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Prognostic nomogram for acute pancreatitis patients: An analysis of publicly electronic healthcare records in intensive care unit

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ABSTRACT

Purpose: The mortality rate of severe acute pancreatitis (AP) is 20–30% even after admission to intensive care unit (ICU). Thus we aimed to develop a laboratory-based nomogram to identify AP patients at high risk for mortality.
Materials and methods: The primary and validation cohorts were extracted from the Medical Information Mart for Intensive Care III database (MIMIC-III). Independent predictors were determined using multiple Cox analysis and then assembled to predict survival. The performance of proposed nomogram was evaluated by Harrell's concordance index (C-index) and area under the receiver operating characteristic (AUC) analysis, and subsequently compared with conventional scoring systems.
Results: A total of 342 AP patients admitted to ICU were enrolled, with 30-day, 180-day and 1-year mortality rate of 10.8%, 16.1% and 17.5%, respectively. Independent factors from multivariate Cox model to prognosticate 30-day and 1-year mortality were retrieved. The C-index of 1-year prediction nomogram (0.758, 95%CI: 0.676–0.840) were superior to several prediction approaches, and these findings were further confirmed by applying time-specific AUC analysis. Decision curve analysis indicated our nomogram was feasible in clinical practice. Similar results were observed in the validation cohort.
Conclusions: The proposed nomogram gives rise to accurately prognostic prediction for critically AP patients admitted to ICU.

1. Introduction

Acute pancreatitis (AP) is regarded as a rapid-onset inflammation that involves the pancreas, peripancreatic as well as remote organs [1]. The severity of AP ranges widely, from self-limiting mild illness to serious disease characterized by systemic complications and multiple organ failure. It is suggested that up to 25% of subjects can proceed to severe conditions, in whom the mortality rate is 20–30% [1,2]. A challenge in predicting the prognosis of AP is that its clinical development is significantly heterogeneous. Systemic complication usually arise early on and locoregional ones may occur anytime, leading to a protracted course. Furthermore, the latter is highly influenced by local practice at site. It is pivotal to predict patient outcomes on initial presence or early in the disease process, thus advantageous in optimal and timely interventions [3].

An impressive number of prediction/scoring models are currently available, however drawbacks and flaws of individual system should not be overlooked. For instance, the Acute Physiology and Chronic Health evaluation (APACHE-II) has >10 variables and is cumbersome to use [4]. Ranson criteria and blood urea nitrogen (BUN) require 48 h of inpatient observation, thereby resulting in delayed triage and management [5,6]. The computed tomography severity index (CTSI) requires an expensive CT examination, which is not necessary for the majority of AP at initial presentation [7]. Although several universal guidelines have recommended the use of certain scoring system in daily practice, the clinical utility of these systems remains elusive [3]. The wide variation in estimated parameters and distinct prognostic accuracy of each prediction model across studies may hamper the generalization of proposed guidelines. Moreover, these severity stratification systems are at best useful for categorizing patients or triage decision (selection of appropriate care level with close monitoring, prompt resuscitation and resource allocation). Although significant advance in the (evidence-based) treatment of these patients has been made in the last decades, there is still a significant heterogeneity in the therapeutic strategy between sites and no specific treatment are available for managing or modulating the inflammatory/microcirculatory destructive process in AP.

More recently, several inflammation-based markers have been intensively verified for prognostication in diverse entities, including AP, by us and other investigators [8,9]. These systemic inflammatory

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indecies comprise red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR) and platelet-to-lymphocyte ratio (PLR) [10]. However, there are few predictive models including these simple but effective factors.

Nomogram is widely performed as a statistical prognostic model in medical literature, by assigning relative risk score to each predictor according to its contribution to the prognosis [11]. Based on various biological and clinical variables, it results in an individual probability of a clinical event, such as death or tumor recurrence. Medical nomogram leads to rapid computation through user-friendly digital interfaces, together with enhanced accuracy and more concrete demonstration, allowing for seamless implementation of nomogram-derived results to help treatment allocation. Additionally, this graphical representation is beneficial for clinicians in the point of time care provision, family and patient counselling and updates/explanation regarding risk that enables them decision making objectively [12]. In this study, we sought to investigate the association between inflammatory makers and mortality in AP. Furthermore, we constructed a nomogram which incorporated routine laboratory parameters to predict mortality for critically AP using a publicly accessible Medical Information Mart for Intensive Cart III (MIMIC-III) database.

2. Patients and methods

2.1. Study design

Subject data were retrieved from MIMIC-III (version 1.4) dataset. MIMIC-III integrates de-identified, comprehensive clinical data of patients admitted to the Beth Israel Deaconess Medical Center in Boston, Massachusetts [13]; the dataset is widely and freely accessible to international researchers upon a use agreement (Our certification number: 6210610). Specifically, MIMIC-III pertains data in regard to 53,423 discrete hospital admissions of adult participants to critical care units between 2001 and 2012. An average of 4597 charted observations and 380 laboratory measurements are available for individual hospital admission. The overall information is saved as a relational database, consisting of patient demographics, laboratory test results (hematology, chemistry and microbiology parameters), discharge summaries, electrocardiogram and imaging examinations, billing-related information such as International Classification of Disease 9th Edition Clinical Modification (ICD-9-CM), in-hospital and out-of-hospital mortality (achieved by Social Security Administration Death Master File).

2.2. Definitions

A diagnosis of AP was made when at least two of the following criteria were fulfilled: (1) abdominal pain characteristic of AP; (2) at least 3-fold elevation of serum amylase and/or lipase concentrations above the normal threshold; (3) classical findings of AP on ultrasonic and/or CT scan [14]. Patients with recurrent pancreatitis were enrolled only at first hospitalization for evaluation. The ICD-9-CM diagnostic code used for selecting patients with AP is 577.0. We regarded 30-day, 180-day and 1-year all-cause mortality as the primary outcome.

2.3. Data retrieval

Patient data were retrieved from MIMIC-III database by performing the Structure Query Language. All documents of baseline characteristics were collected in the initial 24 h following admission.

The physiological measurements (hourly documentation of heart rate, arterial blood pressure, or respiratory rate) were made at bedside from time-stamped, nurse-verified monitor records. The baseline characteristics, including age, sex, survival time and readmission records were collected from the original dataset.

Laboratory measurements, including serum amylase, lipase, white blood cell count (WBC), platelet, hemoglobin, serum creatinine (SCR), glucose, calcium, BUN, RDW, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were allocated into a relational database. NLR is the ratio of neutrophils to lymphocytes; LMR is the ratio of lymphocytes to monocytes; and PLR is the ratio of platelets to lymphocytes [15]. Sequential organ failure assessment (SOFA), systemic inflammatory response syndrome (SIRS) and bedside index of severity in acute pancreatitis (BISAP) scores were calculated to stratify the severity of AP patients admitted to ICU (Table S1).

The following tables from MIMIC III dataset were implemented in our study [16]: ADMISSIONS, CHARTEVENTS, D_ICD DIAGNOSIS, D_ITEMS, D_LABIEVENTS, DIAGNOSIS_ICD, ICUSTAYS, LABEVENTS, NOTEEVENTS, PATIENTS, INPUTEVENTS_CV, INPUTEVENTS_MV and OUTPUTEVENTS.

2.4. Statistical analysis

Data was demonstrated as mean ± standard deviation or simple number as appropriate. Continuous data were compared using an independent Student *t*-test or the Mann-Whitney test for groups without normal distribution. Categorical variables were compared by chi-square test or Fisher's exact test as appropriate. Potential risk factors significant in univariate analysis ($P < 0.1$) were included into multivariable Cox proportional hazard model. The optimal cut-off for each independent parameter was determined using receiver operating characteristic (ROC) curve analysis, while the Youden index achieved the highest value. We also compared area under the ROC (AUC) between nomogram and conventional prediction scores. The survival rates were calculated using the Kaplan-Meier method and compared to detect statistically significant differences using the log-rank test. SPSS (Version 21.0; IBM, New York NY, USA) and MedCalc (Version 15.2.2; MedCalc Inc., Mariakerke, Belgium) software are used for statistical analysis.

A nomogram based on the results of previous multivariable analysis was constructed by using R version 3.3.2 (http://www.r-project.org/). Harrell's concordance index (C-index) was used to measure the performance of the nomogram. Confidence intervals (CIs) were obtained by creating 1000 bootstrap samples from the entire dataset and replicating the estimation process. The calibration curve was used to analyze the agreement between nomogram and ideal observation. The decision curve analysis was conducted to assess the clinical usefulness of the predictive nomogram by quantifying the net benefits at different threshold probabilities. The packages of rms, Hmisc and DCA were involved in this process.

3. Results

3.1. Patient characteristics

The baseline characteristics of patients in the primary and validation cohorts are shown in Table 1. The primary cohort consisted of a total of 135 men (59.2%) and 93 women (40.8%) with AP who were admitted to intensive care unit (ICU). The mean age was 60.0 ± 16.0 years. The predominant etiologies of AP were gallstone (107/228, 46.9%) and alcohol use (46/228, 20.2%). The mortality rates at 30-day, 180-day and 1-year were 27 (11.8%), 38 (16.7%) and 41 (18.0%), respectively.

The validation cohort included 58 men (50.9%) and 56 women (49.1%) with a mean age of 57.1 ± 16.3 years. The mortality rates at 30-day, 180-day and 1-year were 10 (8.7%), 17 (14.9%) and 19 (16.7%), respectively. Overall, there were no significant differences between the primary and validation cohort with the exception of serum amylase or etiologies.

3.2. The optimal cut-off values for age and inflammation-based markers

Considering the availability of variables, we next determined the optimal cut-off values for age and several inflammation response biomarkers for overall survival. The optimal cut-off value of 70 years for

Table 1
Baseline demographic and laboratory characteristics of patients.

Baseline variables	Primary cohort (N = 228)	Validation cohort (N = 114)	*P*
Age (years)	60.0 ± 16.0	57.1 ± 16.3	0.123
Gender, male, n (%)	135 (59.2)	58 (50.9)	0.165
WBC (10^9/L)	13.7 ± 7.1	13.1 ± 5.8	0.446
Platelet (10^9/L)	256.6 ± 122.9	265.5 ± 143.8	0.976
Hemoglobin (g/dL)	12.5 ± 2.2	12.7 ± 2.5	0.327
RDW (%)	14.4 ± 1.5	14.6 ± 1.9	0.813
NLR	13.00 ± 13.65	12.69 ± 10.56	0.836
LMR	3.49 ± 5.41	2.74 ± 1.98	0.659
PLR	287.7 ± 226.6	293.7 ± 286.5	0.839
Amylase (IU/L)	626.6 ± 872.6	438.1 ± 538.2	**0.049**
Lipase (IU/L)	1311 ± 2307	1490 ± 2601	0.337
Albumin (g/dL)	3.2 ± 0.75	3.3 ± 0.72	0.855
ALT (IU/L)	103.2 ± 181.9	110.3 ± 143.5	0.155
AST (IU/L)	120.5 ± 192.0	143.4 ± 182.4	0.291
Serum calcium (mmol/L)	2.05 ± 0.28	1.99 ± 0.32	0.084
Serum glucose (mmol/L)	9.1 ± 5.0	9.1 ± 7.7	0.275
Serum creatinine (mg/dL)	1.4 ± 1.5	1.4 ± 1.2	0.696
BUN (mg/dL)	24.1 ± 17.5	23.8 ± 19.4	0.856
SOFA	3.9 ± 2.9	4.0 ± 3.5	0.618
SIRS	0.6 ± 0.5	0.7 ± 0.5	0.810
BISAP	2.3 ± 1.2	2.3 ± 1.1	0.883
Etiology (1/2/3/4)%[a]	46.9/20.2/3.5/29.4	36.0/39.5/1.8/22.8	**0.002**
Mortality by 30-day, n (%)	27 (11.8)	10 (8.7)	0.463
Mortality by 180-day, n (%)	38 (16.7)	17 (14.9)	0.756
Mortality by 1 year, n (%)	41 (18.0)	19 (16.7)	0.880

Abbreviations: WBC, white blood cell count; RDW, red cell distribution width; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; PLR, platelet-to-lymphocyte ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; SOFA, Sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; BISAP, bedside index of severity in acute pancreatitis.
Values in bold are statistically significant (P< 0.05) in Table 1 and 3.
[a] Etiology (1/2/3/4)%, 1, 2, 3 and 4 represent gallstone/cholelithiasis, alcohol, hypertriglyceridaemia and other/unknown etiologies, respectively.

Table 2
Factors associated with 30-day, 180-day and 1-year survival in multivariate analysis in the primary cohort of patients with acute pancreatitis.

Baseline variables	HR	95% CI	*P*
30-day mortality			
Age (years)	1.038	1.007–1.070	0.017
ALT (IU/L)	1.002	1.000–1.003	0.012
BUN (mg/dL)	1.027	1.011–1.044	0.001
RDW (%)	1.335	1.020–1.747	0.035
180-day mortality			
Age (years)	1.041	1.015–1.067	0.002
WBC (10^9/L)	1.075	1.037–1.114	<0.001
RDW (%)	1.407	1.118–1.770	0.004
SCR (mg/dL)	1.166	1.027–1.321	0.029
1-year mortality			
Age (years)	1.037	1.012–1.062	0.003
WBC (10^9/L)	1.070	1.033–1.109	<0.001
RDW (%)	1.383	1.095–1.747	0.007
SCR (mg/dL)	1.147	1.008–1.304	0.037

Abbreviations: ALT, alanine aminotransferase; BUN, blood urea nitrogen; RDW, red cell distribution width; WBC, white blood cell count; SCR, serum creatinine; HR, hazard ratio; CI, confidence interval.

age was used to dichotomize patients (≤70, n = 156; > 70, n = 72). Optimal cut-off values for RDW, NLR, LMR and PLR were 13.8%, 18.2, 1.75 and 240.6, respectively.

3.3. Prognostic factors for 30-day, 180-day and 1-year mortality

Baseline demographic, clinical and laboratory variables, including inflammation-based markers for the prediction of 30-day, 180-day and 1-year mortality, were further determined by univariate Cox regression model. Results from the univariate analysis were as follows: age, WBC, RDW, LMR, albumin, ALT and BUN were prognostic factors of 30-day survival; age, WBC, RDW, NLR, LMR, albumin, SCR and BUN were precipitating factors of 180-day/1-year survival (Table S2). Thereafter, all of these significant factors were entered into the multiple Cox proportional hazard model for adjusting the confounding effects for 30-day and 1-year mortality, respectively. In that model, we demonstrated age, ALT, RDW and BUN were independent prognostic factors for 30-day; and age, WBC, RDW and SCR were independent prognostic factors for 1-year mortality of AP patients following ICU admission (Table 2).

3.4. Prognostic nomogram for 30-day and 180-day/1-year mortality

Taken account of the distinct indicators for short-term and long-term prognosis of patients with AP, two prognostic nomograms were constructed based on multivariate Cox regression model in terms of the significantly independent predictors (Fig. 1). Specially, the nomogram was generated by assigning a weighed score on the point scale to each of the independent prognostic parameters. A higher score calculated from the sum of the assigned number of points for each predictive indicator in the nomogram correspond to a higher likelihood of decease. For instance, an AP patient aged over 70 years (28 points), with WBC of 20 (40 points), SCR of 2 (9 points) and RDW >13.8 (24.5 points) would score a total of 101.5 points (and therefore have approximate 50% predicted risk of survival on 1-year follow-up).

3.5. Performance of model and clinical usefulness

The discriminatory ability of our final model was assessed using the C-index for 30-day and 1-year survival prediction (Table 3). The nomogram derived from the primary cohort for 30-day mortality had C-index of 0.751 (95%CI: 0.649–0.853), which was comparable with that of the SOFA and BISAP score, and superior to SIRS. Moreover, the C-index for 180-day/1-year survival of the nomogram was 0.758 (95%CI: 0.676–0.840), indicating that it performed a better predictive power than SOFA, BISAP or SIRS.

The calibration curves for probability of 30-day, 180-day and 1-year survival were demonstrated in Fig. 2. The *x*-axis represents the predicted survival resulted from the nomogram, and the *y*-axis exhibits actual survival estimated by the Kaplan-Meier estimate. The calibration plot revealed adequate fit of the nomogram predicting the risk of death. The decision analysis curve implicated that the net benefits gained from the application of our nomogram at 30-day, 180-day and 1-year as threshold probabilities were 0.06–0.71, 0.05–0.68 and 0.05–0.47, respectively (Fig. 3).

3.6. Validation of the predictive accuracy of nomogram

Using the subsequent cohort of 114 consecutive AP subjects from same dataset, the established nomogram gave rise to a C-index of 0.875 (95%CI 0.763–0.987) and 0.856 (95%CI 0.754–0.958) for predicting 30-day survival and 180-day/1-year survival, respectively. Accordingly, calibration curves revealed that prediction of 30-day and 180-day/1-year survival probability using the nomogram were optimal agreement with the actual patient survival values (Fig. S1). In addition, decision analysis curves also unveiled the clinical utility of proposed nomogram (Fig. S2).

3.7. Performance of the nomogram in stratifying risk of patients

We identified the cut-off values by classifying the patients in the primary cohort evenly into three subgroups after dividing by total points (low risk: 11.6–53.3, medium risk: 53.4–89.0; high risk: ≥89.1); every

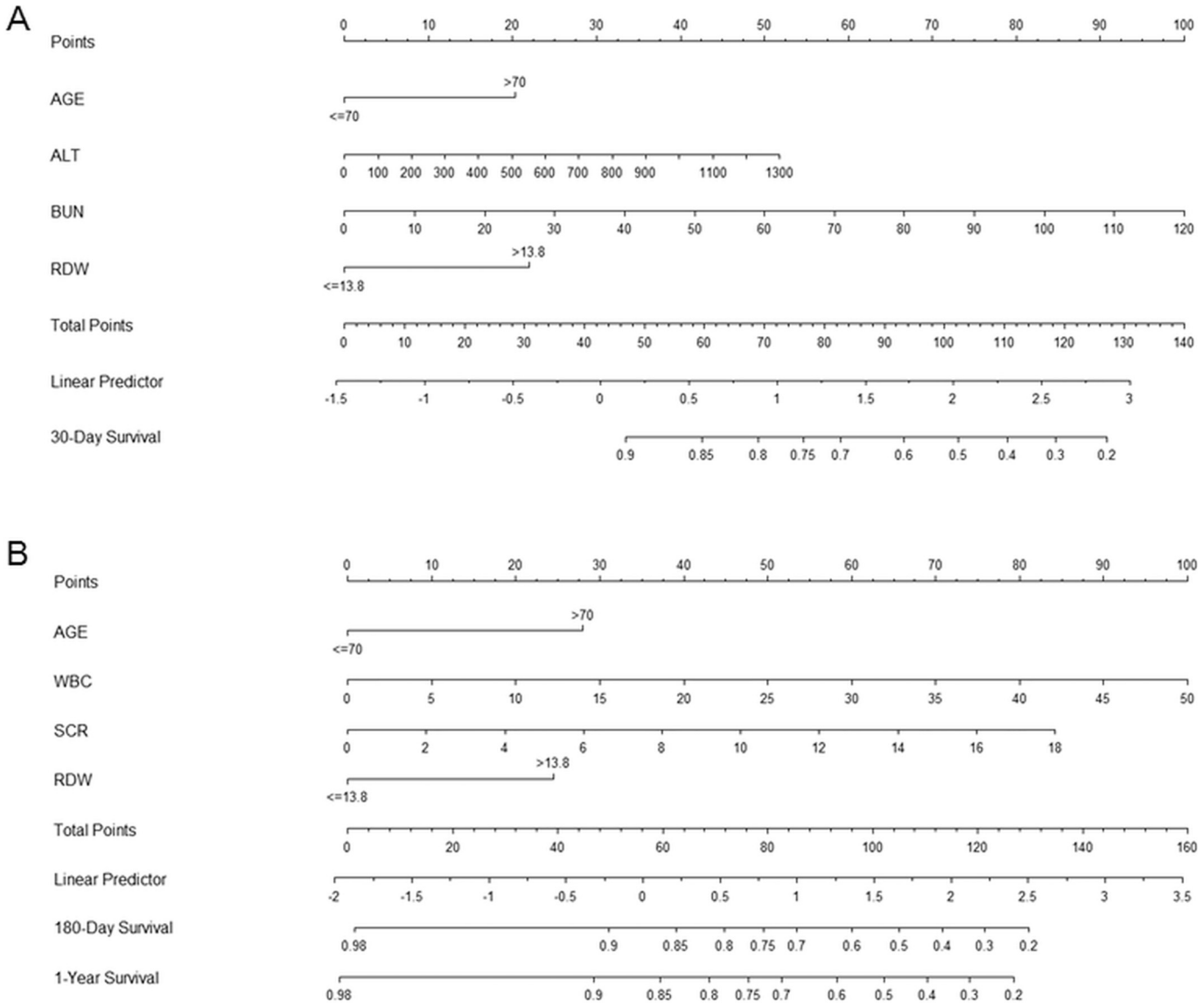

Fig. 1. Nomograms predicting 30-day (A) and 180-day/1-year (B) overall survival in AP patients following ICU admission. To calculate the probability of survival, we first draw a vertical line to the points scale to obtain the value for each indicator and then sum up all the individual values. Finally, we draw a vertical line from the total points axis to the probability at the 30-day line to get 30-day survival rate and at the 180-day and 1-year line to achieve 180-day and 1-year survival rate, respectively. ALT, alanine aminotransferase; BUN, blood urea nitrogen; RDW, red cell distribution width; WBC, white blood cell count; SCR, serum creatinine.

Table 3
The comparison of C-index of nomogram, SIRS, BISAP and SOFA for prognosis in the primary cohort and validation cohort.

Models	Primary cohort		Validation cohort	
	C-index (95% CI)	*P*	C-index (95% CI)	*P*
30-day				
nomogram	0.751 (0.649–0.853)		0.875 (0.763–0.987)	
SIRS	0.600 (0.527–0.673)	<**0.001**	0.528 (0.386–0.670)	<**0.001**
BISAP	0.730 (0.650–0.810)	0.103	0.768 (0.587–0.949)	<**0.001**
SOFA	0.782 (0.695–0.869)	0.052	0.801 (0.629–0.973)	**0.006**
180-day/1-year				
nomogram	0.739 (0.657–0.821)		0.856 (0.754–0.958)	
SIRS	0.573 (0.508–0.638)	<**0.001**	0.501 (0.394–0.608)	<**0.001**
BISAP	0.707 (0.633–0.781)	**0.048**	0.744 (0.612–0.871)	<**0.001**
SOFA	0.687 (0.605–0.769)	**0.011**	0.733 (0.604–0.862)	<**0.001**

Abbreviations: SIRS, systemic inflammatory response syndrome; BISAP, bedside index of severity in acute pancreatitis; SOFA, Sequential organ failure assessment; CI, confidence interval.

group showed a distinct prognosis (Fig. 4A) [17]. While employing the cut-off values to stratify patients in the validation cohort to three subgroups, it also represented significant differences between Kaplan-Meier survival curves (Fig. 4B).

3.8. Comparison of predictive accuracy for mortality among nomogram, SIRS, SOFA and BISAP

Furthermore, the predictive accuracy for mortality of AP patients form different time-points were compared for nomogram, SOFA and BISAP score by calculating time-specific AUC [18]. Fig. 5 demonstrated the ROC curves of nomogram, SIRS, SOFA and BISAP for predicting the mortality of AP at 30-day, 180-day and 1-year, respectively. Accordingly, the value of each model in predicting risk of death followed the order of our developed nomogram > BISAP > SOFA > SIRS for long-term mortality both in the primary and validation cohort. The AUC details were shown in Table S3.

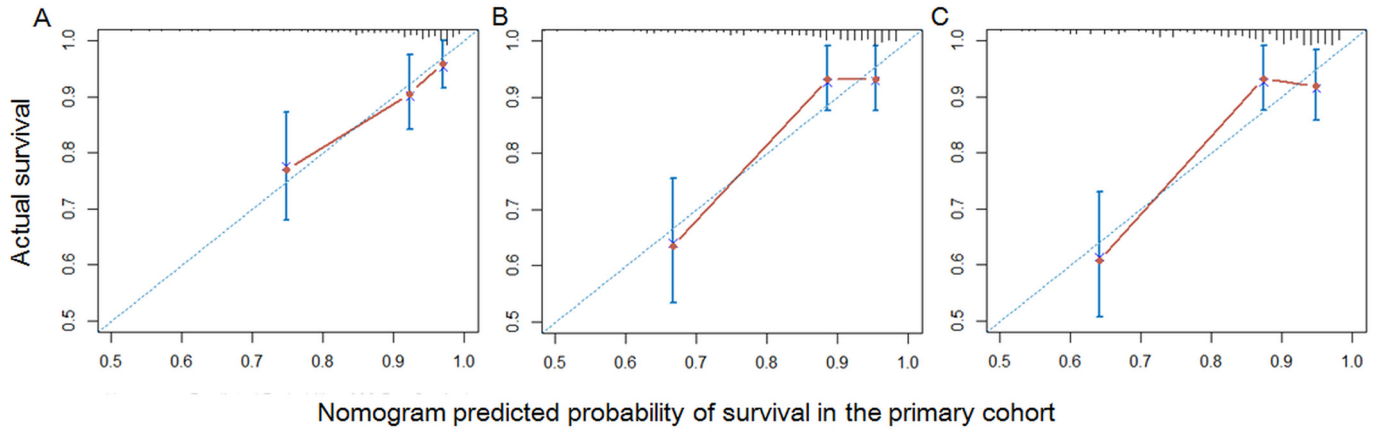

Fig. 2. The calibration curves for predicting critical AP survival at 30 days (A), 180 days (B) and 1 year (C) in the primary cohort. Nomogram-predicted probability of overall survival is plotted on the x-axis, actually observed overall survival (estimated by Kaplan-Meier analysis) is plotted on the y-axis.

3.9. Performance of RDW in the prediction of various end points and correlation analysis

As RDW being the only inflammation-based biomarkers relevant to short- and long-term mortality in the current study, we next investigated the clinical features of RDW. There was no significant difference among RDW in distinct etiologies of AP ($P = 0.610$; Fig. S3). We also found that RDW > 13.8 were not significantly associated with length of hospital or ICU stays (15.4 ± 13.4 *vs* 17.0 ± 19.0 days and 7.4 ± 10.0 *vs* 7.3 ± 11.0 days, $P > 0.05$). In addition, RDW values were positively correlated with the patient's SCR ($r = 0.194$, $P < 0.001$) and SOFA ($r = 0.197$, $P < 0.001$), and were negatively correlated with the hemoglobin ($r = -0.320$, $P < 0.001$), albumin ($r = -0.179$, $P = 0.001$), amylase ($r = -0.141$, $P = 0.012$) and serum glucose ($r = -0.158$, $P = 0.003$). No significant correlations were determined between RDW and age, platelet, BUN, WBC, lipase, calcium, ALT, AST, SIRS or BISAP (Table S4). Kaplan-Meier curves implicated the survival rate was lower in patients with high RDW value (>13.8) than in patients with low RDW level (≤13.8) (Fig. S4).

4. Discussion

In the present study, we evaluated the prognostic power of various inflammation-based markers and routine laboratory parameters to predict survival in AP patients from a publicly available large-scale ICU database. We found that different predictors were independently associated with short- and long-term all-cause mortality, thereby obtained two prognostic nomogram models. Our nomogram estimation gave rise to an accuracy of 0.751 and 0.758 to predict 30-day and 1-year mortality in AP patients, respectively. Moreover, the discriminatory capacity of proposed models were further confirmed by a validation cohort from the same data set with desirable efficacy.

AP varies considerable in disease severity, progressive course and eventual prognosis. During the past decade, a variety of scoring systems have been developed for early identification of poor outcomes in AP such as APACHE-II, Ranson criteria, SIRS, BISAP, SOFA and CTSI [19]. However, some of these prediction models are thought to be impractical due to complex calculation based on multiple data points, unnecessity of imaging examination upon initial assessment or delayed predictive results. On the contrary, a recent study by Kiat et al. has indicated that 48-hour requirement of Ranson criteria for risk stratification is its inherent strength [20]. Specially, the authors believed that severity was a 'continuous phenomenon' rather than a 'time-point' and the 48-hour time frame was necessary. They foresaw that traditional scoring system (for instance, Ranson criteria) was sufficient for prognostication of AP, since novel scoring systems have limited capability to improve outcomes with clinical impact. Additionally, most physicians, in 'real life', continue using careful repetitive clinical examination and simple laboratory parameters to assess the course of AP patient, which accounts

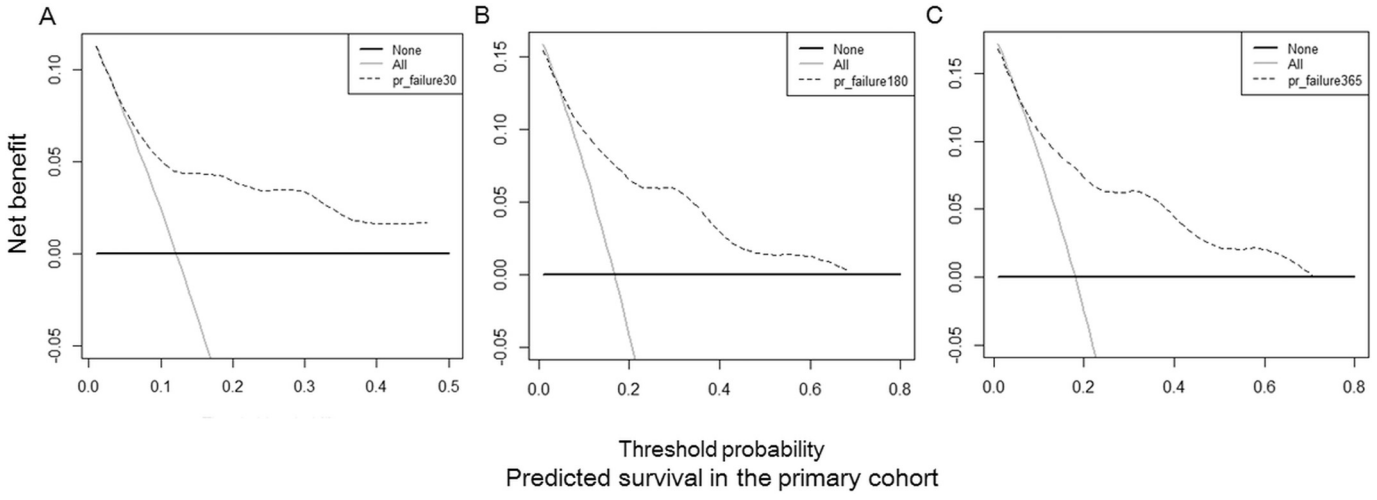

Fig. 3. Decision curve for the primary cohort implicating the net benefit with respect to the use of the nomogram for predicting 30-day (A), 180-day (B) and 1-year (C) mortality in AP patients upon ICU admission.

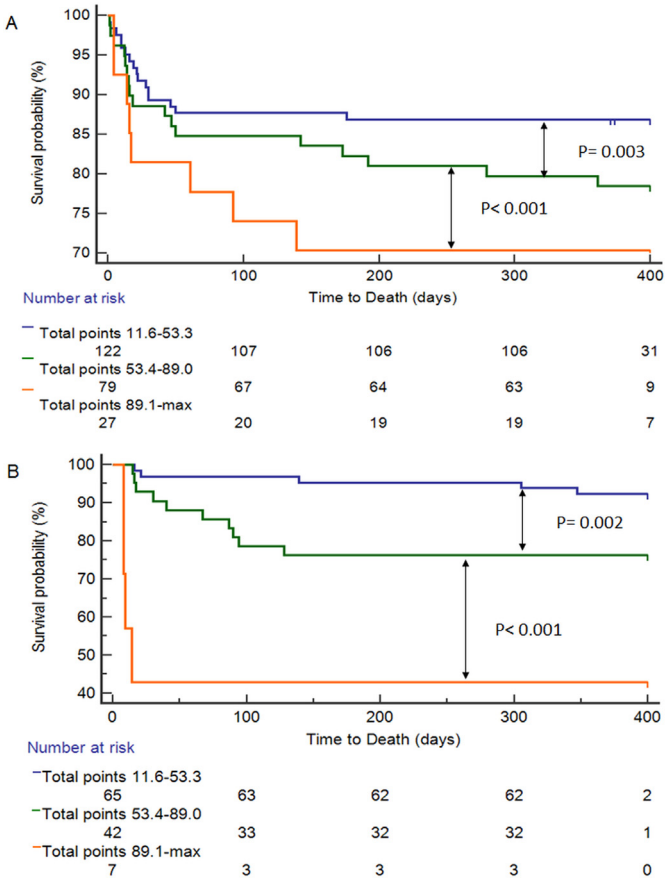

Fig. 4. Kaplan-Meier curves of 1-year overall survival for the three risk group stratifications. Nomogram risk group stratifications for the 33 and 66 percentiles are shown for the primary cohort (A) and validation cohort (B).

for comparative predictive 30-day mortality accuracy of the SOFA and BISAP scores with the developed nomogram in the present study. The last but not the least, a systemic review including 94 unique studies has evaluated 18 scores in 53, 547 AP patients and suggested that further studies with improved methodological rigor are needed as well as the development of new justified scoring systems [3]. The practical issue, including ease of use and avoiding the use of subjective variables, should be considered thoroughly.

Nomogram provides prognostic information tailored to the individuals, by generating a simple graphical representation of a statistical predictive model which creates a numerical probability of a clinical event [21]. In the current study, we first identified independent predictors for mortality in AP patients at different time points, ranging from 30 days to 1 year. Intriguingly, we obtained a 2-compartment prediction model based on retrieved indexes. Specifically, our early-phase predictive nomogram (compartment 1) included age, ALT, BUN and RDW; while age, WBC, SCR and RDW were determined as precipitating factors for 180-day/1-year mortality (compartment 2). We speculate above findings partly reflects potential pathophysiologic states while considering temporal process of AP and specific treatment allocation [22].

It is generally realized that advanced age was related to poor prognosis in a variety of entities. Moreover, several universally acknowledged scoring systems have incorporated age for predicting disease severity or mortality in AP in the medical field [3]. However, no consensus has been reached concerning optimal cut-off value of age to assess AP progression; for instance, Ranson criteria suggests that subjects aged over 55 years at initial admission as risk-stratifying indicator while BISAP score recommends that of >60 years old. Specially, our nomograms verified age > 70 years as appropriate demarcation point for death from an ICU setting, which is consistent with a newly defined grading model, known as new Japanese severity score, for mortality in AP [23].

Activation of inflammation is the underlying pathophysiology of AP. The excessively inflammatory process may result in local and systemic complications, including infected pancreatic necrosis and irreversible organ failure. Additionally, inflammatory response can be reflected by the ratios of neutrophils, lymphocytes, monocytes, platelets as well as the levels of acute-phase proteins. The association between biomarkers of systemic inflammation, such as RDW, NLR and LMR, and AP prognosis or severity has been extensively investigated and described [8,24]. Herein, we identified elevated RDW was readily available and reproducible indicator among various inflammation-based markers in an ICU database. We defined that RDW >13.8% as an independent risk factor of mortality. Conventionally, RDW is one issue of the complete blood count test, representing the variability of erythrocyte volume. To date, mounting evidence has shown that elevated RDW is positively related to the severity, risk stratification and prognosis of various entities, such as sepsis [25], malignancies [26], cardiovascular and pulmonary diseases [27,28]. In addition, some scholars have explored the usefulness of RDW for prediction of severity and mortality in AP. Most recently, a systemic review by Goyal et al., derived from seven retrospective studies, found admission RDW could be used as an independent biomarker to identify the AP patients at high death risk [19]. The authors also hypothesize the underlying pathophysiologic mechanism is partially ascribed to excessively inflammatory activities. However, some drawbacks of the above studies should be addressed as follows: First, the majority of available research included relatively small sample size with only one study comprising more subjects than ours (359 *vs* 342 AP patients); Second, low proportion of non-survivors, ranging from 4.3%–13.3%, may give rise to concern about investigation bias and dramatically hamper the predictive power; Third, the analyzed data were collected from heterogeneous source, such as emergency, surgery department or ICU, which impacting the representativeness and generalizability; Last, all of the studies have only investigated mortality at fixed time-point without taking account of dynamic effect with respect to RDW values for prediction of mortality in critically AP patients. Therefore, we conducted a retrospective study, using critical care data with detailed information and complete survival status, from MIMIC III dataset.

The role of BUN and SCR for prediction of prognosis in AP is controversial owing to a wide spectrum of end-points. As a matter of fact, few previous studies have incorporated and analyzed BUN and SCR in their prediction model together or adjusted confounders by employing multiple regression analysis. Yang et al. reported that SCR level served as a preferable predictor for severe AP, whereas the BUN level did not offer a good predictive value [29]. The authors of aforementioned paper suggest that SCR is more sensitive than BUN in stratifying AP patients. Regardless of the distinct predictive purpose, we propose another possible explanation that may be invoked to interpret our findings. The initial elevated BUN most likely reflects under-resuscitation leading to pre-renal azotemia [18]. If the hypovolemic state of the AP patients at early stage can not be adequately and immediately corrected, the subjects are prone to constitutive depletion in effective circulatory blood volume, subsequent reduction of glomerular filtration rate and finally deterioration of renal function. Thus, our nomogram model imply that BUN is predisposed to predict short-term mortality at early step of AP course, while SCR serves as an enduring index for persistent organ failure closest to 1-year mortality.

The strong association between WBC and mortality of AP has been previously reported elsewhere [24,30,31]. Additionally, ALT represents the most frequent cited biochemical factor associated with gallstone, and higher ALT concentrations are more often observed in AP of the biliary etiology than in other etiologies (in our study almost half of the patients were diagnosed as gallstone etiology) [32,33].

Our study embraces several strengths. First, this is the first study aiming to propose a nomogram with easily obtainable laboratory

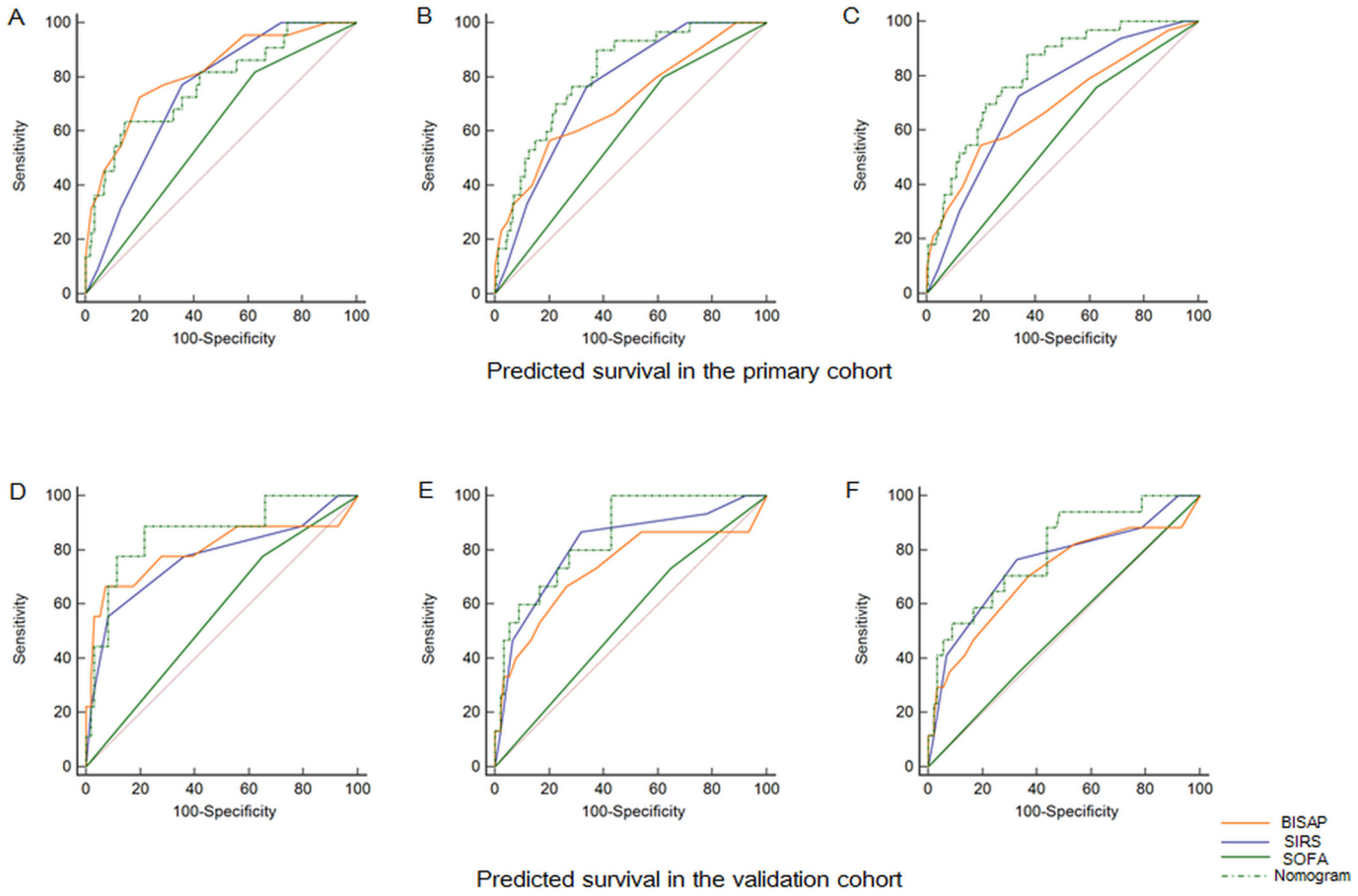

Fig. 5. Time-specific ROC of the prognostic nomogram, BISAP, SIRS and SOFA for patients in the primary and validation cohorts. Comparison of time-specific ROC of the prognostic nomogram, BISAP, SIRS and SOFA for predicting 30-day survival (A), 180-day survival (B) and 1-year survival (C) in the primary cohort and 30-day survival (D), 180-day survival (E) and 1-year survival (F) in the validation cohort. The time-specific ROC curve was applied to assess the predictive performance of survival. ROC, receiver operating characteristic; SOFA, Sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; BISAP, bedside index of severity in acute pancreatitis.

measures. It provides a probability of certain outcome (death due to AP in our study) and allows practitioner to clearly interpret with a patient using individual nomogram estimate. Second, although enrolled cases were determined by ICD-9-CM code number rather than the more stringent revised Atlanta symposium criteria [34], the consistent diagnostic criteria of AP and homogenous data source make our results valid. Third, a two-compartment nomogram is more in line with daily practice while considering sharply progressive activities of AP.

Our study still has several limitations. First, it included only critically-ill AP patients from a single center, which may caution us from generalizing the proposed nomogram to a larger population. Second, although we attempted to adjust for confounders and differences by performing multiple Cox regression model, residual confounding by unmeasured covariates might not have been completely eliminated. In particular, the treatment effects (for example, conservative *versus* invasive therapy) may dramatically influence the outcomes in AP patients, and the differences with respect to treatment protocols during a 10-year period also hamper the utility of proposed nomogram among sites. Third, we reported all-cause mortality instead of AP specific decease. This is due to the out-of-hospital mortality rates were obtained using the social society file.

In conclusion, we propose a refined nomogram with easily obtainable biochemical parameters. This laboratory-based model allows practitioners at the bedside for early risk-stratification for AP patients following ICU admission, whose performance matches or even outperforms other conventional multiple scoring systems.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.10.030.

Declaration of interest

The authors declare no conflicts of interests.

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Author contributions

XHJ, ZYS and CS conceived and planned the study. XHJ, ZYS, YW and YD collected data. XHJ, ZYS and CS wrote the first draft of manuscript. All authors contributed to the interpretation of finding and reviewed the manuscript. KJ reviewed the statistical analyses and made changes to the content of the manuscript. All authors have also provided intellectual contribution to the manuscript.

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