A Mobile Terminal-based Nomogram for Early Predicting Severity of Acute Pancreatitis

Na Shi
Sichuan University West China Hospital
Xiaoxin Zhang
Sichuan University West China Hospital
Wenhua He
First Affiliated Hospital of Nanchang University
Lihui Deng
Sichuan University West China Hospital
Lan Li
Sichuan University West China Hospital
Ping Zhu
Sichuan University West China Hospital
Liang Xia
First Affiliated Hospital of Nanchang University
Tao Jin
Sichuan University West China Hospital
Thomas Ward
University of Liverpool
Peter Sztamary
University of Liverpool
Wenhao Cai
Sichuan University West China Hospital
Linbo Yao
Sichuan University West China Hospital
Xinmin Yang
Sichuan University West China Hospital
Ziqi Lin
Sichuan University West China Hospital
Kun Jiang
Sichuan University West China Hospital
Jia Guo
Sichuan University West China Hospital
Xiaonan Yang
Sichuan University West China Hospital
Vikesh K. Singh
Johns Hopkins Medical Institutions: Johns Hopkins Medicine
Robert Sutton
University of Liverpool
John A. Windsor
University of Auckland
Nonghua Lu
First Affiliated Hospital of Nanchang University
Yin Zhu
First Affiliated Hospital of Nanchang University
Wei Huang (wei.huang.scu@vip.163.com)
Sichuan University West China Hospital https://orcid.org/0000-0001-8659-322X
Qing Xia
Sichuan University West China Hospital

Research Article

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Abstract

Background: Early prediction of the severity of acute pancreatitis (AP) is important but there is no preferred method in China. We aimed to develop and validate a simple-to-use predictive nomogram for persistent organ failure (POF) on admission in patients with AP.

Methods: Data from 816 consecutive patients was obtained from internal (Chengdu) retrospective datasets and formed the training cohort for nomogram development. Data from 398 and 880 consecutive patients from internal (Chengdu) and external (Nanchang) prospective datasets formed the validation cohorts (all admitted < 48 hours of symptom onset). Univariate and multivariate logistic regressions were used to identify independent prognostic factors to establish the nomogram for POF. The calibration curves, concordance index (C-index), decision curve analysis (DCA), and clinical impact curve (CIC) were used to evaluate the performance of the nomogram and its clinical utility. The area under the receiver-operating characteristic curve (AUC) with 95% CI and likelihood ratio as well as post-test probability were applied.

Measurements and main results: Age, respiratory rate, albumin, lactate dehydrogenase, oxygen support, and pleural effusion were identified as independent prognostic factors for POF and were included in the nomogram model (web-based calculator: https://shina.shinyapps.io/DynNomapp/). This predictive nomogram had good predictive ability for POF (C-indexes of 0.88, 0.91 and 0.81 for the training and two validation cohorts) and promising clinical utility (DCA: better or equivalent than prognostic scores; CIC: high clinical net benefit). The AUC of (0.91 [0.88-0.94] and 0.81 [0.79-0.84]), negative likelihood ratio (NLR 0.11 and 0.29), post-test probability of negative (0.9% and 6.7%) of the nomogram were superior in predicting POF than all other routinely used clinical prognostic scoring systems in both validation cohorts. Similar findings were observed for predicting major infection (superior to other prognostic scores) and mortality (superior or equally to others).

Conclusions: The validated nomogram comprises 6 independent prognostic factors to predict major clinical outcomes of patients with AP in two distinct Chinese centers. This mobile terminal-based nomogram should be validated in other settings and considered for clinical practice and trial allocation, until more accurate biomarkers are discovered.

Introduction

Acute pancreatitis (AP) is a protean and heterogenous disease with a spectrum of severity ranging from mild to critical [1]. The early prediction of the severity of AP is a cornerstone of management because it informs clinical decisions about triage, transfer and intervention [2]. Early prediction is also important in the research setting, where the accurate allocation of patients into trial arms based on predicted severity is critical for the testing of treatments for AP. The key determinants of AP severity are organ failure and infected pancreatic necrosis [3, 4]. With the recent improvements in treating infected pancreatic necrosis, persistent organ failure (POF) has become the most important determinant for mortality [5–9], and is the basis for the grade of severe AP (SAP) in the revised Atlanta classification (RAC) [10]).

Since the Ranson score was introduced in 1974 [11], more than 20 prognostic scores have been studied for AP severity prediction [12]. However, their clinical utility is limited by an accuracy of predicting POF at circa 75% and many of them are cumbersome to use [13]. Recent systematic reviews and meta-analyses conclude that current early predictors of POF [14], infected pancreatic necrosis [14], and mortality [12] do not have sufficient accuracy for the decision making in individual patients. The ideal predictor of POF would be applied on patient admission and within 24 hours of the onset of symptoms. It would be cost-effective, easy to use and have an accuracy between 95–100%. Considerable progress has been made in identifying serum biomarkers to stratify early risk and severity in patients with AP [15]. However, due to their rapid time-course changes in serum concentration, non-specificity, cost, complexity, and suboptimal accuracy, none of the biochemical biomarkers have been adopted into routine clinical practice. In recent years, different nomograms have been applied for predicting severity (mortality) [16–19], splanchnic vein thrombosis [20], abdominal infection [21], computed tomography index for assessing AP outcomes [22] and catheter drainage in necrotizing AP [23, 24] as well as for oral refeeding intolerance during hospital stay [25] and new-onset diabetes after AP [26] (Table 1). However, of the 4 studies investigated the predictive value of nomograms for severity or mortality, 3 used online Critical Care Database (Medical Information Mart for Intensive Care III database [MIMIC-III] [16, 18], eICU Collaborative Research Database [eICU-CRD] [17]) and 1 was retrospective [19] in nature. Besides, none of these studies reported the time of symptom onset to hospital admission. Therefore, the early prediction of AP severity at primary admission or early transfer remains to a challenge.

Table 1
Summarize of the present developed nomograms in AP

Nomograms for predicting SAP or mortality

	Predicted outcome		Study design	Symptom onset time	Data collection time	Indicators of the Nomogram	Training cohort		Validation cohort		Main findings
							N	C-index	N	C-index	
Jiang et al 2019 [16]	Mortality	30-day	MIMIC-III	NA	Within 24 h	age, ALT, RDW, BUN	228	0.751	114	0.875	Nomogram > BISAP > SOFA > SIRS for long-term mortality both in cohorts.
		180-day/ 1-year			Within 24 h	age, WBC, RDW, SCR		0.758		0.856	
Li et al 2020 [17]	In-hospital mortality		eICU-CRD	NA	Within 24 h	age, BUN and lactate	378	0.896	123	0.892	The nomogram and APACHE IV demonstrated comparable power in predicting in-hospital mortality.
Xu et al 2020 [18]	SAP		MIMIC-III	NA	On admission	SOFA, hemoglobin, albumin, TBIL, BUN	708	0.855	477	0.879	Nomogram > SOFA / OASIS for SAP and mortality in both cohorts.
	In-hospital mortality				On admission	Age, SOFA, WBC, TBIL, albumin		0.821		0.822	
Cao et al 2021 [19]	SAP		Retrospective	NA	Within 24 h	Sex, Ca^{2+}, SCR, NE%, LYMPH%, EO%	571	0.69	150	0.71	No comparison with others.

Other nomograms in AP

	Predicted outcome	Statistical methods	Indicators of the Nomogram	Training cohort		Validation cohort	
				N	C-index	N	C-index
Hollemans et al 2016 [23]	Success of catheter drainage in infected necrotizing pancreatitis	Univariate and multivariate logistic regression	Sex, percentage of pancreatic necrosis, density collection, multiple organ failure	130	0.76	NA	NA
Zhou et al 2016 [20]	Symptomatic splanchnic vein thrombosis in necrotizing acute pancreatitis	Univariate and multivariate logistic regression	Balthazar's CT score, intra-abdominal pressure and superior mesenteric vein thrombosis	104	0.842	NA	NA
Bevan et al 2017 [25]	Oral feeding intolerance	Univariate and multivariate logistic regression	Day 2 GCSI nausea/vomiting subs-core, etiology	217	NA	NA	NA
Ma et al 2019 [26]	New-onset diabetes mellitus after the first attack of acute pancreatitis	Univariate and multivariate logistic regression	Age, BMI, glucose, triglyceride, and LDL-C	616	0.686	NA	NA

SAP, severe acute pancreatitis; MIMIC-III, Medical Information Mart for Intensive Care III; NA, not available; ALT, alanine aminotransferase; RDW, red cell distribution width; BUN, blood urea nitrogen; WBC, white blood cell count; SCR, serum creatinine; BISAP, Bedside Index of Severity in Acute Pancreatitis; SOFA, Sequential Organ Failure Assessment; SIRS, Systemic Inflammatory Response Syndrome; ICU, intensive care unit; eICU-CRD, eICU Collaborative Research Database; APACHE, Acute Physiology, Age, and Chronic Health Evaluation; TBIL, total bilirubin; OASIS, Outcome and Assessment Information Set; NE%, neutrophil ratio; LYMPH%, lymphocyte Ratio; eosinophil ratio, EO%; GCSI, Gastroparesis Cardinal Symptom Index; LDL-C, low density lipoprotein-cholesterol; PCD, percutaneous catheter drainage; CTSI, computed tomography severity index.

Nomograms for predicting SAP or mortality							
Bellam et al 2019 [24]	Success of percutaneous catheter drainage in patients with acute pancreatitis having acute fluid collection	Univariate and multivariate logistic regression	volume of collection after PCD and organ failure resolution after PCD	51	0.915	NA	NA
Gupta et al 2021 [22]	Mortality	Binomial logistic regression	Pancreatic necrosis, ascites, pleural effusion	103	0.79	20	0.74
	ICU stay		Number of collection, pleural effusion		0.66		0.70
	hospital stay ≥ 4 weeks		Pancreatic necrosis, number of collection, amount PE		0.75		0.77
	Readmission		Number of collection, coeliac artery		0.70		0.52
	ICU stay ≥ 2 weeks		Pancreatic necrosis, largest dimension of collection, pleural effusion		0.83		0.45
	SAP		Number of collection, liver steatosis		0.64		0.69
Zhu et al 2021 [21]	Intra-abdominal infection	LASSO regression	Intra-abdominal pressure, APACHE II score, CTSI, ICU admission, and severity grade	417	0.99	294	0.98

SAP, severe acute pancreatitis; MIMIC-III, Medical Information Mart for Intensive Care III; NA, not available; ALT, alanine aminotransferase; RDW, red cell distribution width; BUN, blood urea nitrogen; WBC, white blood cell count; SCR, serum creatinine; BISAP, Bedside Index of Severity in Acute Pancreatitis; SOFA, Sequential Organ Failure Assessment; SIRS, Systemic Inflammatory Response Syndrome; ICU, intensive care unit; eICU-CRD, eICU Collaborative Research Database; APACHE, Acute Physiology, Age, and Chronic Health Evaluation; TBIL, total bilirubin; OASIS, Outcome and Assessment Information Set; NE%, neutrophil ratio; LYMPH%, lymphocyte Ratio; eosinophil ratio, EO%; GCSI, Gastroparesis Cardinal Symptom Index; LDL-C, low density lipoprotein-cholesterol; PCD, percutaneous catheter drainage; CTSI, computed tomography severity index.

The aim of this study was to (1) develop and validate a nomogram for early predicting POF in patients with AP and (2) compare the performance of the nomogram with conventional prognostic scores in two distinct large tertiary hospitals in China.

Methods

Study design and ethics

This study followed the STROBE guidelines [27] for observational studies. The study protocol was approved by respective Institutional Review Board in these two hospitals. Data were obtained from two AP cohorts in West China Hospital of Sichuan University (WCH/SCU): retrospective datasets between 1st July 2009 and 30th June 2013 as the training cohort [9]; prospective datasets between 1st January 2016 and 31th August 2017 as the internal validation cohort [28]. For the purpose of external validation, we obtained the datasets from AP database of The First Affiliated Hospital of Nanchang University from January 2005 to December 2012 [29].

Inclusion and exclusion criteria

Inclusion criteria: (1) AP diagnosed by the RAC [10], (2) age > 18 or ≤ 80 years old, (3) time from abdominal pain onset to admission ≤ 48 hours, and (3) primary admission directly to WCH/SCU [9, 28].

Exclusion criteria included patients admitted to another hospital prior to WCU/SCU, re-admitted during the same episode of AP, chronic pancreatitis, pancreatic neoplasia, trauma, or pregnancy as AP etiologies, and advanced pre-existing comorbidities consistent with previous studies [6, 9, 28, 30]. The external validation cohort also contained transferred patients and the cases with the final formulized nomogram factors missing were excluded.

Definitions, variables, and outcome measures

Demographic features collected on admission, such as age, gender, underlying disease to score Charlson co-morbidity index and abdominal pain onset time to admission. Vital signs, laboratory parameters (routine blood and biochemical indices), details of oxygen treatment and presence of pleural effusion that were mostly obtained from nonenhanced computed tomography scan on admission. Experienced PhD students and resident doctors specializing in management of AP were stringently trained for data collection according to pre-defined *proforma* and standard operating procedures in both centers. Each *proforma* was checked and signed off by attending or more senior doctors.

Etiologies

Hypertriglyceridemia as the etiology was defined as admission serum triglyceride (TG) level > 1000 mg/dl (11.3 mmol/l) or TG > 500 mg/dl (5.65 mmol/l) with lipemic serum or a previous history of hypertriglyceridemia [31, 32]. Biliary etiology was considered if gallstones or biliary sludge was present on radiological imaging or had alanine aminotransferase over three times the upper limit of normal [33, 34]. Alcohol excess was referred if with drinking history > 35 standard drinks per week for > 5 years [35] or was deduced according to our center's own practice according to the drinking history after ruling out other etiologies.

Organ failure, local complication, and major infection

POF was defined as at least one of the systems (respiratory, circulatory, and renal) having a SOFA score ≥ 2 and lasting ≥ 48 hours [36]. Acute necrotic collection and acute peripancreatic fluid collection were defined as per RAC criteria [10]. Major infection included infected pancreatic necrosis, bacteremia, or pneumonia alone or in combination [37]. Mortality (including those who were automatically discharged with persistent multiple organ failure and had high possibility of death) and length of hospital stay were recorded for the index hospitalization.

The prognostic scores evaluated in this study were National Early Warning Score (NEWS) [38], Systemic Inflammatory Response Syndrome (SIRS) [39], Bedside Index for Severity in Acute Pancreatitis (BISAP) [40], modified Glasgow criteria [41], Acute Physiology and Chronic Health Examination (APACHE) II [42], and Sequential Organ Failure Assessment (SOFA) [43]. These were all calculated on admission (or within 6 hours of admission if absent earlier in minority of cases).

Statistical analysis

Continuous variables were expressed as median with 25th -75th percentile and were compared by Mann-Whitney *U* test (2 groups) or Kruskal-Wallis *H* test (3 groups). Categorical data were reported as number with percentage and were compared by means of χ^2 or Fisher's exact test.

The significance of each variable in the training cohort was assessed by univariate logistic regression analysis for investigating the independent risk factors of POF. All variables significantly associated with POF were candidates for stepwise multivariate analysis and the results were used to formulate a nomogram. The predictive performance of the nomogram was measured by concordance index (C-index) and calibration with 1000 bootstrap samples to decrease the overfit bias [44]. Decision curve analysis (DCA) and clinical impact curve (CIC) were used to evaluate the clinical utility of the novel model [45]. DCA is a simple, novel method of evaluating predictive models with decision analyses of diagnostic and prognostic tests by using a risk-benefit ratio [46]. CIC is another type of plot produced by Decision Curve that shows the estimated number who would be declared to having high risk for each risk threshold and visually shows the proportion of those who are cases (true positives) [45].

The area under curve (AUC) of the receiver operating characteristic (ROC) curves with 95% confidence intervals (CI) of all potential predictors were calculated. An AUC of 0.5, 0.7 to 0.8, 0.8 to 0.9, and > 0.9 was suggestive of no discrimination, acceptable, excellent and outstanding, respectively [47]. Statistical significance of the AUCs between any two predictors was compared by method of DeLong et al [48]. The optimum cut-offs for sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR) and post-test probabilities of the top predictors were derived from the ROC curves. The interpretation of the likelihood ratio was as follows: > 10, 5–10, 2–5, 1–2, and 1 representing large with often conclusive, moderate, small, minimal, and no change, respectively, for increase in the likelihood of disease (positive test), while 0.5-1.0, 0.2–0.5, 0.1–0.2, and < 0.1 representing minimal, small, moderate, and large with often conclusive, respectively for decrease in the likelihood of disease (negative test).

The analyses were performed using IBM SPSS Statistics V26.0 software (SPSS, IBM Corp; Armonk, New York, USA) and R software version 4.0.4 (http://www.Rproject.org). Two-tailed *P* value with statistical significance set at < 0.05 was used for all tests.

Results

Patient characteristics

There were 816 and 398 patients in the training and internal validation cohorts, respectively, that met the eligibility criteria (**Additional file 1: Figure S1A, B**). After removing missing values, the external validation cohort contained 880 records. The demographic profiles of the three cohorts are outlined in Table 2. The median age was 45 years old and about 70% patients were male in both training and internal validation cohorts, while median age of the external cohort was 50 years old and 60.6% were male. Hypertriglyceridemia (32.7% and 42%) was the most common etiology in our internal two cohorts when biliary (57.5%) was the main etiology in the external cohort. The baseline characteristics of patients as per RAC of the training and validation cohorts are displayed in **Additional file 2: Table S1a-c**, respectively. These results are similar to previous published studies [9, 28, 29].

Table 2
Baseline characteristics and clinical outcomes in training and validation cohorts

Variables	Training cohort	Validation cohorts	
	n = 816	(Internal) n = 398	(External) n = 880
Demographics			
Age, years*	45 (37–55)	45 (38–51)	50 (41–62)
Male	568 (69.6)	273 (68.6)	533 (60.6)
Charlson comorbidity index*	1 (0–1)	1 (0–2)	0 (0–0)
Etiology			
Biliary	230 (28.2)	78 (19.6)	506 (57.5)
Hypertriglyceridemia	267 (32.7)	167 (42.0)	184 (20.9)
Alcohol	30 (3.7)	31 (7.8)	61 (6.9)
Unknown or others	291 (35.6)	122 (30.7)	129 (14.7)
Time to admission, hours*	12 (7–24)	15 (9–24)	NA
Clinical outcomes			
Persistent organ failure	80 (9.8)	30 (7.5)	178 (20.2)
Respiratory	77 (9.4)	30 (7.5)	169 (19.2)
Circulatory	14 (1.7)	2 (0.5)	12 (1.4)
Renal	10 (1.2)	3 (0.8)	28 (3.2)
Need for HDU/ICU	59 (7.2)	29 (7.3)	168 (19.1)
Local complication			
Acute peripancreatic fluid collection	163 (20.0)	119 (29.9)	332 (37.7)
Acute necrotic collection	59 (7.2)	55 (13.8)	204 (23.2)
Major infection	45 (5.5)	20 (5.0)	53 (6.0)
Infected pancreatic necrosis	12 (1.5)	9 (2.3)	36 (4.1)
Bacteremia	15 (1.8)	6 (1.5)	13 (1.5)
Lung	35 (4.3)	9 (2.3)	18 (2.0)
Necrosectomy	14 (1.7)	13 (3.3)	17 (1.9)
Mortality	10 (1.2)	4 (1.0)	20 (2.3)
RAC			
Mild	508 (62.3)	190 (47.7)	328 (37.3)
Moderately severe	228 (27.9)	178 (44.7)	374 (42.5)
Severe	80 (9.8)	30 (7.5)	178 (20.2)
Length of hospital stay (days)*	9 (6–13)	8 (6–11)	8 (6–13)
NA, not available; HDU, high dependency unit; ICU, intensive care unit; RAC, revised Atlanta classification.			
Values in parentheses are percentages unless indicated otherwise *values are median (IQR).			

Developing and validating a nomogram for predicting POF

Demographic characteristics of clinical importance, vital signs, routine blood tests, biochemical indices, and other established risk factors on admission, but not existing prognostic scores were considered as candidate variables for developing the predictive nomogram. The independent prognostic factors for POF after univariate and multivariate logistic regression analysis were age (OR 1.03 [95% CI 1.01–0.05]; $P = 0.01$), respiratory rate (1.25 [1.10–1.42]; $P = 0.001$), albumin (0.92 [0.87–0.98]; $P = 0.013$), lactate dehydrogenase (LDH; 1.002 [1.000-1.003]; $P = 0.036$), oxygenation (5.17

[2.91–9.20]; $P < 0.001$), and pleural effusion (3.61 [1.97–6.61]; $P < 0.001$) (Table 3). These variables were finally used to construct our predictive nomogram (Fig. 1A). To facilitate the clinical application of our findings, we developed a mobile terminal-based calculator (https://shina.shinyapps.io/DynNomapp/) of the predictive nomogram (Fig. 1B, C). In the training cohort, the C-index of the nomogram was 0.88 (Fig. 2A) with good consistency between the predicted SAP and the actual POF observed shown by the calibration curve (Fig. 2B). In the internal validation cohort, the C-index of the nomogram for predicting SAP reached 0.91 (Fig. 2C) and with a better consistency (Fig. 2D) compared to the training cohort. The C-index was 0.81 (Fig. 2E) in the external validation cohort and the calibration curve also showed satisfactory consistency (Fig. 2F).

Table 3
Univariate and multivariate logistic regression analysis with stepwise variable selection

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Demographics				
Age, years	1.036 (1.019–1.053)	**< 0.001**	1.030 (1.007–1.053)	**0.01**
Gender	1.263 (0.777–2.053)	0.346		
Charlson comorbidity index	0.96 (0.684–1.346)	0.811		
Etiology	0.861 (0.711–1.043)	0.127		
Time to admission, hours	1.005 (0.984–1.026)	0.658		
Admission vital signs				
Body temperature	1.377 (0.902–2.102)	0.138		
Respiratory rate	1.352 (1.207–1.514)	**< 0.001**	1.249 (1.099–1.420)	**0.001**
Heart rate	1.029 (1.016–1.042)	**< 0.001**	1.006 (0.989–1.023)	0.499
Admission laboratory parameters				
Amylase, IU/l	1.000 (1.000-1.001)	**0.001**	1.000 (1.000–1.000)	0.448
Lipase, IU/l	1.000 (1.000–1.000)	0.096		
White blood cell, 10^9/l	1.112 (1.062–1.165)	**< 0.001**	1.085 (0.854–1.379)	0.505
Neutrophils, 10^9/l	1.115 (1.063–1.169)	**< 0.001**	0.974 (0.755–1.257)	0.839
Lymphocytes, 10^9/l	0.958 (0.709–1.293)	0.777		
NLR	1.007 (0.996–1.018)	0.186		
Platelet, 10^9/l	1.000 (0.997–1.003)	0.868		
Hematocrits, l/l	2.973 (0.023–377.4)	0.659		
Hemoglobin, g/l	1.011 (1.000-1.022)	0.057		
ALT, IU/l	1.001 (0.999–1.002)	0.247		
AST, IU/l	1.001 (1.000-1.002)	0.125		
Albumin, g/l	0.884 (0.844–0.925)	**< 0.001**	0.924 (0.868–0.984)	**0.013**
Glucose, mmol/l	1.063 (1.021–1.106)	**0.003**	1.003 (0.945–1.066)	0.915
Urea, mmol/l	1.219 (1.124–1.321)	**< 0.001**	1.105 (0.973–1.256)	0.123
Creatinine, μmol/l	1.012 (1.005–1.018)	**< 0.001**	1.001 (0.992–1.009)	0.904
Triglycerides, mmol/l	1.017 (0.993–1.041)	0.162		
Cholesterol, mmol/l	1.041 (0.977–1.109)	0.211		
Lactate dehydrogenase, IU/l	1.003 (1.002–1.004)	**< 0.001**	1.002 (1.000-1.003)	**0.036**
Calcium, mmol/l	0.093 (0.033–0.263)	**< 0.001**	0.719 (0.174–2.970)	0.648
Oxygen supporting	5.722 (3.486–9.393)	**< 0.001**	5.170 (2.905–9.202)	**< 0.001**
Pleural effusion	3.802 (2.318–6.237)	**< 0.001**	3.611 (1.973–6.610)	**< 0.001**

NLR, neutrophil to lymphocyte ratio; LDH, lactate dehydrogenase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Clinical utility of the nomogram

The nomogram of training cohort (Fig. 3A, B), internal validation cohort (Fig. 3C, D), and external validation cohort (Fig. 3E, F) exhibited better or equal clinical utility (DCA) with the other prognostic scores and had good clinical net benefits (CIC) for the identification of SAP patients. Of particular note, the nomogram outperformed all other indices in the internal validation cohort suggesting that it could help clinicians to obtain maximum benefit when making clinical decisions as it showed more benefit than the extreme situation of diagnosing POF in all patients or none.

Comparison the nomogram with prognostic scores

Prediction of POF

There were 9.8% (80/816), 7.5% (30/398) and 20.2% (178/880) patients that developed POF in the training, internal validation and external validation cohorts, respectively (Table 2). BISAP had the highest predictive value (AUC 0.89 [0.87–0.91], PLR 7.24) for POF compared with the other indices (Table 4; *upper panel*) and followed by the nomogram (AUC 0.88 [0.86–0.91], PLR 4.26), both higher than APACHE II (0.79 [0.76–0.82], PLR 3.61) and Glasgow (0.75 [0.72–0.78], PLR 2.89) ($P < 0.05$, **Table S2**) in training cohort. The nomogram showed the best predictive value (0.91 [0.88–0.94], PLR 7.89, Table 4; *middle panel*) in internal validation cohort and higher than all other clinical scoring systems ($P < 0.05$; **Additional file 2: Table S2**), followed by NEWS (0.79 [0.75–0.83], PLR 2.80) and BISAP (0.75 [0.71–0.79], PLR 5.72). In addition, the NLR (0.11) of the nomogram ranked the best among all the comparative indices, with the lowest post-test probability of not being POF (0.9%) indicating a high negative prediction value. The nomogram also ranked the top AUC (0.81 [0.79–0.84]), lowest NLR (0.29) and post-test probability of not being POF (6.7%) among all the indices in the external validation cohort (Table 4; *lower panel*), with the AUC higher than NEWS, BISAP, APACHE II and SIRS ($P < 0.05$; **Additional file 2: Table S2**).

Table 4
Predictive value of the nomogram and clinical prognostic scores for persistent organ failure

	AUC	*P* value	Cut-off	Sensitivity (%)	Specificity (%)	PLR	NLR	Post_Prob_Pos (%)	Post_Prob_Neg (%)
Training cohort *(9.8% pre-test probability)*									
Nomogram	**0.88** (0.86–0.91)	< 0.001	91.2	78.8	81.5	4.26	0.26	31.7	2.8
NEWS	0.85 (0.82–0.87)	< 0.001	4	66.3	88	5.54	0.38	37.6	4
BISAP	**0.89** (0.87–0.91)	< 0.001	2	78.8	89.1	**7.24**	0.24	44.0	2.5
APACHE II	0.79 (0.76–0.82)	< 0.001	6	61.3	83	3.61	0.47	28.2	4.9
SIRS	0.84 (0.81–0.86)	< 0.001	2	91.3	74.6	3.59	0.12	28.1	1.3
Glasgow	0.75 (0.72–0.78)	< 0.001	2	61.3	78.8	2.89	0.49	23.9	5.1
SOFA	0.87 (0.84–0.89)	< 0.001	1	85	81.2	4.53	0.18	33.0	1.9
Validation cohort									
Internal validation (7.5% pre-test probability)									
Nomogram	**0.91** (0.88–0.94)	< 0.001	79.2	90	88.6	**7.89**	**0.11**	39.1	**0.9**
NEWS	**0.79** (0.75–0.83)	< 0.001	4	70.0	75.0	2.80	0.40	18.5	3.1
BISAP	0.75 (0.71–0.79)	< 0.001	2	46.7	91.9	5.72	0.58	31.7	4.5
APACHE II	0.66 (0.61–0.71)	0.005	6	36.7	89.4	3.46	0.71	21.9	5.4
SIRS	0.68 (0.63–0.72)	< 0.001	2	70.0	61.4	1.81	0.49	12.8	3.8
Glasgow	0.69 (0.64–0.73)	< 0.001	3	46.7	80.7	2.42	0.66	16.4	5.1
SOFA	0.73 (0.68–0.77)	< 0.001	2	63.3	75.8	2.62	0.48	17.5	3.7
External validation (20.2% pre-test probability)									
Nomogram	**0.81** (0.79–0.84)	< 0.001	69.4	79.8	70.9	2.75	**0.29**	41	**6.7**
NEWS	0.76 (0.73–0.79)	< 0.001	5	62.4	78.6	2.92	0.48	42.5	10.8
BISAP	0.75 (0.72–0.78)	< 0.001	2	53.4	84.3	3.41	0.55	46.3	12.3
APACHE II	0.75 (0.72–0.78)	< 0.001	9	56.2	80.8	2.92	0.54	42.6	12.1
SIRS	0.73 (0.70–0.76)	< 0.001	2	68.0	69.2	2.21	0.46	35.9	10.5
Glasgow	0.78 (0.75–0.81)	< 0.001	3	59.6	82.5	3.4	0.49	46.3	11.1
SOFA	0.80 (0.77–0.83)	< 0.001	2	63.5	85.0	4.24	0.43	51.8	9.8

AUC, area under curve; PLR, positive likelihood ratio; NLR, negative likelihood ratio; Post_Prob_Pos, post-test probability of a positive test; Post_Prob_Neg, post-test probability of a negative test; NEWS, National Early Warning Score; BISAP, Bedside Index for Severity in Acute Pancreatitis; APACHE II, Acute Physiology and Chronic Health Examination II; SIRS, Systemic Inflammatory Response Syndrome; SOFA, Sequential Organ Failure Assessment.

Prediction of major infection

There was 5.5% (45/816), 5.0% (20/398) and 6.0% (53/880) had infection in the training, internal and external validation cohorts, respectively. In the training cohort, the accuracy of these predictors was generally low with BISAP (0.75 [0.72–0.78], PLR 4.29) having the highest predictive value compared with the other indices in training cohort (**Additional file 2: Table S3**; *upper panel*), but there was no statistical difference between any of them (**Additional file 2: Table S2**). In both the internal and external validation cohorts, the nomogram showed the best predictive value (highest AUC 0.78 [0.73–0.82]/0.80 [0.77–0.83]; lowest NLR 0.47/0.22; lowest post-test probability of not being major infection 2.4%/1.4 %; **Additional file 2: Table S3**; *middle and lower panels*).

Prediction of mortality

There was 1.2% (10/816), 1.0% (4/398) and 2.3% (20/880) mortality in the training, internal validation and external validation cohorts, respectively. All the deaths were from patients with POF in the three cohorts (12.5%, 13.3% and 11.2%; **Additional file 2: Table S1a-c**). In both the training and external cohorts, the nomogram (AUC 0.88 [0.85–0.90], 0.89 [0.87-.91]) showed the equivalent predictive values for mortality with most of the clinical scoring systems (**Additional file 2: Table S4**). In the internal validation cohort, the nomogram had the highest predictive values (0.99 [0.98-1.00], PLR 32.8, NLR 0.26) for mortality, followed by BISAP (0.95 [0.92–0.97], PLR 9.85), and NEWS (0.90 [0.86–0.93], PLR 29.6, NLR 0.26), all higher than the remaining clinical scores (**Additional file 2: Table S4**).

Discussion

In this study, we developed and validated a mobile terminal-based nomogram for predicting POF, major infection, and mortality using six independent prognostic factors (age, respiratory rate, albumin, lactate dehydrogenase, oxygenation, and pleural effusion) that readily available on admission. This nomogram was found to be superior with the both internal and external validation cohort compared with other prognostic scores recommended for clinical use for predicting POF and major infection. As POF is the diagnostic criteria for SAP, this nomogram is recommended for routine clinical use to predict SAP on admission or to rule it out (validation NLR 0.11/0.29). Therefore, these findings encourage the use of the simple-to-use web-based nomogram before new markers are developed and introduced in our settings. The consecutive nature of patient recruitment and short time from onset of pain to admission, stringently applied in two large different Chinese centers, adds strength to these conclusions.

Age is recognized as an individual risk factor for increased severity of AP and has been used by several prognostic scores [12, 13] and practice guidelines [49–51]. To investigate the role of age and comorbidity in the severity of AP, Frey *et al.* [52] carried out a retrospective study in 84,713 patients with a first-attack AP. They found that the 65 to 75 age group, and age > 75 are strong predictors of early death with an odds ratio (OR) of 2.6 and 5.2, respectively. Similar findings also applied to patients with two chronic comorbidities (OR: 3.5) or ≥ 3 comorbidities (OR: 7.4). Moreover, the mortality rate was only 0.1% (14/14,280) for younger patients (age < 55) without chronic comorbidities compared to 5.9% (701/24,852) for elderly patients (age > 64) with ≥ 3 comorbidities in the first 14 days. In addition, they showed that recent cancer, heart failure, and renal and liver diseases are strongly correlated with outcomes. Further, in acute interstitial AP, which is known to have low mortality, the Charlson comorbidity index was strongly associated with adverse clinical outcomes [53]. Because of the significant impact of the degree and number of comorbidities on clinical outcomes, we therefore excluded patients with advanced (end-stage) comorbidities with an emphasizing on assessing the intrinsic prognostic factors for AP severity.

Hypoalbuminemia occur in critically ill patients due to several factors including dilution from resuscitation, increased interstitial loss, altered liver function, and catabolic nutritional state [54]. It is strongly associated with poor clinical outcomes in acutely ill patients [55] and it has also been shown to independently associated with POF and mortality in AP patients [56, 57]. Whitcomb *et al.* [58] has recently found that albumin dropped rapidly in AP patients with multiple organ failure resulting in unregulated capillary leak with continued loss of larger plasma proteins. In contrast, the plasma albumin levels only dropped slightly in patients without multiple organ failure who tended to recover quickly unless they develop complications (infected pancreatic necrosis or sepsis). The therapeutic effect of albumin in inflammatory states is not only by affecting plasma volume dilation, but also by regulating inflammation and oxidative stress [59, 60]. Therefore, serum albumin level has been incorporated in some AP severity prognostic indices (Glasgow criteria [41] and nomogram [18]).

Raised lactate levels has been observed in many critical acute illness situations including sepsis [61] and AP [62–64]. Elevated lactate may serve as a protective mechanism and has been shown to reduce Toll-like receptor and inflammasome-mediated pancreatic and liver injury via its receptor GPR81 [65]. LDH can reversibly catalyze the oxidation of lactate to pyruvate and has been employed by Ranson, Glasgow, Japanese Severity Score [13], and a nomogram [17] for early AP severity prediction and reported as a simple and useful parameter for predicting POF [66, 67], and pancreatic necrosis [68]. Moreover, urinary LDH has also been reported as an useful biomarker for septic acute kidney injury [69].

Respiratory rate and oxygen support reflect respiratory status and with respiratory failure as one most common organ dysfunction in AP [9], the early recognition of respiratory dysfunction is considered important. Our results showed a positive association between the development of POF and an increased respiratory rate or requirement for oxygen support on admission. Therefore, both respiratory rate and oxygen support have been adopted in NEWS [38] for their convenience and prognostic value. The significance of pleural effusion in AP patients has been long reported [70], and is part of BISAP [40]. Our results showed that pleural effusion (odds ratio: 3.61 95%CI 1.97–6.6, $P < 0.001$) was an independent predictor for SAP, consistent with a previous study [71].

In our univariate analysis before establishing the predictive nomogram, we also found white blood cell count [13], glucose [13, 72], urea (or blood urea nitrogen) [6, 13], creatinine [13], and ionized calcium [13] were independent individual prognostic factors for POF, consistent with previously published literature. However, when these parameters were fitted into our multiple logistic regression model, they only had negligible impact on the final nomogram. Unlike most previously published studies included high proportion of SAP patients, we used a training consecutive cohort constituted only up to 10% of SAP patients which may partially explain different weights of individual prognostic factors in varied epidemiology situations. For example, three of the four existing predictive nomograms for AP severity were conducted in the ICU settings which cannot be generalizable for emergence departments or general wards where patients are primarily admitted.

Some of the six independent prognostic factors of our nomogram are included as part of NEWS (respiratory rate and oxygen support) and BISAP (age, respiratory rate, and pleural effusion), the two that we found had justifiable good predictive values for POF in both our training and internal validation cohorts. However, the nomogram was simpler than BISAP and more AP-specific than NEWS to quantitatively predict clinical outcomes in a personalized way. In addition, we validated the nomogram in another Chinese tertiary hospital with the etiological composition different from ours. The results showed that the nomogram with stable clinical applicability in both AP cohorts with hypertriglyceridemia (internal validation) or biliary (external validation) as the main etiology, adding strength to its applicability.

Our study also has some limitations. Firstly, the nomogram model was developed mainly based on the variables that were easy to get in our retrospective sets, but did not include other factors that may influence the precision of the model. For example, the oxygenation index was not included in our analysis because only paucity data were available. In a most recent study [73], the authors found that oxygenation index had low prognostic power (AUC 55.3%) for acute respiratory distress syndrome. Secondly, the nomogram did not have specific markers for circulatory and renal failure. The reasons for this may be attributed to low incidence of circulatory and renal failure of the study population and at the early disease stage respiratory failure commonly precedes other organ failures [5, 8]. Thirdly, the lack of international validation may limit the extrapolation and generalizability of the nomogram.

Conclusions

Our nomogram based on six readily available factors accurately predicted POF on admission in patients with AP. This nomogram can be routinely used for early AP severity prediction in our clinical practice if further validated in multiple center studies.

Abbreviations

AP: acute pancreatitis; POF: persistent organ failure; SAPS: severe acute pancreatitis; RAC: revised Atlanta classification; MIMIC-III: Medical Information Mart for Intensive Care III; eICU-CRD: eICU Collaborative Research Database; WCH/SCU: West China Hospital of Sichuan University; NEWS: National Early Warning Score; SIRS: Systemic Inflammatory Response Syndrome; BISAP: Bedside Index for Severity in Acute Pancreatitis; APACHE: Acute Physiology and Chronic Health Examination; SOFA: Sequential Organ Failure Assessment; C-index: concordance index; DCA: decision curve analysis; CIC: clinical impact curve; AUC: area under curve; ROC: receiver operating characteristic; CI: confidence intervals; PLR: positive likelihood ratio; NLR: negative likelihood ratio; LDH: lactate dehydrogenase.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of West China Hospital of Sichuan University and The First Affiliated Hospital of Nanchang University.

Consent for publication

All authors have provided consent for publication of the manuscript.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

QX, WH, and YZ obtained funding, and concepted, designed and supervised the study. NS collected, analyzed all retrospective and prospective data of Chengdu center, and drafted the manuscript. XZ collected and analyzed all retrospective data. WHe, LX, NL, and YZ provided and analyzed external validation datasets. LL, WC, LY, XY (Xinmin Yang) and RZ supported collecting data. PZ assisted data analysis. LD, TJ, ZL and KJ audited data quality. GJ and XY (XiaonanYang) supervised the patients' treatment. WH and QX designed, TW and PS assisted, RS reviewed the proforma and e-database. VKS, RS, and JAW had important intelligence input. WH and JAW critically revised the manuscript. All authors read and approved the final manuscript.

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Figures

Fig 1

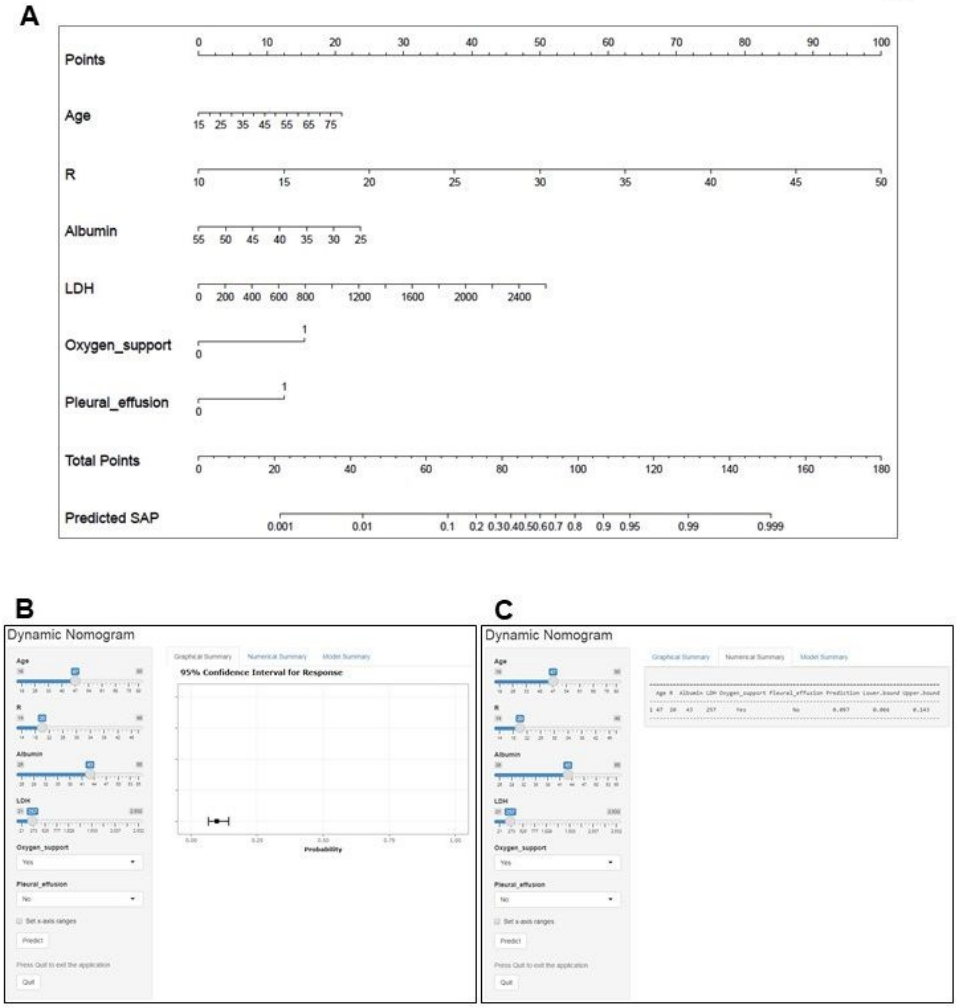

Figure 1

Nomogram for predicting POF in patients with AP and dynamic web-based calculator. The score for each value is assigned by drawing a line upward to the points line, and the sum of the six scores is plotted on the total points line (A). Web POF rate calculator with 95% CI in both graphical (B) and numerical (C) summary.

Fig 2

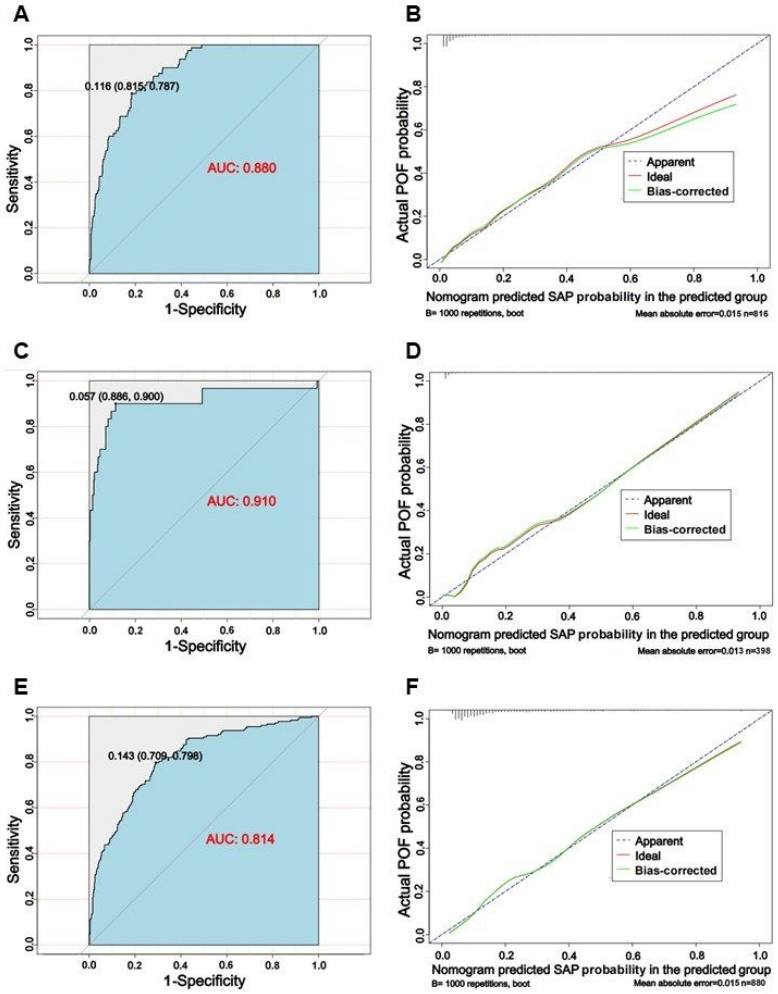

Figure 2

Assessment of the nomogram in all three cohorts. The accuracy of the model was determined using AUC analysis and the distribution of the predicted probabilities presented by calibration curve for cohorts of the training (A, B), internal validation (C, D), and external validation (E, F).

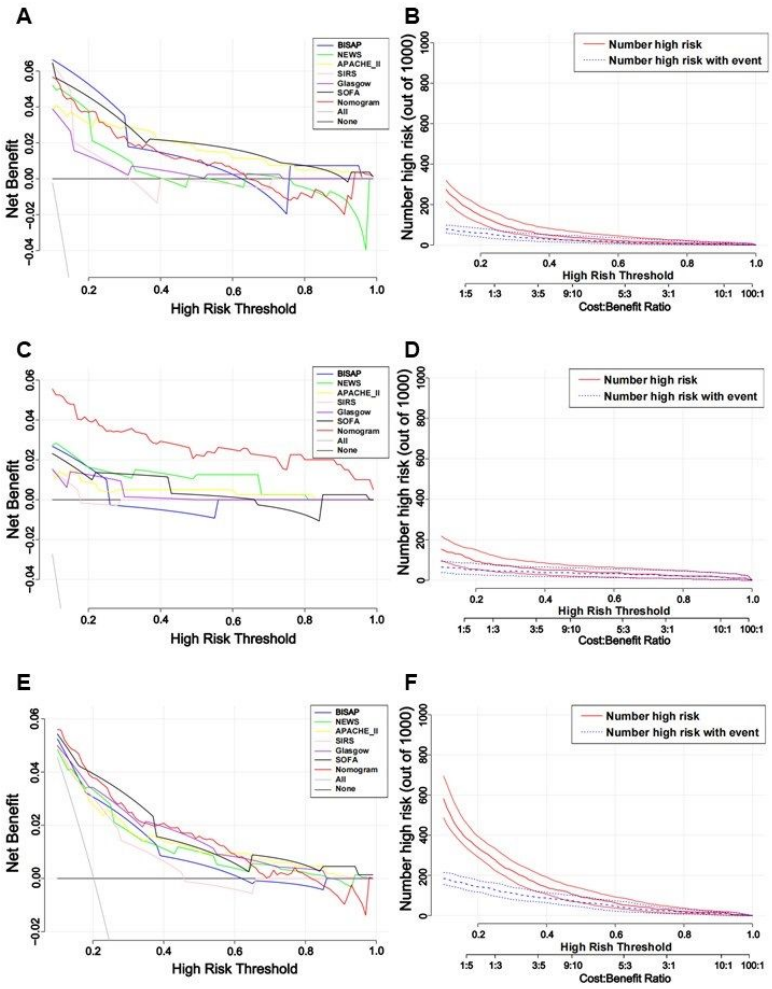

Figure 3

Clinical utility of the nomogram. The DCA and CIC of the nomogram for predicting POF in cohorts of training (A, B), internal validation (C, D), and external validation (E, F).

Supplementary Files

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