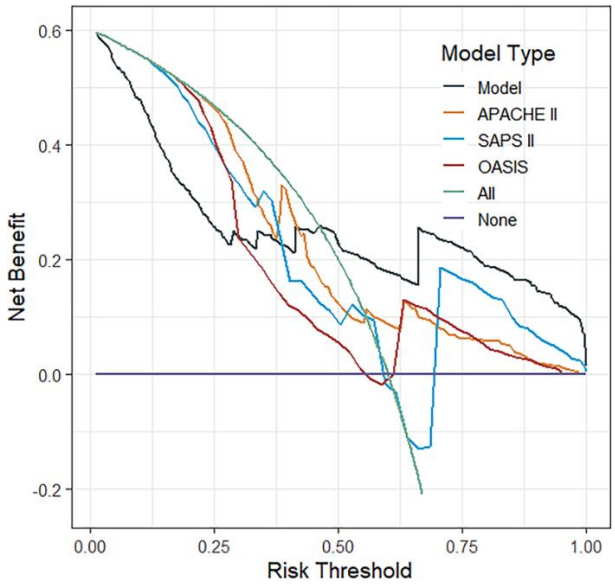

Figure 3. Decision curve analysis's comparison of the prognostic model with SAPS II, APACHE II, and OASIS for survival in ICU

The x-axis showed the threshold probability. The y-axis represents the net benefit. The green line meant that all patients were dead and the purple line represented that none patients were dead. The black line displayed the benefit of the model. The yellow line displayed the benefit of APACHE II. The blue line displayed the benefit of SAPS II. The red line displayed the benefit of OASIS.

4. Discussion

SLE has become the leading cause of admission to ICU among autoimmune diseases(4). The demand rate for critical care services for SLE patients is approximately 13.8%(15). Early identification of patients at increased risk of death can prevent fatal outcomes through changes in follow-up and treatment, which is the reason for many attempts to identify predictive models for mortality in SLE patients. The severity score most associated with mortality in ICU patients is the APACHE II(7). However, there is no consensus in the literature regarding the role of APACHE II in SLE patients admitted to the ICU. Novel prediction models are of great interest to clinicians since they could facilitate early interventions to improve mortality rates in SLE admitted to the ICU.(16)

In this study of 301 individuals from a cohort of critically ill patients with SLE from the MIMIC-IV database, we analyzed the individual patients' status on admission to ICU and developed and validated a prognostic model to predict all-cause mortality in ICU lupus patients. We identified six independent risk factors affecting mortality, namely co-morbid peripheral vascular disease, peptic ulcer disease and metastatic solid tumor, GCS motor upon ICU admission, lowest SBP, and lowest AG, and developed a prognostic model that reflected good discrimination,

calibration, and clinical utility. In addition, we compared the prediction model with APACHE II, SAPS II, and OASIS scores, and the results showed that the model outperformed the other three scores. Thus, this model could be efficiently and effectively applied in clinical practice.

Previous studies have found that approximately one-quarter of SLE patients are hospitalized each year for infections, associated co-morbidities, and side effects of immunosuppressive therapy and that the leading causes of ICU admissions are infections and organ involvement. The most common comorbidities among SLE patients hospitalized in the ICU are cardiovascular diseases, mainly hypertension, cerebrovascular disease, and congestive heart failure.(3, 17-19) Our study also found co-morbid peripheral vascular disease to be an independent risk factor for SLE patients. In agreement with our study, a paper from Sweden found that established arterial disease was one of the strongest predictors for all-cause mortality.(20) Shazib Sagheer et al. also found that the higher inpatient mortality appears to be driven by peripheral vascular disease in patients who have AMI and SLE. (21) In addition, our study found that critically ill SLE patients are more likely to have peptic ulcer disease. Gastrointestinal (GI) symptoms are common in patients with systemic lupus erythematosus (SLE). These symptoms can be due to primary GI disorders like peptic ulcer disease, pancreatitis, or intestinal obstruction. But they can also be due to SLE itself or complications of treatment of SLE. SLE patients may experience gastric ulcers for a variety of reasons, including iatrogenic and autoimmune. Glucocorticoids are the most commonly used immunosuppressants in SLE patients. A case report by Gayam et al. identified that although glucocorticoids are commonly used in SLE patients, glucocorticoids alone are not associated with an increased risk for peptic ulcer disease; instead, there is a synergistic ulcerating effect on gastric tissue with concurrent NSAID use.(22) Therefore, gastrointestinal (GI) involvement is common in SLE, but the symptoms are usually mild. More severe GI complications including acute pancreatitis and peptic ulcer bleeding are rare but represent a significant risk of morbidity and mortality. Metastatic solid tumor was previously shown to be an important predictor of high 30-day mortality in the ICU.(23) In the present study, the HR value for metastatic tumor as a predictor of ICU mortality was 16.80 (95% CI 3.95-71.90; $p < 0.001$), which is similar to that reported by Barth et al. for the outcome of patients with metastatic lung cancer admitted to the ICU (OR 4.22 (1.40–12.40); $p = 0.008$).(24) Several studies have shown that lupus patients have an increased risk of malignant tumors, including hematological system tumors, cervical cancer, lung cancer, thyroid cancer, liver cancer, and breast cancer.(25) A few studies also have examined the association between cancer and immunosuppressant use among patients with SLE, indicating a possible higher cancer risk with immunosuppressant use.(26) Therefore, metastasis tumors should be considered in the decision-making process in ICU lupus patients. Hypotension occurs more frequently in non-survivors, and hypotension may reflect poor clinical status. Other studies have confirmed that aggressive use of vasoactive drugs improves the prognosis of ICU lupus patients. Hypoxemia is another common prognostic factor. Several studies have reported its impact on the poor prognosis of SLE patients.(23, 27) Relative hyperlactatemia (1.36–2.00 mmol/L) within the first 24 h of ICU admission was reported to be an independent predictor for ICU mortality in critically ill -patients.(28) Our study found an elevated anion gap (AG) in the non-survivor group because elevated AG is often present in metabolic acidosis. AG is a more sensitive indicator that can assist in determining compound acid-base imbalances that blood gas indicators cannot reveal.

Compared with other scores, our model is advantageous in its application because it uses easily measured and available parameters, does not increase the burden of disease, and is suitable for resource-limited settings. our model was developed as a practical tool that can rapidly and effectively estimate clinical death risk using only six simple and basic physiological parameters which can be acquired from patient's electronic medical records automatically.(29) Our study has several limitations. First, due to the retrospective study, some crucial variables may need to be included due to insufficient data. Our study lacked some drug use, such as the use of corticosteroids, immunosuppressants, hydroxychloroquine, and biologic agents, and some information that reflects participants' disease activity, including Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)(16, 30), and British Isles Lupus Assessment Group (BILAG) disease activity index(31, 32). Second, the mean event of predictive outcome indicators was insufficient. Third, this study lacks external validation. So, we would require multicenter prospective studies to further investigate the clinical practice of our model. Additionally, due to incomplete data collection and inaccurate data elements from the MIMIC-IV database, the potential for bias cannot be excluded.

In conclusion, in the present study, we analyzed the clinical characteristics and outcomes of SLE patients in the ICU from the MIMIC-IV database. Six independent prognostic factors were used to fit a simple and effective tool to predict in-hospital ICU mortality in patients with SLE, including peripheral vascular disease, peptic ulcer disease, metastatic solid tumor, GCS motor, lowest SBP, and lowest AG. The model is advantageous in its application because it uses easily measured and available parameters, does not increase the burden of disease and

is suitable for resource-limited settings. These findings may help clinicians to classify patients into different ICU mortality risk groups and to provide intensive and targeted management of patients with SLE.

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References

[1] Durcan, L., O'Dwyer, T., & Petri, M. (2019). Management strategies and future directions for systemic lupus erythematosus in adults. *Lancet*, *393*(10188), 2332-2343. https://doi.org/10.1016/S0140-6736(19)30237-5

[2] Arnaud, L., & Tektonidou, M. G. (2020). Long-term outcomes in systemic lupus erythematosus: trends over time and major contributors. *Rheumatology (Oxford, England)*, *59*(Suppl 5), v29-v38. https://doi.org/10.1093/rheumatology/keaa265

[3] Ocampo-Piraquive, V., Nieto-Aristizábal, I., Cañas, C. A., & Tobón, G. J. (2018). Mortality in systemic lupus erythematosus: causes, predictors and interventions. *Expert Review of Clinical Immunology*, *14*(12), 1043-1053. https://doi.org/10.1080/1744666X.2018.1541300

[4] Quintero, O. L., Rojas-Villarraga, A., Mantilla, R. D., & Anaya, J. M. (2013). Autoimmune diseases in the intensive care unit. An update. *Autoimmunity Reviews*, *12*(3), 380-395. https://doi.org/10.1016/j.autrev.2012.08.006

[5] Gasparotto, M., Gatto, M., Binda, V., Doria, A., & Moroni, G. (2020). Lupus nephritis: clinical presentations and outcomes in the 21st century. *Rheumatology (Oxford, England)*, *59*(Suppl 5), v39-v51. https://doi.org/10.1093/rheumatology/keaa263

[6] Suárez-Avellaneda, A., Quintana, J. H., Aragón, C. C., Gallego, L. M., Gallego, C.-N., Bolaños, J. D., ... & Iglesias-Gamarra, A. (2020). Systemic lupus erythematosus in the intensive care unit: a systematic review. *Lupus*, *29*(11), 1364-1376. https://doi.org/10.1177/0961203320944061

[7] Knaus, W. A., Draper, E. A., Wagner, D. P., & Zimmerman, J. E. (1985). APACHE II: a severity of disease classification system. *Critical Care Medicine*, *13*(10), 818-829.

[8] Le Gall, J. R., Lemeshow, S., & Saulnier, F. (1993). A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA*, *270*(24), 2957-2963.

[9] Fatemi, A., Shamsaee, S., Raeisi, A., Sayedbonakdar, Z., & Smiley, A. (2017). Prognostic factors of mortality in Iranian patients with systemic lupus erythematosus admitted to intensive care unit. *Clinical Rheumatology*, *36*(11), 2471-2477. https://doi.org/10.1007/s10067-017-3783-6

[10] Zamir, G., Haviv-Yadid, Y., Sharif, K., Bragazzi, N. L., Watad, A., Dagan, A., ... & Amital, H. (2018). Mortality of patients with systemic lupus erythematosus admitted to the intensive care unit - A retrospective single-center study. *Best Practice & Research Clinical Rheumatology*, *32*(5), 701-709. https://doi.org/10.1016/j.berh.2019.01.002

[11] Hochberg, M. C. (1997). Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis and Rheumatism*, *40*(9), 1725.

[12] Jiang, D., Bian, T., Shen, Y., & Huang, Z. (2023). Association between admission systemic immune-inflammation index and mortality in critically ill patients with sepsis: a retrospective cohort study based on MIMIC-IV database. *Clinical and Experimental Medicine*, 1-10. https://doi.org/10.1007/s10238-023-01188-4

[13] Moons, K. G., Altman, D. G., Reitsma, J. B., Ioannidis, J. P., Macaskill, P., Steyerberg, E. W., ... & Collins, G. S. (2015). Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Annals of Internal Medicine*, *162*(1), W1-W73. https://doi.org/10.7326/M14-0697

[14] Wolff, R. F., Moons, K. G., Riley, R. D., Whiting, P. F., Westwood, M., Collins, G. S., ... & Reitsma, J. B. (2019). PROBAST: A Tool to Assess the Risk of Bias and Applicability of Prediction Model Studies. *Annals of Internal Medicine*, *170*(1), 51-58. https://doi.org/10.7326/M18-1376

[15] Siripaitoon, B., Lertwises, S., Uea-Areewongsa, P., & Khwannimit, B. (2015). A study of Thai patients with systemic lupus erythematosus in the medical intensive care unit: epidemiology and predictors of mortality. *Lupus*, *24*(1), 98-106. https://doi.org/10.1177/0961203314549320

[16] Su, B., & Li, H. (2023). Development and validation of models for risk of death in patients with systemic lupus erythematosus admitted to the intensive care unit: a retrospective study. Clinical Rheumatology. 2023;42(11):2987-99.

[17] Hsu, C. L., Chen, K. Y., Yeh, P. S., Hsu, Y. L., Chang, H. T., Shau, W. Y., ... & Tsai, S. H. (2005). Outcome and prognostic factors in critically ill patients with systemic lupus erythematosus: a retrospective study. *Critical Care*, *9*(3), R177-R183. https://doi.org/10.1186/cc3461

[18] Lee, J., Dhillon, N., & Pope, J. (2013). All-cause hospitalizations in systemic lupus erythematosus from a large Canadian referral centre. *Rheumatology (Oxford, England)*, *52*(5), 905-909. https://doi.org/10.1093/rheumatology/kes376

[19] Mageau, A., Sacré, K., Perozziello, A., Ruckly, S., Dupuis, C., Bouadma, L., ... & Pène, F. (2019). Septic shock among patients with systemic lupus erythematosus: Short and long-term outcome. Analysis of a French nationwide database. *The Journal of Infection*, *78*(6), 432-438. https://doi.org/10.1016/j.jinf.2019.03.012

[20] Gustafsson, J. T., & Svenungsson, E. (2014). Definitions of and contributions to cardiovascular disease in systemic lupus erythematosus. *Autoimmunity*, *47*(2), 67-76. https://doi.org/10.3109/08916934.2013.847134

[21] Sagheer, S., Deka, P., Pathak, D., Khan, U., Zaidi, S. H., Akhlaq, A., ... & Dhillon, S. S. (2022). Clinical Outcomes of Acute Myocardial Infarction Hospitalizations With Systemic Lupus Erythematosus: An Analysis of Nationwide Readmissions Database. *Current Problems in Cardiology*, *47*(11), 101086. https://doi.org/10.1016/j.cpcardiol.2022.101086

[22] Gayam, V., Mandal, A. K., Khalid, M., Kaler, J., Thapa, S., Garlapati, P., ... & Reddy, M. (2018). A Rare Case of Systemic Lupus Erythematosus with Gastric Ulcer and Acute Pancreatitis: A Case Report and Literature Review. *Gastroenterology Research*, *11*(4), 321-325. https://doi.org/10.14740/gr1087w

[23] Ha, F. J., Weickhardt, A. J., Parakh, S., Vincent, A. D., Glassford, N. J., Warrillow, S., ... & Bellomo, R. (2017). Survival and functional outcomes of patients with metastatic solid organ cancer admitted to the intensive care unit of a tertiary centre. *Critical Care and Resuscitation*, *19*(2), 159-166.

[24] Barth, C., Soares, M., Toffart, A. C., Timsit, J. F., Burghi, G., Irrazabal, C., ... & Azoulay, E. (2018). Characteristics and outcome of patients with newly diagnosed advanced or metastatic lung cancer admitted to intensive care units (ICUs). *Annals of Intensive Care*, *8*(1), 80. https://doi.org/10.1186/s13613-018-0428-2

[25] Hsu, C.-Y., Lin, M.-S., Su, Y.-J., Cheng, T.-T., Lin, Y.-S., Chen, Y.-C., ... & Yu, C.-L. (2016). Cumulative immunosuppressant exposure is associated with diversified cancer risk among 14 832 patients with systemic lupus erythematosus: a nested case–control study. *Rheumatology*. https://doi.org/10.1093/rheumatology/kew287

[26] Scheurer, M., Cao, L., Tong, H., Xu, G., Liu, P., Meng, H., ... & Huang, C. (2015). Systemic Lupus Erythematosus and Malignancy Risk: A Meta-Analysis. *PLoS ONE*, *10*(4), e0123683. https://doi.org/10.1371/journal.pone.0123683

[27] Peng, J. C., Gong, W. W., Wu, Y., Yan, T. Y., & Jiang, X. Y. (2022). Development and validation of a prognostic nomogram among patients with acute exacerbation of chronic obstructive pulmonary disease in intensive care unit. *BMC Pulmonary Medicine*, *22*(1), 306. https://doi.org/10.1186/s12890-022-02116-4

[28] Rishu, A. H., Khan, R., Al-Dorzi, H. M., Tamim, H. M., Al-Qahtani, S., Al-Ghamdi, G., ... & Arabi, Y. M. (2013). Even mild hyperlactatemia is associated with increased mortality in critically ill patients. *Critical Care*, *17*(5), R197. https://doi.org/10.1186/cc12892

[29] Zhang, X., Yang, R., Tan, Y., Zhou, Y., Lu, B., Ji, X., ... & Zhang, Z. (2022). An improved prognostic model for predicting the mortality of critically ill patients: a retrospective cohort study. *Scientific Reports*, *12*(1), 21450. https://doi.org/10.1038/s41598-022-25807-6

[30] Bombardier, C., Gladman, D. D., Urowitz, M. B., Caron, D., & Chang, C. H. (1992). Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis and Rheumatism*, *35*(6), 630-640.

[31] Hay, E. M., Bacon, P. A., Gordon, C., Isenberg, D. A., Maddison, P., Snaith, M. L., ... & Zoma, A. (1993). The BILAG index: a reliable and valid instrument for measuring clinical disease activity in systemic lupus erythematosus. *The Quarterly Journal of Medicine*, *86*(7), 447-458.

[32] Isenberg, D. A., Rahman, A., Allen, E., Farewell, V., Akil, M., Bruce, I. N., ... & Yee, C. S. (2005). BILAG

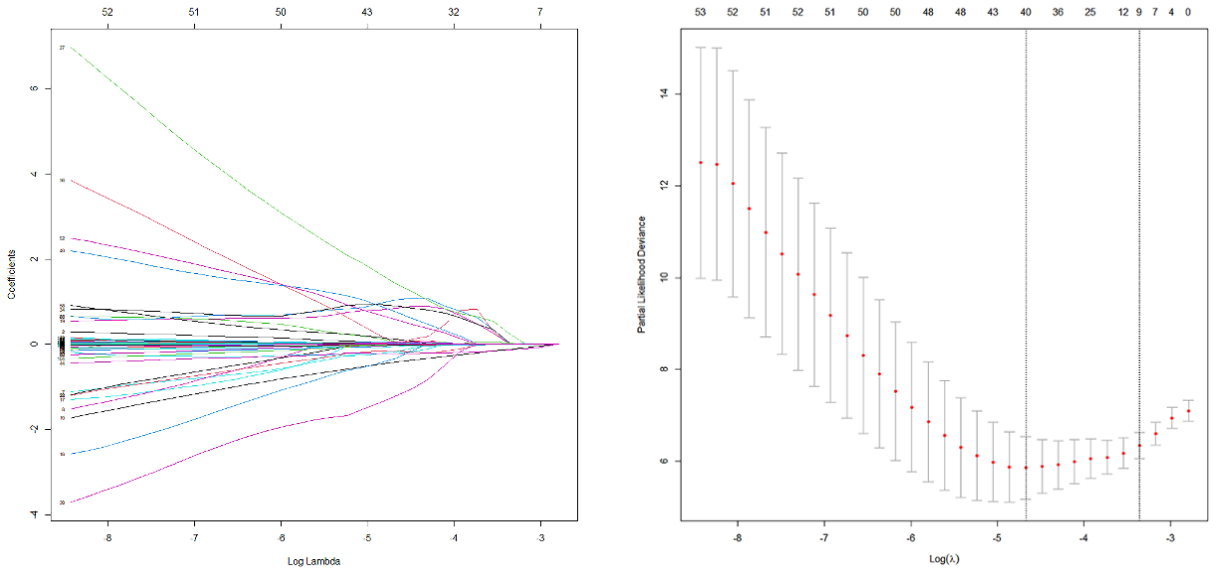
2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology (Oxford, England)*, *44*(7), 902-906. https://doi.org/10.1093/rheumatology/keh588

Table S1. Vital signs and laboratory data on ICU admission of the 301 patients.

	In-hospital deaths (n=25[1])	Survivors (n=276[1])	P
HR			
Min	81 (65, 85)	73 (65, 84)	0.606
Max	107 (96, 130)	104 (91, 120)	0.143
RP			
Min	16.0 (11.0, 17.0)	12.0 (10.0, 15.0)	0.068
Max	30 (28, 37)	27 (23, 31)	0.004
Temperature			
Min	36.2 (35.2, 36.7)	36.4 (35.8, 36.7)	0.220
Max	37.3 (36.8, 39.0)	37.3 (37.0, 37.9)	0.643
SBP			
Min	81 (72, 89)	92 (84, 107)	<0.001
Max	133 (121, 155)	150 (135, 173)	0.014
DBP			
Min	44 (36, 50)	47 (41, 55)	0.053
Max	89 (82, 94)	90 (77, 107)	0.417
MBP			
Min	56 (45, 64)	60 (53, 69)	0.016
Max	103 (90, 120)	106 (93, 123)	0.588
RBC	3.20 (2.65, 3.64)	3.47 (3.04, 4.02)	0.051
HB			
Min	8.80 (7.60, 10.60)	9.40 (8.30, 10.93)	0.164
Max	10.70 (8.90, 12.00)	10.60 (9.38, 11.83)	0.770
WBC			
Min	11.0 (9.9, 14.4)	7.6 (5.0, 10.9)	0.002
Max	16.0 (11.3, 20.3)	10.0 (6.5, 14.4)	0.001
PLT			
Min	145 (68, 305)	172 (108, 244)	0.450
Max	205 (120, 360)	200 (138, 275)	0.966
SPO2, %			
Min	91.0 (82.0, 96.0)	93.0 (91.0, 96.0)	0.035
Max	100.0(100.0,100.0)	100.0(100.0,100.0)	0.063
PO2			
Min	71 (40, 134)	74 (42, 123)	0.951
Max	174 (82, 294)	139 (74, 282)	0.277
PCO2			
Min	32 (25, 35)	37 (32, 44)	<0.001
Max	45 (32, 66)	44 (36, 52)	0.688
PH			
Min	7.32 (7.13, 7.38)	7.33 (7.24, 7.40)	0.316
Max	7.43 (7.36, 7.49)	7.39 (7.33, 7.44)	0.056
Lactate			
Min	2.70 (1.30, 4.10)	1.40 (1.00, 2.80)	0.064
Max	2.30 (1.10, 4.60)	1.90 (0.90, 4.05)	0.311
AG			
Min	15.0 (14.0, 18.0)	13.0 (11.0, 15.0)	0.001
Max	20.0 (16.0, 24.0)	16.0 (13.0, 19.0)	<0.001
HCO3-			
Min	18.0 (15.0, 22.0)	22.0 (19.0, 25.0)	0.001
Max	21.0 (18.0, 24.0)	24.0 (22.0, 27.0)	0.002
Globulin			
Min	111 (95, 138)	98 (83, 120)	0.109
Max	161 (133, 192)	126 (107, 166)	0.005
Bun			
Min	29 (18, 53)	19 (12, 36)	0.006
Max	36 (27, 55)	24 (14, 46)	0.004
Cr			
Min	1.50 (1.00, 3.70)	1.10 (0.70, 3.70)	0.113

Max	2.00 (1.10, 4.30)	1.30 (0.80, 4.60)	0.134
ALT			
Min	39 (23, 125)	26 (16, 119)	0.251
Max	49 (26, 284)	30 (16, 183)	0.138
AST			
Min	64 (32, 369)	56 (28, 304)	0.375
Max	104 (40, 759)	52 (29, 309)	0.021
INR			
Min	1.40 (1.20, 2.20)	1.20 (1.10, 1.50)	0.048
Max	1.60 (1.20, 3.30)	1.30 (1.10, 1.70)	0.008
PT			
Min	16 (13, 23)	13 (12, 16)	0.033
Max	18 (14, 34)	14 (12, 18)	0.003
PTT			
Min	35 (27, 39)	31 (27, 38)	0.496
Max	42 (31, 63)	35 (29, 48)	0.065
TBil			
Min	0.60 (0.30, 1.10)	0.40 (0.30, 0.90)	0.230
Max	0.90 (0.40, 1.70)	0.50 (0.30, 0.90)	0.047
CK-MB			
Min	3 (2, 11)	5 (2, 12)	0.574
Max	5 (2, 21)	9 (3, 18)	0.396
CPK			
Min	142 (61, 352)	121 (46, 299)	0.341
Max	121 (74, 971)	112 (53, 267)	0.434

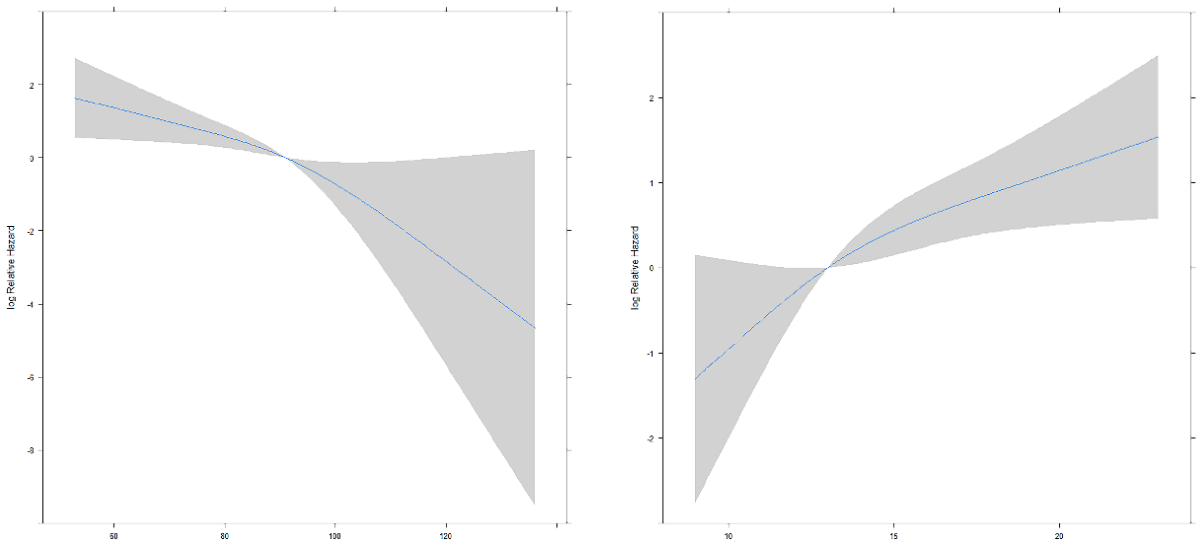
1, Median (IQR); n (%); HR, heart rate; RP, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; RBC, red blood cell count; HB, hemoglobin; WBC, white blood cell count; PLT, platelet count; PH, potential of hydrogen; AG, anion gap; Bun, Blood urea nitrogen; Cr, creatinine; ALT, alanine transaminase; AST, aspartate aminotransferase; INR, International Normalized Ratio; PT, prothrombin time; PTT, partial thromboplastin time; TBil, total bilirubin; CK-MB, creatine phosphokinase-MB; CPK, creatine phosphate kinase.



A **B**

Supplementary Figure 1. Variable selection by LASSO

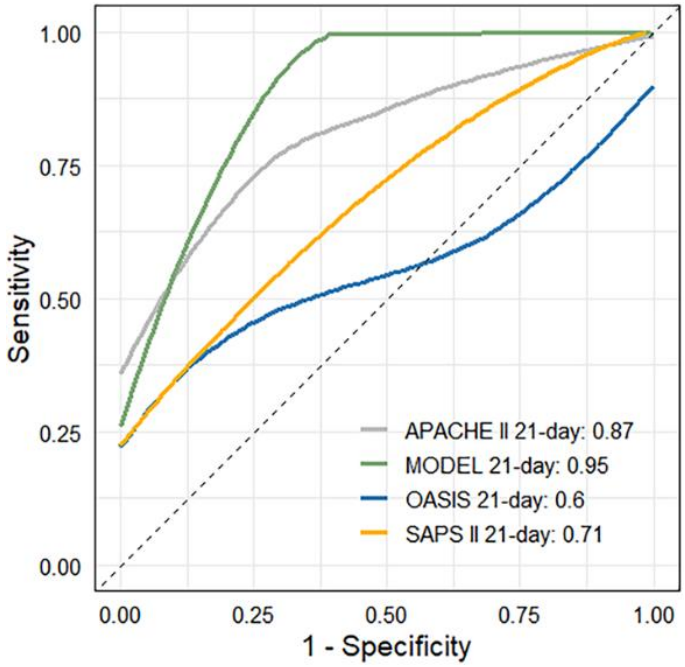
A: a coefficient profile plot was produced against the log lambda sequence. B: twelve variables with non-zero coefficients were selected by selective lambda.



A **B**

Supplementary Figure 2. Restricted cubic spline for the association between SBP/AG and mortality

A: adjusted factors were Peripheral vascular disease, Peptic ulcer disease, Metastatic solid tumor, GCS motor upon ICU admission, and lowest AG. B: adjusted factors were Peripheral vascular disease, Peptic ulcer disease, Metastatic solid tumor, GCS motor upon ICU admission, and lowest SBP.



Supplementary Figure 3. The time-dependent receiver operating characteristic curve's comparison of the prognostic model with SAPS II, APACHE II, and OASIS

The time-dependent ROC-AUC of Model, APACHE II, SAPS II, and OASIS in predicting mortality among SLE patients in ICU were 0.95, 0.87, 0.71, and 0.60 at 21 days, respectively.