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Establishment and verification of a nomogram for predicting severe acute pancreatitis

X. CAO[1], H.-M. WANG[1], R. LU[1], X.-H. ZHANG[2], Y.-L. QU[3], L. WANG[1], S.-L. WANG[1], S.-W. BAI[1], X. LIU[1], L. MA[1], Y. XIONG[1], X.-F. YANG[1], Z.-F. SHE[1]

[1]Department of General Surgery, Ordos Central Hospital, [2]Ordos Clinical Medical College of Inner Mongolia Medical University, Inner Mongolia, P.R. China
[3]XiangYa School of Medicine, CSU, P.R. China

Xi Cao and Huai-Ming Wang equally to this study are co-first authors

Abstract. – OBJECTIVE: The purpose of this study was to establish a nomogram for predicting the severity of acute pancreatitis (AP) and verify its predictive value.

PATIENTS AND METHODS: A total of 571 AP patients received by Ordos Central Hospital from January 2015 to December 2018 were included in this study. According to the 2012 Revised Atlanta classification, the included subjects were classified into severe AP (SAP) group and non-severe AP (NSAP) group [including patient with mild AP (MAP) and moderately SAP (MSAP)]. The baseline characteristics, imageological data and pathological data within 24 h after the disease onset between the two groups were analyzed using One-way analysis of variance (one-way ANOVA). R language was used for establishing a predictive nomogram, whose performance was verified by clinical data of 150 AP cases collected from December 2018 to December 2019.

RESULTS: One-way ANOVA shows that SAP and NSAP patients show significant differences in sex, calcium ions, creatinine, neutrophils ratio, lymphocytes ratio and eosinophils ratio ($p<0.05$). A predictive nomogram was accordingly established using the six indicators. Validation on this predictive nomogram showed high internal validation concordance index (C-index) of 0.69 (95% CI, 0.64-0.74), and high external validation C-index of 0.71 (95% CI, 0.67-0.76).

CONCLUSIONS: This nomogram can be used as a clinical tool to predict the severity of SAP.

Key Words:
Severe acute pancreatitis, Nomogram, Prediction, Validation.

Introduction

Acute pancreatitis (AP) is a common type of acute abdominal diseases, characterized by sudden onset, rapid progress and wide variances in the severity. The Atlanta Classification Criteria for AP revised in 2012[1] classified AP into three categories: mild AP (MAP), moderate severe AP (MSAP) and severe AP (SAP). MAP, accounting for the majority of all AP cases, is manifested by controllable symptoms such as abdominal pain, gastrointestinal symptoms and pancreatic edema. In addition to these clinical manifestations, MSAP also had transient organ failure which can self-recover within 48 hours. Fortunately, most MASP patients have good prognosis and low fatality rate. However, SAP, characterized by persistent organ failure, as well as local complications, had a mortality rate of 36-50%[2].

Therefore, early assessment of AP severity, especially the prediction of SAP, together with appropriate clinical intervention and treatment, will greatly improve the prognosis of SAP patients[3]. Various scoring systems are available for AP assessment, including Ranson, BISAP, APACHE-II and MCTSI scores[4-6]. Moreover, many studies have demonstrated that laboratory indicators, such as the neutrophil-lymphocyte ratio[7], red blood cell distribution width and serum calcium[8] can also predict the severity of AP. However, the above-mentioned scoring systems are complicated and require considerable data collection. Some standards, such as the APACHE-II score system, are not initially used for AP assessment and thus not sensitive enough. In this case, clinical evaluation of sensitive indicators for AP is of great value for AP classification.

Factors from above-mentioned scoring systems and laboratory detections were selected for analysis with clinical data from AP patients admitted from January 2015 to December 2018 to establish an early prediction model of SAP. The nomogram

Corresponding Author: Zhan-Fei She, MD; e-mail: 3534626406@qq.com

prediction model was verified with data collected from patients admitted in hospital from December 2018 to December 2019. By establishing a nomogram prediction model, this study aims to provide a basis for early clinical prevention and treatment of SAP.

Patients and Methods

Sample Selection

Patients diagnosed with AP after admission to the Ordos Central Hospital were selected in this study. The diagnosis of AP was strictly in accordance with the 2012 revised Atlanta classification[1] and confirmed by any two or more of the following criteria: (1) abdominal pain consistent with AP (acute onset of a persistent, severe epigastric pain, often radiating to the back); (2) serum amylase and/or lipase activity at least three times higher than the upper limit of normal; and (3) characteristic findings of AP on contrast-enhanced computed tomography (CECT) and magnetic resonance imaging (MRI) or transabdominal ultrasonography. Patients meeting any of the following criteria were excluded: (1) have or had pancreatic malignancies; (2) concurrent immune diseases; (3) incomplete clinical data or received midway; (4) chronic pancreatitis. This study was approved by the Ethics Committee of Inner Mongolia Ordos Central Hospital, and all participants had signed the informed consents.

Research Method

A retrospective analysis was conducted on data of 571 AP cases from January 2015 to December 2018. These patients were classified into non-severe AP (NSAP) group (including MAP and MSAP patients) and SAP group. General information (sex, age, disease history, etiology and body mass index (BMI), imageological data (with or without necrosis) and laboratory detection data (alanine aminotransferase, aspartate aminotransferase, albumin, blood urea nitrogen, creatinine, blood glucose, serum kalium, sodium ion, calcium ion, white blood cells, red blood cells, red cell distribution width, platelet, platelet distribution width, neutrophil ratio, lymphocyte ratio, eosinophil ratio, fibrinogen) of AP patients within 24 hours of onset were statistically analyzed. Variables with significant differences were used for establishing a predictive nomogram, whose accuracy was verified by prospective analysis on the 48-hour data of 150 AP patients from December 2018 to December 2019.

Statistical Analysis

Statistical analysis was conducted using SPSS 23.0 software (SPSS Corp., Armonk, NY, USA). Normally distributed data were described as $x \pm s$, and the differences between groups were analyzed by two independent samples *t*-test. Data of non-normal distribution were compared by the rank sum test, and comparison between groups was conducted using chi-square test. $p<0.05$ is considered of statistical significance. R language was used to incorporate statistically significant variables to draw the nomogram. Concordance index (C-index) was used to verify its performance by internal (predicted group data) and external validation (verification group data).

Results

Baseline and imaging characteristics. There were no significant differences in age, history of diabetes, etiology or body mass index between MAP/SMAP and SAP group. The primary etiology of acute pancreatitis was gallstone disease (192 in the MAP/SMAP group and 10 in the SAP group), followed by hyperlipemia (141 in the MAP/SMAP group and 10 in the SAP group). Differences in necrosis was not statistically significant in the early stages of pancreatitis in the two groups. The male by patients in the SAP group was significantly higher than patients in the MAP/SMAP group (both $p<0.05$; Table I).

Between the MAP/SMAP and SAP group, no significant differences in alanine aminotransferase, aspartate aminotransferase, albumin, blood urea nitrogen, creatinine, blood glucose, serum kalium, Sodium ion, calcium ion, white blood cells, red blood cells, red cell distribution width, platelet, platelet distribution width, neutrophil ratio, lymphocyte ratio, eosinophil ratio, fibrinogen were determined. Differences in calcium ion (Ca^{2+}), creatinine (Cr), neutrophil ratio (NE%), lymphocyte ratio (LYMPH%) and eosinophil ratio (EO%) were statistically significant ($p<0.05$; Table II).

A total of six parameters were used in the comparative analysis between the two groups (Sex, Ca^{2+}, Cr, NE%, LYMPH% and EO%), which were assessed by univariate regression analysis. The results of the bootstrap analysis of 200 resamples (Figure 1) indicated that univariate analysis conformed six predictors of SAP.

The nomogram was designed (Figure 2) to determine the association of these six factors with the probability of SAP. The corresponding score

Table I. Baseline and imaging characteristics between MAP/SMAP and SAP group.

Characteristics	MAP/SMAP	SAP	p
Number	538	33	
Male/Female	386/152	30/3	0.016
Age(years)	47.1±15.0	47.1±12.6	0.987
History of diabetes mellitus	35	5	0.068
Etiology			
Gallstone	192	10	0.873
Hyperlipemia	141	10	
Alcohol abuse	125	7	
Other	80	6	
Body mass index (kg/m^2)	28.4±4.3	29.1±4.6	0.775
Necrosis (yes/no)	44/484	6/27	0.235

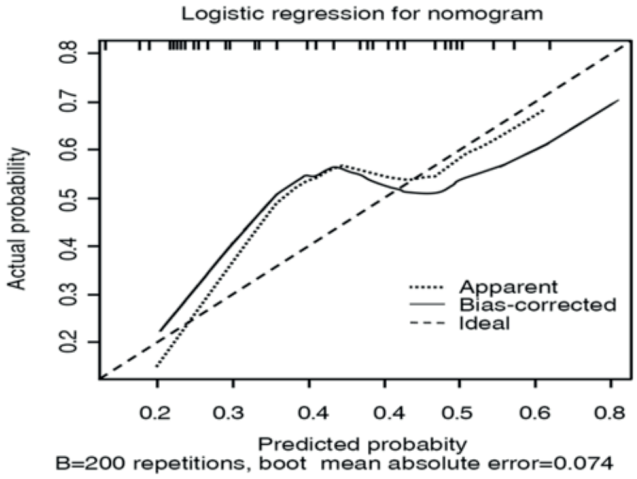

Figure 1. The model with the identified predictors was further conformed by bootstrapping based on 200 bootstrap resamples. These predictors include a reduction of Sex, Ca2+, Cr, NE%, LYMPH% and EO%. Data from these predictors were applied for the calibration. The bias corrected curve was close to the ideal curve, which indicated that the nomogram was well calibrated.

Table II. The laboratory parameters between MAP/SMAP and SAP group.

Variable	MAP/SMAP	SAP	p
ALT (u/l)	74.8±128.0	79.6±104.2	0.842
AST (u/l)	75.8±153.5	91.6±160.8	0.594
Albumin (g/l)	42.3±6.4	39.6±8.2	0.075
BUN (mmol/l)	5.6±13.8	7.1±4.3	0.535
Cr (umol/l)	70.7±35.7	91.8±52.9	0.031
Glucose (mmol/l)	8.4±3.7	9.2±3.9	0.253
k (mmol/l)	4.0±0.5	3.9±0.5	0.565
Na (mmol/l)	137.8±7.8	136.0±4.0	0.199
Ca (mmol/l)	2.2±0.5	2.0±0.5	0.048
WBC (10^9/l)	12.3±4.9	13.8±4.9	0.093
RBC (10^{12}/l)	4.9±0.6	4.9±0.8	0.974
RDW(%)	13.1±2.3	14.5±4.9	0.122
PLT (10^9/l)	216.3±72.8	191.5±73.7	0.067
PDW (%)	13.0±6.7	12.1±2.2	0.462
NE%	78.1±12.6	83.5±8.3	0.002
LYMPH%	13.7±9.0	8.9±6.1	0.000
EO%	0.8±1.3	0.2±0.3	0.000
Fibrinogen (g/l)	3.6±2.1	3.6±1.7	0.967

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BUN, blood urea nitrogen; Cr, Creatinine; K, serum kalium; Na, Sodium ion; Ca^{2+}, calcium ion; WBC, white blood cells; RBC, red blood cells; RDW, red cell distribution width; PLT, platelet; PDW, platelet distribution width; NE%, neutrophil ratio; LYMPH%, lymphocyte ratio; EO%, eosinophil ratio.

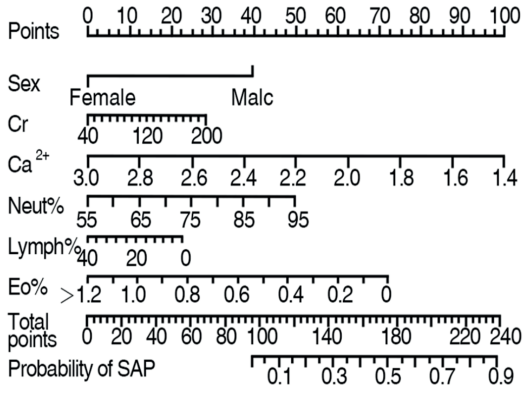

Figure 2. Nomogram for the predictors of SAP in patients with acute pancreatitis. The sum of the 6 results can be found on the 'Total points' line. The line 'Probability of SAP (%)' was synchronized with the 'Total points' line, which determines the probability of SAP. SAP, severe acute pancreatitis.

of each variable is calculated by the R language nomogram Ex package. Each patient can calculate the total score based on the nomogram or the score of a single variable in Figure 2. Then, we obtained the corresponding probability of SAP on the nomogram based on the total score.

Verification of nomogram prediction accuracy. The nomogram was drawn based on the above six independent risk factors. The internally verified (predictive group) C-index is 0.69 (95% CI 0.64-0.74), externally verified (validation group) C index is 0.71 (95% CI is 0.67-0.76) and probability of SAP calibration curve suggests good consistency in both internal validation and external validation groups (Figure 3A and 3B).

Discussion

With the annually increasing prevalence of AP, early, quick and effective screening of patients with high-risk of SAP poses a huge challenge for clinical treatment. Collected evidence showed that in clinical practice, the classification and prognosis of AP are mainly assessed based on scoring systems.

The Ranson scoring system, initially proposed by Ranson et al[9] in 1974, assesses 11 relevant indicators collected at the time of admission and within the first 48 hours after admission. The Ranson scoring system is sensitive and specific for AP with certain value in predicting AP-related systemic complications[10]. In 2018, Kiat et al[11] used the Ranson scoring system to predict the AP severity of 669 patients with well-documented information, and demonstrated the value of Ranson scoring system in assessing the severity of AP within 48 hours of disease onset. Yet, Ranson scoring system had a low specificity, which requires the attending physician to have keen judgment and clinical diagnosis ability. In the same year, Harshit Kumar et al[12] prospectively analyzed 50 AP cases using the Ranson, APACHE II or BISAP scores, and the results

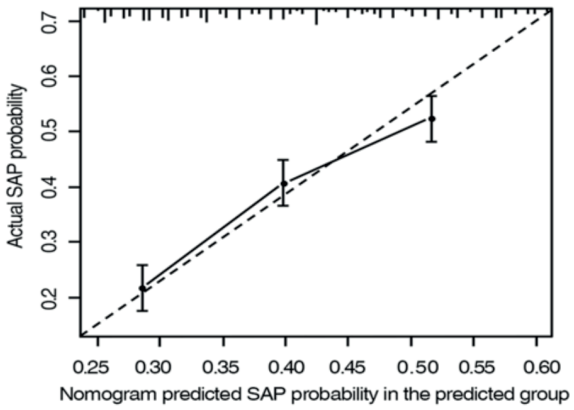

Figure 3A. Probability of SAP calibration curve on the predictive group (X-axis represents the SAP rate Predicted by the nomogram, Y-axis represents the actual SAP rate of the patient, and the accuracy of the nomogram is reflected by the fit between the solid line and the dotted line in the figure, which indicates that the fit is good.

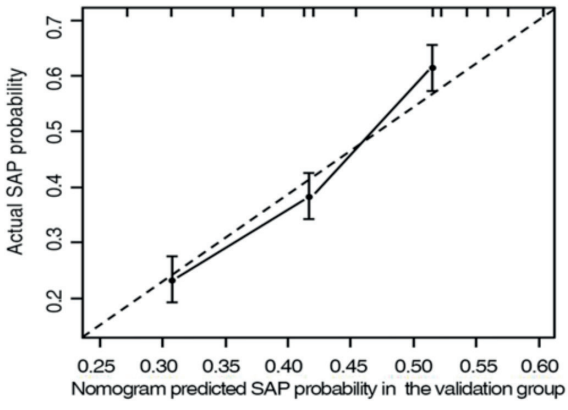

Figure 3B. Probability of SAP calibration curve on the validation group (X-axis represents the SAP rate predicted by the nomogram, Y-axis represents the actual SAP rate of the patient, and the accuracy of the nomogram is reflected by the fit between the solid line and the dotted line in the figure, which indicates that the fit is good.

show that the Ranson scoring system requires 48 hours after admission to obtain the complete data, among which some data, such as arterial PO2 and fluid retention, are difficult to obtain using routine methods. In addition, Ranson scoring system cannot dynamically display disease progress. In this case, the critical period of AP treatment will be missed, which may in turn upset the clinical application of the Ranson scoring system. APACHE II is currently the most widely used and authoritative evaluation system for critical illness in ICU. It was firstly proposed by Knaus et al[13] in 1981 and has been thereafter applied for ICU evaluation and prognosis. The APACHE II scoring system includes assessment of acute physiology, age and chronic health. This scoring system is generally feasible because it involves considerable indexes. Wu et al[14] proposed the BISAP score in 2008 which consists of five major indicators: blood urea nitrogen, impaired mental status, systemic inflammatory response syndrome, age and pleural effusion. The BISAP scoring system, once published, has been widely used in clinical practice due to the simple operation, short time period and easy acquisition of each variable. The prognostic value of BISAP score for AP has been verified by more and more scholars. In a comparison analysis of the same-staged AP scored by BISAP, APACHE-II, Ranson, CT severity index (CTSI) and other laboratory indicators, BISAP and APACHE-II were found to exhibit great value for predicting AP severity, organ failure and mortality. BISAP was more effective than Ranson score, CTSI, and laboratory indicators such as C-reactive protein (CRP), hematocrit and BMI[4].

Our analysis on the collected AP cases suggests that there are six indicators that can predict the onset of SAP, and that males are more likely to have SAP. Among studies published in the past five years, few were conducted for the association between sex and SAP. Nonetheless, Weitz et al[15] found that female are more commonly affected by biliary pancreatitis while male are by alcoholic pancreatitis. The high prevalence of SAP in male can be explained by the following two reasons. First, patients with alcoholic pancreatitis are at high risk of pancreatic hemorrhage and necrosis as well as persistent organ failure. Moreover, alcohol can cause reoccurrence of pancreatitis, which damages endocrine and exocrine functions of the pancreas and finally leads to SAP. At the early stage of SAP, exocrine cell injury and pancreatic duct blockage impede the normal release of pancreas-secreted lipase to small intestine. These lipases effuse to the periphery of the pancreas and liquefy the adjacent adipose tissue, thereby resulting in the production and accumulation of fatty acids which later enter the blood and cause abnormally increased blood content of lipase[16]. Fatty acids combine with calcium to form fatty acid calcium and blood calcium is thereby decreased as a large amount of calcium ions (Ca^{2+}) are consumed. As AP worsens, blood calcium will continue to decrease.

Gravito-Soares et al[8] analyzed the blood calcium content in 312 AP patients and found that calcium was a determinant of the severity and mortality of AP. The area under curve of calcium in assessing AP is 0.820 (0.743-0.897), with a cutoff value of 1.671, sensitivity of 85.7% and specificity of 76.4. Analysis of the cut-off value in the nomogram obtained a high score of 85, indicating for the high possibility of SAP. Another study detected that MAP patients had a higher level of blood calcium than SAP patients, which suggested that serum calcium might be a potential indicator for the severity of AP[17]. Ca^{2+} level accounts for a large proportion in our nomogram, with lower Ca^{2+} indicating higher risk of SAP.

Creatinine (Cr) is a critical indicator for kidney function. The increase of Cr in SAP may be attributed to the following reasons: (1) pancreatic inflammation-induced release of pancreatic enzymes which damage body tissues including muscles, leading to the elevated Cr in blood; (2) activation of a large number of inflammatory cytokines also increases the Cr; (3) simultaneous attack of hypotension or shock leads to insufficient renal perfusion and prerenal dysfunction. Hong et al[18] collected the serum creatinine (SCr) values of 647 patients upon admission and 24 hours later, and found that SCr was significantly related to the occurrence of SAP ($p<0.01$).

Neutrophils (NE) accumulate locally by chemotaxis during the inflammatory process of AP and cause microvascular embolism and thrombosis by adhesion to pancreatic duct endothelial cells, which aggravates pancreatic microcirculation disorders. Activated NE produces oxygen free radicals and proteolytic enzymes, which directly cause damage to the pancreas and surrounding tissues. AP is further exacerbated as NE activation progresses to an inflammatory cascade and induces syndromes like systemic inflammatory response syndrome (SIRS) and mul-

tiorgan dysfunction syndrome (MODS)[19]. Meanwhile, due to enhanced apoptosis of peripheral blood lymphocytes (LYMPH), blood LYMPH is relatively reduced and the amount of reduction is closely related to the severity of AP[20]. Therefore, NE and LYMPH are oppositely altered during AP, and thus, have potential in predicting the severity of this disease.

Eosinophil (EO) is mainly investigated in the fields of chronic obstructive pulmonary disease[21], variant rhinitis[22] etc., but seldom in AP. Evidence suggests that in case of infection of unknown origin, EO (< 0.04g/L) can serve as a sign of bacterial infection[23]. In our research, lower EO% indicates higher risks of infection and SAP. Since the role of EO in AP has rarely been reported, it is still necessary to further clarify the association between AP and EO.

The present research extracts data of interest from AP patients according to clinical, imageological and laboratorial detections. Six clinically significant and easily detectable indicators (sex, Cr, Ca^{2+}, NE%, LYMPH% and EO%) were selected to establish the nomogram for predicting SAP. The accuracy of the nomogram is validated by internal and external validation. The nomogram score is of great significance for clinicians to quickly monitor and assess the progress of AP. For example, an AP patient admitted to the hospital for the first attack (male, Cr = 90, Ca^{2+} = 2.1, NE% = 80%, LYMPH% = 11%, and EO% = 0.2%) is scored 213 points (40, 10, 55, 30, 20 and 60 points respectively) based on the nomogram, which indicates for 75% possibility for developing into SAP. All the above indicators are biochemical, and the occurrence possibility of SAP can be obtained within 1 minute using this nomogram (Figure 2). This nomogram model established in this study may be an effective clinical tool for predicting the severity of first-onset AP. However, there may be data bias since this is a single-center study with limited sample size. Substantial verification is still needed to verify the performance of this nomogram.

Conclusions

This nomogram for predicting severe acute pancreatitis is expected to become a clinical tool to predict the severity of SAP. The novelty of article is to draw the nomogram through retrospective analysis of pancreatitis data and perform prospective verification.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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