Clinical characteristics and early identification of acute pancreatitis in pregnancy with risk for organ failure: a retrospective study

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Abstract

Background: Acute pancreatitis in pregnancy (APIP) with organ failure (OF) is a rare but serious disease. Here, we describe the primary characteristics associated with APIP, and explore potential predictors for early recognition of OF among the patients.

Methods: A total of 3154 patients with AP from January 2018 to December 2021 were retrospectively reviewed. After screening, we enrolled 49 patients with APIP and 184 non-pregnant AP patients. Clinical characteristics and blood biochemical information were assessed using IBM SPSS 26.0 software and the rms package in R.

Results: The most primary cause of APIP was hypertriglyceridemia (59.2%), while respiratory failure (46.9%) was the main type in all OF patients. Age, hemoglobin (Hb), hematocrit (HCT), aminotransferase (ALT), creatinine (Cr), blood urea nitrogen (BUN), albumin (ALB) and sodium ion (Na^+) in the pregnant group were lower than in the non-pregnant group ($P<0.05$), while body mass index (BMI), triglyceride (TG) and total cholesterol (TC) in the pregnant group were higher ($P<0.05$). Among the APIP patients, BUN, TG and TC were independent risk factors for predicting OF, ($P < 0.05$) and they were used to create a nomogram with accurate prediction performance. (AUC=0.941)

Conclusions: APIP was highly correlated with hypertriglyceridemia and respiratory failure. Higher BMI was a distinguishing feature of OF-APIP patients. The data indicate that close monitoring of BUN, TG and TC levels is essential for early prevention of OF in APIP patients.

Introduction

Characterized by edema, hemorrhage, and necrosis,[1, 2]acute pancreatitis (AP) is a potentially fatal disease with a mortality rate of 25% in severe cases.[3, 4] Some authors have previously reported that the key measures to reduce the high mortality of AP are probably the early prediction and diagnosis, which can guide the subsequent definitive treatment.[5] Rapid diagnosis of AP caused by common etiologies in most populations has become possible in recent years.[6] However, it is noteworthy that there are still special types of pancreatitis induced in a small number of patients, for which the diagnosis presents a challenge and which generally results in catastrophic consequences, such as acute pancreatitis in pregnancy (APIP).[7, 8]

APIP is one of the rare but serious complications of pregnancy, with an incidence that varies from 1.37 to 2.27%.[1, 2] Recent studies reported a significant incidence of maternal death and fetal loss due to APIP.[9–11] For example, Luo et al. revealed an overall maternal and fetal mortality rate as high as 3.3% (4/121) and 11.6% (14/121), respectively. [12] Shi et al. reported a fetal mortality of 31.1% (28/90), and further analysis found that fetal intrauterine death was an independent risk factor for maternal AP severity. [13]The close relationship between the severity of AP and poor outcomes was also shown in other studies.[2, 9, 14] Of note, as the primary feature of moderate or severe AP, the influence of organ failure (OF) on AP has also been widely investigated.[4, 5, 15, 16] Some scholars believe that OF

contributes to almost all the mortality in AP patients.[17] Werge et al.[18] showed a mortality of 19.8% associated with OF while the mortality of patients without OF was only 1.4%. In another population-based cohort of 1024 patients, all deaths caused by AP were analyzed[19], and the results indicated that the occurrence of OF advanced the death period by 3 days. Taken together, early identification of APIP and especially patients at risk of OF warrants great attention to help the clinical management and avoid adverse events.

Although several studies have provided ideas for accurate diagnosis and evaluation of APIP patients, [20] [21] [12] different regions and populations may have significantly different clinical characteristics. Furthermore, due to the low incidence of APIP, most studies included small case series and had a relatively long reference time span. For these reasons, further investigation in more APIP patients is warranted.

In this study, we conducted a retrospective analysis of 233 AP cases from the First Affiliated Hospital of Nanchang University, among which 49 patients were diagnosed with APIP. A comparison between pregnant and non-pregnant AP patients was conducted to determine the crucial characteristics of AP in pregnancy. In addition, a new model for predicting high risk of OF in APIP patients was verified, showing some clinical references to clinicians.

Materials and methods

Patient Selection and Clinical Data

This study was conducted consistent with the principles of the Helsinki declaration. And ethical approval was obtained from the First Affiliated Hospital of Nanchang University. A total of 3154 patients with AP were prospectively and consecutively enrolled from database (Approval Number: 2011001) between January 1, 2018 to December 31, 2021. Exclusion criteria included male patients, patients younger than 18 or older than 50 years of age, patients hospitalized over 5 days after onset, recurrent pancreatitis, chronic pancreatitis and other pancreatic diseases. The specific inclusion and exclusion criteria are displayed in Fig. 1. We ultimately enrolled 233 women of childbearing age (18 to 50 years) with AP in our study. The total population is divided into two groups: 49 patients in the pregnant group and 184 in the non-pregnant group.

Informed consent

was obtained from each patient in the database during hospitalization. Clinical data included age, sex, history of diabetes, hypertension, smoking and drinking, pancreatitis-related characteristics (etiology, severity, complications of AP during hospitalization), type of OF (i.e. cardiovascular, respiratory and renal failure), imaging examinations [including computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, etc.], the length of hospital stay (LOS), admission to intensive care unit (ICU). Laboratory tests were collected within 48 h of admission, including Neutrophil count (NEU), Hematocrit (HCT), Alkaline phosphatase (AKP), Creatinine (Cr), Sodium ion (Na), D-Dimer (DD), etc. BMI (kg/m2) is

defined as weight in kilograms divided by height in square metres. AP Severity Bedside Index is calculated from patient data.

Diagnosis and Definition

APIP was defined as AP occurring from the time of conception to within one week postpartum. At least two of the following three features were required for the diagnosis: (1) abdominal pain in keeping with acute pancreatitis (acute onset of a severe, persistent, epigastric pain radiating to the back); (2) serum lipase or amylase level was three times higher than the upper limit of normal; (3) The cross-sectional imaging findings of abdomen are consistent with acute pancreatitis.[3] The differential diagnosis of APIP includes acute appendicitis in pregnancy, acute cholecystitis in pregnancy, ectopic pregnancy rupture and placental abruption. These disorders can be differentiated by ultrasound, features of abdominal pain, lipase and amylase.[22–24] For this study, the etiology, severity categories and local complications of APIP were defined according to the revised Atlanta classification.[3] OF was determined according to the modified Marshall scoring system, and the persistent OF refers to the same organ system failed over 48 hours.[3] Death was considered a death during hospitalization. Specific definitions are exhibited in Supplementary table 1.

Statistics

Statistical processing of the data was performed using SPSS 26.0 software (IBM Corp., USA). The data distribution of continuous variables was estimated using the Kolmogorov–Smirnov test. Normally distributed data were presented as mean ± standard deviation (SD) and the between-group differences were conducted using Student’s t test. Non-normally distributed data were expressed as median (interquartile range) and analyzed using Mann–Whitney U-test. Categorical data were presented in absolute numbers and percentages, and Pearson chi-square tests or Fisher's exact tests (when the number of observations was < 5) was used for comparative analysis between groups. Univariate and multivariate logistic regression analysis were then performed to determine the independent risk factors associated with OF in APIP. Potential risk factors with probability value of $p < 0.05$ in univariate analysis were enrolled into the multivariate analysis, and the results were shown as odds ratios (ORs) along with 95% confidence intervals (CIs). Receiver operating characteristic (ROC) was conducted to assess the predictive value of risk factors parameters. All the optimum cutoff values were determined according to the highest sensitivity and specificity values generated by ROC curves. Area under the curve (AUC), Youden index (YDI), Positive predict value (PPV), Negative predict value (NPV), Positive likelihood ratio (+ LR), Negative likelihood ratio (-LR) were calculated. Ultimately, a nomogram for OF on the basis of selected predictors was founded using the rms package in R, and the model’s predictive performance was evaluated using ROC curves and calibration curves. In this study, a 2-sided P value < 0.05 was thought to be statistically significant.

Results

General features of APIP patients

In order to compare APIP with AP in non-pregnant women, a total of 233 female AP patients were recruited for the present study. The main features which differentiate AP occurring in non-pregnant female patients from the disease occurring in pregnancy are exhibited in Tables 1 and 2. Compared to non-pregnant AP patients, the APIP patients were significantly younger (29.0±5.6 vs 40.4±7.7, $p < 0.001$), had a higher BMI (25.3±3.7 vs 24.1±2.9, $p < 0.001$) and longer total hospital stay (16.9±20.5 vs 10.5±10.6, $p < 0.05$). As expected, APIP patients were more likely to be admitted to the ICU [26(53.1%) vs 43(23.4%), $p < 0.001$]. Furthermore, the etiology composition of the two groups was also significantly different. HTG-AP accounted the largest for 59.2% of pregnant patients, which was significantly higher than 46.7% in the non-pregnant group ($P<0.05$). In terms of the severity of AP, despite moderately severe acute pancreatitis (MSAP) accounting for the largest proportion in the pregnant group (55.1% vs. 47.3% in the non-pregnant group, the difference was not statistically significant ($P=0.320$). In addition, Table 1 also shows that there was no significant difference among the two groups in mortality, shock and history of diabetes, smoking, drinking. There was almost no pre-existent hypertension in the pregnant group, while there were 17 cases (9.2%) among non-pregnant patients ($P=0.027$).

Nearly half of APIP patients suffered from OF, among which renal failure and circulatory failure seldom occurred. Respiratory failure patients among all pregnant and non-pregnant patients accounted for a majority of 46.9% and 26.6% respectively. The difference was statistically significant ($p = 0.006$). Notably, persistent OF ($p = 0.759$) or multiple OF ($p = 0.126$) occurred, independent of pregnancy status. Acute peripancreatic fluid collection (APFC) (28.6%) was the main local complication among the pregnant patients, with a similar ratio in the non-pregnant group (33.2%). Pancreatic pseudocyst (PPC) mainly occurred in 4.1% of APIP patients, but no PPC occurred in non-pregnant patients. The difference was significant ($P < 0.05$). More information is depicted in Supplementary Table 2.

Commonly used laboratory findings of all AP patients were summarized in Table 2. With the non-pregnant group by contrast, triglyceride (TG) and total cholesterol (TC) level of the pregnant group were significantly increased ($P < 0.05$). And the pregnant group had significant lower hemoglobin (Hb), hematocrit (HCT), aminotransferase (ALT), creatinine (Cr), blood urea nitrogen (BUN), albumin (ALB) and sodium ion (Na^+) level compared to the non-pregnant group ($P < 0.05$). However, White blood cell (WBC), Neutrophil count (NEU), Platelet count (PLT), Aspartate Transaminase (AST), Alkaline phosphatase (AKP), Creatine Kinase (CK), Total bilirubin (TBIL), Direct Bilirubin (DBIL), Amylase (AMY), Glucose (GLU), Potassium ion (K+), Calcium ion (Ca2+), Prothrombin Time (PT), Activated partial thromboplastin time (APTT) and D-Dimer (DD) showed no connection with the pregnancy status.

Independent risk factors for OF development in APIP patients

According to the previous analysis, results point toward OF as a potential factors for the prognosis of APIP. To thoroughly investigate the impact of various factors on the OF of APIP patients, we further compared clinical characteristics and laboratory indices among the 49 APIP patients. Tables 3 and 4. By

the time of discharge, 23 OF occurred (46.9%). Among which 23 cases (100%) were respiratory failure, while renal failure and circulatory failure were all 0 cases. Comparative analysis included general conditions between OF group and non-OF group at the time of admission. And there were no statistical differences in age, etiology, history of diabetes, hypertension, smoking and drinking. The BMI in the OF group was significantly higher compared to the non-OF group ($P < 0.05$). As anticipated, the most common severity of OF group were MSAP (52.2%) and severe acute pancreatitis (SAP) (47.8%), whereas mild acute pancreatitis (MAP) (42.3%) and MSAP (57.7%) accounted for the largest proportion in non-OF group. The difference was statistically significant ($p < 0.001$). All these data support worse circumstances related to OF. In addition, further analysis also found that OF patients had longer total hospital stay (22.3±25.3 vs 10.4±8.3, $p < 0.05$) and were more likely to be admitted to ICU ($p < 0.001$). In terms of complications, statistical differences between the two groups were shown in local complications ($p < 0.05$). As exhibited in Supplementary Table 3, walled-off necrosis (WON) infection was found in 5(21.7%) patients in the OF group, compared to 0 patients in the non-OF group ($p < 0.05$).

To investigate the relation of the OF with laboratory parameters, comparisons were made among the two groups. Table 4 indicated the results. In comparison, the levels of HCT, BUN, TG, TC, GLU and PT were significantly higher in APIP patients with OF than those without OF (all $P < 0.05$). However, the level of PLT was significantly lower in the OF group ($P < 0.05$). And there was no difference in levels of WBC, NEU, Hb, ALT, AST, AKP, CK, Cr, TBIL, DBIL, ALB, AMY, K+, Na+, Ca2+, APTT and DD between the two groups.

To further explore the risk factors contributing to the occurrence of OF, we screened the potential variables on the basis of previous results and analyzed them through univariate analysis, as depicted in Table 5. Higher levels of BMI (OR, 1.23, 95% CI, 1.03-1.47, P=0.022), HCT (OR, 1.22, 95% CI, 1.03-1.43, P=0.021), BUN (OR, 2.08, 95% CI, 1.17-3.69, P=0.012), TG (OR, 1.09, 95% CI, 1.03-1.17, P=0.007), TC (OR, 1.33, 95% CI, 1.11-1.59, P=0.002), GLU (OR, 1.25, 95% CI, 1.03-1.51, P=0.021), and PT (OR, 1.81, 95% CI, 1.13-2.92, P=0.014) were found to be significantly related to the development of OF (all $P < 0.05$). We then introduced the variables with P values <0.05 in univariate analysis into the multivariate analysis. The results indicated that increased levels of BUN (OR, 8.6, 95% CI, 1.19-61.7, P=0.032), TG (OR, 1.18, 95% CI, 1.00-1.38, P=0.046), and TC (OR, 1.68, 95% CI, 1.02-2.76, P=0.041) were associated with a higher risk of developing OF.

The biomarkers' power for predicting OF

Based on our previous results, YDI of the three potential variables (i.e. BUN, TG and TC) were calculated using ROC curve analysis, after which we characterize their cutoff values, sensitivity, specificity, PPV, NPV, +LR and -LR to investigated the utility in distinguishing APIP patients with or without OF. Specific information was displayed in Figure 2 and Table 6-7. TC had the highest ability in predicting OF ((AUC = 0.788, P = 0.001, 95% confidence interval (CI) 0.656 to 0.920). And the optimal cutoff value of TC was obtained to be 9.215 based on Youden index, suggesting that an APIP patient with concentration of TC≥9.215 mmol/L was likely to be diagnosed with OF. TG ((AUC = 0.763, P = 0.002, 95% confidence interval (CI) 0.630 to 0.896) had a moderate prediction accuracy, with the highest specificity (92.3%), YDI

(0.575) and -LR (0.518). Relatively speaking, BUN ((AUC = 0.751, P = 0.003, 95% confidence interval (CI) 0.615 to 0.887) had the lowest prediction accuracy, with the lowest specificity (69.2%), YDI (0.388), PPV (0.693) and +LR (2.259).

With the aim to further determine the clinical value of combined detection of each index, BUN, TG and TC were detected in pairs and analyzed in series or in parallel. Notably, it has been established that parallel detection can improve the diagnostic sensitivity and serial detection can increase the diagnostic specificity. Similar to the consensus, we were pleasantly surprised to find that the specificity and sensitivity increased remarkably when BUN, TG and TC were detected in series (100.0%) and in parallel (100.0%) (Table 8).

Nomogram model for OF

On the basis of the previous analysis, a nomogram was constructed combining all potential predictive factors for OF. Figure 3. The predictive factors included BUN, TG and TC. Each variable was matched with the corresponding score using the nomogram, after which the scores assigned to the corresponding factors were added to determine the total score. Subsequently, it's reasonable to identify the possibility of OF by drawing a line down from the axis of total score to the probability axis. To assess the predictive accuracy of the nomogram model, the calibration plot of OF probability was conducted. Remarkably, Figure 4 showed great consistency between the predicted results of the nomogram and the actual observation. At the same time, the performances of the planted nomogram for predicting OF were assessed by ROC curve analyses (Figure 5), and AUC=0.941 supported a good discrimination ability of nomogram. Hence, these analysis provided the pivotal evidence of the nomogram as useful predictor of OF in APIP patients.

Discussion

In comparison with the incidence of APIP in other studies, [21; 22] APIP patients in our study accounted for a larger proportion of 1.97% among the AP population. This higher incidence suggests a new perspective to explore statistically significant differences in pregnant and non-pregnant AP patients. On the relationship between age and pancreatitis, a previous study by Yadav et al. indicated that the risk of AP gradually increases with age.[23] However, another study that included postpartum cases suggested that women with postpartum period pancreatitis were younger than non-pregnant patients with pancreatitis due to gallstones but not pregnancy.[24] Our study ruled out postpartum, student's t test revealed that AP was more likely to occur during pregnancy in younger patients. Thus, more attention should be paid to the onset of gestation in younger women.

In terms of past medical history, several population-based cohort studies found that patients with diabetes have an approximate 1.5–2.9 fold increase in risk of AP.[25–27] The possible mechanism might point toward the abnormal pancreatic secretion affected by metabolic disorder in diabetic patients, and

anti-diabetic medications used to manage diabetes was confirmed to decrease the excess risk.[26, 28, 29] Interestingly, no statistical differences with regard to pre-existent diabetes was shown in our AP-based research between pregnant and non-pregnant patients. The result illustrated that compared with the non-pregnant female AP patients, prior diabetes history would not considered as characteristics for APIP patients. In addition, drinking and smoking rarely happen to Chinese women due to the local culture, and we found that smoking and drinking were also not the characteristics of APIP patients. Hypertensive disorders of pregnancy remain a troublesome problem in obstetrics, about 5–10% of pregnancies were associated with fetal, neonatal or maternal mortality.[30, 31] Consequently, pregnancies are usually advised to actively control blood pressure during pregnancy preparation and pregnancy stage. Within this context, even though our analysis manifested statistical difference in pre-existent hypertension between pregnant and non-pregnant AP patients, we did not consider pre-existent hypertension to be a major feature of APIP. Notably, pre-existent hypertension, diabetes, smoking and drinking were also not listed as risk factors for OF following our analysis of OF in APIP patients.

The most common causes of AP in this study were gallstones and HTG (36.5% and 49.4%, respectively). The results were in line with the published literature in China.[12, 32] Importantly, we also found that compared with the non-pregnant patients in which the proportion of AP cases caused by gallstones (41.8%) was equal to that caused by hyperlipidemia (46.7%), the proportion of APIP patients caused by hyperlipidemia was significantly higher (59.2% vs 16.3%), and there were no alcohol-caused APIP patients. This finding contrasted with those made in other parts of Europe and America, where gallstones were considered to be the most common cause and cases of AP among pregnant women were partly caused by alcohol. [33–36] A possible explanation would be the differences in race and dietary habits. On the one hand, the prevalence of gallstone-related AP cases in Asian countries was significantly lower compared with patients in western countries.[37, 38] On the other hand, regularly alcohol-drinking was thought to be rare in Chinese maternal population, and chronic pancreatitis that closely related to alcohol was not included in our study. In addition, prevalent high-fat diet among pregnant women in China may also partly explain the higher incidence of HTG-AP during pregnancy. As far as pathophysiological mechanism is concerned, estrogen related to pregnancy would reduce the activity of lipoprotein lipase which decreased the clearance of TG and eventually lead to HTG.[39, 40] At the same time, lipid metabolism disorder caused by insulin resistance during pregnancy capably increase triglyceride level to 2–3 times of non-pregnant standard. All these reasons together contribute to the significant incidence of HTG as well as the higher level of TG among APIP patients compared with non-pregnant AP women, as Table 1–2 proved. On the influence of etiology on the development of OF, there was no research found etiology as an independent risk factor for OF.

So far, the pathogenesis of APIP caused by HTG still remain unclear. We speculated that this pathophysiological mechanism may be attributable to the following possibilities. Firstly, hyperlipoproteinemia produced by hyperlipidemia increases blood flow resistance, which leads to the disturbance of microcirculation.[41] Secondly, amount of TG is hydrolyzed into excess free fatty acids (FFAs) by pancreatic lipase that diffusing from pancreatic acinar cells.[12] Afterwards, a great deal of FFAs infiltrate into the pancreatic cells and the acidic environment accelerates the activation of

trypsinogen, which leads to severe self-digestion of pancreas and activation of inflammatory cells.[42] Owing to the cascade reaction of various inflammatory mediators, intensive systemic inflammatory response is marked in AP. And increased infiltration of inflammatory cells that observed in multiple organs according to other reports provide the additional evidence of our hypothesis.[43] Among these organs, the lung is considered the most vulnerable one that may fail at an early stage. Broadly similar to studies based on AP population, we also found respiratory failure as the commonest OF in APIP patients.[19, 44]

Some scholars found that the risk of developing AP may increase due to obesity.[45] BMI (kg/m2) is considered as the most commonly used approach. In a previous meta-analysis, compared with normal-BMI patients, the risk of AP, severe AP, systemic or local complications were particularly higher among obese patients.[46] This can be explained by the pathogenesis of HTG-AP caused by fat accumulation that have been described above. In our study, BMI was an independent risk factor for the development of OF in APIP patients. Of note, there was also a statistically significant difference of BMI between the pregnant and non-pregnant patients with AP. The results demonstrated that higher BMI is a distinguishing feature of OF-APIP patients.

According to the 2012 Atlanta classification, AP is classified as mild, moderate or severe on the basis of local (or systemic) complications and OF.[3] AP without complications and OF is defined as mild acute pancreatitis (MAP). Moderately severe acute pancreatitis (MSAP) is defined as transient OF with/or (local or systemic) complications. Persistent OF with/or (local or systemic) complications characterizes severe acute pancreatitis (SAP). In a Chinese study of 90 APIP patients, 85.7% of fetal death occurred in the MSAP and SAP groups.[13] Another study reported a more remarkable result that all the maternal and fetal deaths occurred in the SAP group.[12] Namely, the severity of APIP might play a role in determining the risk for maternal and fetal health, and early prediction of MSAP or SAP is the key measure to improve the outcome. With this in mind, predicting the development of OF is the problem related to severity of APIP. Several studies have shown that OF caused the main mortality peak in an early stage of AP.[47, 48] Our study observed that the presence of OF increased the length of hospital stay (22.3 ± 25.3 vs 10.4 ± 8.3, P = 0.041). This result possibly also described the disease aggravation induced by OF in APIP.

To our knowledge, prediction of AP severity, pancreatic necrosis and infections has been available using existing biomarkers, computed tomography (CT) and clinical scoring systems.[49–51] Recent research has started to show interest in predicting the severity of APIP as well, including predicting MSAP, SAP, and persistent organ failure (POF).[52, 53] However, only a small portion of high-risk cases can be predicted by existing algorithms. According to previous studies, OF is an independent risk factor in determining death.[19, 47, 48] All OF-at-risk individuals ought to be regarded as high-risk patients. Therefore, a multifactor model for early OF prediction in patients with APIP needs to be developed. In our study, a new model based on multivariable logistic regression that contains BUN, TG and TC was established and validated for the individualized, non-invasive prediction of OF.

Observations of the non-pregnant HTG population revealed that TG levels > 1000 mg/dL (11.3 mmol/L) elevated the risk for triggering AP.[54] Up to date, the relationship between TG level and the course of AP has been explored in more and more studies.[17, 55, 56] In a Spanish study of 1457 AP patients, Pascual et al. compared the normal triglycerides-mild HTG (< 200 mg/dl), moderate HTG (200–749 mg/dl), severe HTG (≥ 750 mg/dl) groups and found that patients with higher serum triglyceride levels were at elevated risk of OF, acute peripancreatic collections, pancreatic necrosis and mortality.[57] Similarly, some other well-conducted studies also reported that higher TG level in AP patients may be linked to adverse prognosis.[58, 59] The related pathophysiological mechanism has been mentioned already in our discussion. Blood purification, medical treatment with heparin and/or insulin can help in improve triglycerides and further promote the recovery of HTG-AP patients.[54, 60, 61] Yet, considering the harmfulness of HTG-AP in pregnant women, it is very important to monitor the blood TG level during pregnancy. According to Manasvi et al., high-risk women should have their TG levels monitored every three months. Monthly checks should be performed on pregnant women with fasting triglycerides > 250 mg/dL. [62] Owing to the elevated risk of OF in APIP patients with higher levels of TG,[21] the cut-off value of TG concentration was counted as 13.865 mmol/L in our study to predict the occurrence of OF. With a sensitivity of 52.2%, a specificity of 92.3%, and AUC of 0.763.

Cholesterol plays a role as a cell membrane component, the relationship between cholesterol and cardiovascular disease risk has been well confirmed over the years.[63–65] With the deepening of research, the mechanism of cholesterol in the pathogenesis of AP has also been revealed, including the activation of TLR signaling,[66] activated neutrophils,[67, 68] reduced nitric oxide (NO),[69] the presence of reactive nitrogen species (RNS) and reactive oxygen species (ROS).[70] In the study by Peng et al,[71] cholesterol was thought to be inversely correlated with the disease severity in AP patients. However, another study in 648 cases of AP showed that there was a U-shaped correlation between TC level and severity within 24 hours of admission. Their results showed that comparable to patients with moderate TC levels (160–240 mg/dL), significantly higher rates of SAP were revealed in groups with low TC levels (< 160 mg/dL) and high TC levels (> 240 mg/dL).[72] The low TC levels may be attributed to a decrease in energy, increased catabolism, and reduced cholesterol synthesis.[73, 74] Cholesterol as well as triglyceride levels in blood are might increased due to the decompose of fat, which endanger pancreatic blood circulation. Using 9.215 mmol/L as the threshold to predict OF in APIP patients, elevated risk of OF along with higher TG level was shown in our study.

As a single and cheap marker, BUN at admission might characterize the underlying physiologic state of patients, including intravascular volume status and pre-renal azotemia.[75] Furthermore, the fluctuation of BUN during the follow-up treatment is particularly susceptible to pancreatic ischemic injury.[76] And its elevation reflects the failure of blood volume to fully resuscitate in their disease course, worsening renal function or negative nitrogen balance induced by AP.[77] For these grounds, BUN might potentially play pivotal roles in the early assessment and late management efforts of AP. Several scoring systems has been reported by previous studies to incorporate BUN for prediction of prognosis in AP.[78–81] In a recent study,[82] Liu et al. enrolled 155 patients with acute necrotizing pancreatitis (ANP), and found that although no superiority was shown in BUN to predict OF and POF, its predictive performance was

significantly improved to 0.83 and 0.85 respectively after combined with the mean CT density and necrosis volume. Of note in our study, the specificity and sensitivity of predicting OF in APIP patients also increased remarkably when BUN incorporate with TG and TC in series (100.0%) and (100.0%) parallel.

Our prediction model was connected with above parameters within 48 hours of admission, which can predict the probability of OF in APIP patients. It must be stated that a higher predicted probability generally indicates a higher likelihood of OF in a patient. However, the diagnosis of OF still needs to be based on the relevant guidelines. Similar to many other comparable articles, the nomogram model in this study was constructed based on multivariate analysis, and integrate the results of logical regression to a great extent. As a prognostic model, nomogram can not only visualize the related indexes that affect the outcome of multivariate regression analysis, but also presents the probability of a certain outcome of the patient with intuitive graphics, making the prediction more accurate and intuitive.[83] Since ROC curve analyses and the calibration plot of OF proved that the model had high discrimination and calibration accuracy. Consequently, did the nomogram model acquire certain clinical application value.

In the end, several limitations should be noted with our study. Firstly, this was a retrospective research while the related information was prospectively captured from our AP data. Secondly, because of the low incidence of APIP, our analysis was based on a small sample size that would limit the extrapolation of conclusions obtained in this study. In addition, follow-up data of patients after their discharge were not available due to the hiding of some personal information. Thirdly, there are still some factors that we have not taken into account. Such as serum amylase and lipase. One explanation for this was that serum amylase and lipase levels in more than 50% of HTG-AP patients may be normal at or during the hospital course.[84, 85] What’s more, studies involving the APIP population had reported that neither lipase nor amylase could predict the severity of APIP.[86] Fourthly, previous studies have shown that the gestational age, preterm delivery, fetal distress and fetal loss were strongly correlated with the severity of APIP.[1, 53, 87, 88] However, we did not collect fetal outcomes and obstetrics information such as the gestational age of the APIP patients, which may have missed some new findings. Finally, a predictive model to help identify APIP patients at high risk of OF was constructed and confirmed in our research, but a further distinction of transient and persistent OF cannot be achieved. Further studies with a larger sample size are needed to validate the model.

Conclusions

Acute pancreatitis in pregnancy (APIP) is a potentially dangerous disease, and the development of organ failure (OF) may lead to disastrous consequences for both the foetus and the mother. An in-depth insight into the characteristics and primary predictors of APIP, particularly in OF-APIP patients would be useful in clinical decision-making. According to our analysis, the most primary cause of APIP was hypertriglyceridemia (HTG), and respiratory failure was the main type in all included OF patients. Higher BMI is a distinguishing feature of OF-APIP patients. In addition, we established and validated a nomogram model consisting of three risk factors BUN, TG and TC with good accuracy for the prediction

of OF among APIP patients. Hoping to contribute to the prompt diagnosis and treatment of APIP in China, further more multicenter studies with larger sample size are warranted to verify our results.

Abbreviations

acute pancreatitis=AP, mild acute pancreatitis=MAP, moderately severe acute pancreatitis =MSAP, severe acute pancreatitis=SAP, acute pancreatitis in pregnancy=APIP, organ failure=OF, computed tomography=CT, magnetic resonance imaging=MRI, the length of hospital stay=LOS, admission to intensive care unit=ICU, Neutrophil count=NEU, Hematocrit=HCT, Alkaline phosphatase=AKP, Creatinine=Cr, Sodium ion=Na, D-Dimer =DD.

Declarations

Ethics approval and consent to participate

This study was conducted consistent with the principles of the Helsinki declaration. And ethical approval was obtained from the First Affiliated Hospital of Nanchang University. (Approval Number: 2011001) Informed consent was obtained from each patient in the database during hospitalization.

Consent for publication

Not applicable.

Availability of data and materials

Data are available from the authors based on the reasonable request and permission of the First Affiliated Hospital of Nanchang University.

Competing interests

The authors report no commercial or financial relationships regard to the submitted work that could be considered as a potential conflict of interest.

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Authors' contributions

Bingjun, Lingyu Luo, Liqing Yu, Yun Ke designed the study. Jiarong Li, Yun Ke, Ling Gui, Fengwen Xie, Yupeng Lei, Xin Huang, Xiaoyu Yang, Yong Zhu, Cong He, Nianshuang Li, Liang Xia and Wenhua He contributed to the acquisition, analysis and interpretation of data. Bingjun Yu, Yin Zhu and Nonghua Lu wrote the main manuscript text. Jiarong Li, Yun Ke, Ling Gui, Fengwen Xie, Yupeng Lei, Xin

Huang, Xiaoyu Yang, Yong Zhu, Cong He, Nianshuang Li, Liang Xia and Wenhua He helped review and edit the manuscript. All authors read and provided final approval of the published article.

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References

1. Tang M, Xu JM, Song SS, Mei Q, Zhang LJ: **What may cause fetus loss from acute pancreatitis in pregnancy: Analysis of 54 cases**. *Medicine (Baltimore)* 2018, **97**(7):e9755.
2. Zhang DL, Huang Y, Yan L, Phu A, Ran X, Li SS: **Thirty-eight cases of acute pancreatitis in pregnancy: a 6-year single center retrospective analysis**. *J Huazhong Univ Sci Technolog Med Sci* 2013, **33**(3):361-367.
3. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS, Acute Pancreatitis Classification Working G: **Classification of acute pancreatitis–2012: revision of the Atlanta classification and definitions by international consensus**. *Gut* 2013, **62**(1):102-111.
4. Mofidi R, Duff MD, Wigmore SJ, Madhavan KK, Garden OJ, Parks RW: **Association between early systemic inflammatory response, severity of multiorgan dysfunction and death in acute pancreatitis**. *Br J Surg* 2006, **93**(6):738-744.
5. Zhao B, Sun S, Wang Y, Zhu H, Ni T, Qi X, Xu L, Wang Y, Yao Y, Ma L *et al*: **Cardiac indicator CK-MB might be a predictive marker for severity and organ failure development of acute pancreatitis**. *Ann Transl Med* 2021, **9**(5):368.
6. Mathuram Thiyagarajan U, Ponnuswamy A, Thomas R: **Predictivity of Biochemical Markers on Aetiology and Length of Hospitalisation in Acute Pancreatitis**. *Cureus* 2020, **12**(12):e11989.
7. Ramin KD, Ramin SM, Richey SD, Cunningham FG: **Acute pancreatitis in pregnancy**. *Am J Obstet Gynecol* 1995, **173**(1):187-191.
8. Hughes DL, Hughes A, White PB, Silva MA: **Acute pancreatitis in pregnancy: meta-analysis of maternal and fetal outcomes**. *Br J Surg* 2021, **109**(1):12-14.
9. Sun L, Li W, Geng Y, Shen B, Li J: **Acute pancreatitis in pregnancy**. *Acta Obstet Gynecol Scand* 2011, **90**(6):671-676.
10. Lankisch PG, Apte M, Banks PA: **Acute pancreatitis**. *Lancet* 2015, **386**(9988):85-96.
11. Ducarme G, Chatel P, Alves A, Hammel P, Luton D: **Management of necrotizing pancreatitis in the third trimester of pregnancy**. *Arch Gynecol Obstet* 2009, **279**(4):561-563.
12. Luo L, Zen H, Xu H, Zhu Y, Liu P, Xia L, He W, Lv N: **Clinical characteristics of acute pancreatitis in pregnancy: experience based on 121 cases**. *Arch Gynecol Obstet* 2018, **297**(2):333-339.
13. Shi X, Hu Y, Pu N, Zhang G, Zhang J, Zhou J, Ye B, Li G, Ke L, Liu Y *et al*: **Risk Factors for Fetal Death and Maternal AP Severity in Acute Pancreatitis in Pregnancy**. *Front Pediatr* 2021, **9**:769400.

14. Geng Y, Li W, Sun L, Tong Z, Li N, Li J: **Severe acute pancreatitis during pregnancy: eleven years experience from a surgical intensive care unit**. *Dig Dis Sci* 2011, **56**(12):3672-3677.
15. Padhan RK, Jain S, Agarwal S, Harikrishnan S, Vadiraja P, Behera S, Jain SK, Dhingra R, Dash NR, Sahni P *et al*: **Primary and Secondary Organ Failures Cause Mortality Differentially in Acute Pancreatitis and Should be Distinguished**. *Pancreas* 2018, **47**(3):302-307.
16. Liu C, Zhou X, Ling L, Chen S, Zhou J: **Prediction of mortality and organ failure based on coagulation and fibrinolysis markers in patients with acute pancreatitis: A retrospective study**. *Medicine (Baltimore)* 2019, **98**(21):e15648.
17. Garg PK, Singh VP: **Organ Failure Due to Systemic Injury in Acute Pancreatitis**. *Gastroenterology* 2019, **156**(7):2008-2023.
18. Werge M, Novovic S, Schmidt PN, Gluud LL: **Infection increases mortality in necrotizing pancreatitis: A systematic review and meta-analysis**. *Pancreatology* 2016, **16**(5):698-707.
19. Mole DJ, Olabi B, Robinson V, Garden OJ, Parks RW: **Incidence of individual organ dysfunction in fatal acute pancreatitis: analysis of 1024 death records**. *HPB (Oxford)* 2009, **11**(2):166-170.
20. Zhang L, Wang Y, Han J, Shen H, Zhao M, Cai S: **Neutrophil-lymphocyte ratio, gamma-glutamyl transpeptidase, lipase, high-density lipoprotein as a panel of factors to predict acute pancreatitis in pregnancy**. *Medicine (Baltimore)* 2018, **97**(26):e11189.
21. Sheng C, Wang Y, Xu Z, Wang J: **The Effect of Admission Serum Triglyceride Level on the Prediction of Severity of Acute Pancreatitis in Pregnancy**. *Risk Manag Healthc Policy* 2021, **14**:3209-3222.
22. Xu Q, Wang S, Zhang Z: **A 23-year, single-center, retrospective analysis of 36 cases of acute pancreatitis in pregnancy**. *Int J Gynaecol Obstet* 2015, **130**(2):123-126.
23. Abdullah B, Kathiresan Pillai T, Cheen LH, Ryan RJ: **Severe acute pancreatitis in pregnancy**. *Case Rep Obstet Gynecol* 2015, **2015**:239068.
24. Augustin G, Majerovic M: **Non-obstetrical acute abdomen during pregnancy**. *Eur J Obstet Gynecol Reprod Biol* 2007, **131**(1):4-12.
25. Girman CJ, Kou TD, Cai B, Alexander CM, O'Neill EA, Williams-Herman DE, Katz L: **Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes**. *Diabetes Obes Metab* 2010, **12**(9):766-771.
26. Lai SW, Muo CH, Liao KF, Sung FC, Chen PC: **Risk of acute pancreatitis in type 2 diabetes and risk reduction on anti-diabetic drugs: a population-based cohort study in Taiwan**. *Am J Gastroenterol* 2011, **106**(9):1697-1704.
27. Noel RA, Braun DK, Patterson RE, Bloomgren GL: **Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study**. *Diabetes Care* 2009, **32**(5):834-838.
28. Li Q, Hou C, Peng Y, Zhu X, Shi C, Zhang K, Tu M, Guo F, Huang D, Miao Y: **Diabetes and Younger Age Are Vital and Independent Risk Factors for Acute Pancreatitis in Patients with Severe Hypertriglyceridemia**. *Biomed Res Int* 2019, **2019**:2620750.

29. Gonzalez-Perez A, Schlienger RG, Rodriguez LA: **Acute pancreatitis in association with type 2 diabetes and antidiabetic drugs: a population-based cohort study**. *Diabetes Care* 2010, **33**(12):2580-2585.
30. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, Blomstrom-Lundqvist C, Cifkova R, De Bonis M, Iung B, Johnson MR, Kintscher U, Kranke P *et al*: **2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy**. *Eur Heart J* 2018, **39**(34):3165-3241.
31. Malik R, Kumar V: **Hypertension in Pregnancy**. *Adv Exp Med Biol* 2017, **956**:375-393.
32. Zhang T, Wang G, Cao Z, Huang W, Xiao H, Wei H, Lu J, Liu R, Yin C: **Acute pancreatitis in pregnancy: a 10-year, multi-center, retrospective study in Beijing**. *BMC Pregnancy Childbirth* 2022, **22**(1):414.
33. Eddy JJ, Gideonsen MD, Song JY, Grobman WA, O'Halloran P: **Pancreatitis in pregnancy**. *Obstet Gynecol* 2008, **112**(5):1075-1081.
34. Ducarme G, Maire F, Chatel P, Luton D, Hammel P: **Acute pancreatitis during pregnancy: a review**. *J Perinatol* 2014, **34**(2):87-94.
35. Mali P: **Pancreatitis in pregnancy: etiology, diagnosis, treatment, and outcomes**. *Hepatobiliary Pancreat Dis Int* 2016, **15**(4):434-438.
36. Kumar MP, Singh AK, Samanta J, Birda CL, Kumar N, Dhar J, Gupta P, Kochhar R: **Acute pancreatitis in pregnancy and its impact on the maternal and foetal outcomes: A systematic review**. *Pancreatology* 2022, **22**(2):210-218.
37. Shaffer EA: **Gallstone disease: Epidemiology of gallbladder stone disease**. *Best Pract Res Clin Gastroenterol* 2006, **20**(6):981-996.
38. Lammert F, Gurusamy K, Ko CW, Miquel JF, Mendez-Sanchez N, Portincasa P, van Erpecum KJ, van Laarhoven CJ, Wang DQ: **Gallstones**. *Nat Rev Dis Primers* 2016, **2**:16024.
39. Lippi G, Albiero A, Montagnana M, Salvagno GL, Scevarolli S, Franchi M, Guidi GC: **Lipid and lipoprotein profile in physiological pregnancy**. *Clin Lab* 2007, **53**(3-4):173-177.
40. Cruciat G, Nemeti G, Goidescu I, Anitan S, Florian A: **Hypertriglyceridemia triggered acute pancreatitis in pregnancy - diagnostic approach, management and follow-up care**. *Lipids Health Dis* 2020, **19**(1):2.
41. Qihui C, Xiping Z, Xianfeng D: **Clinical study on acute pancreatitis in pregnancy in 26 cases**. *Gastroenterol Res Pract* 2012, **2012**:271925.
42. Gok F, Koker S, Kilicaslan A, Sarkilar G, Yosunkaya A, Otelcioglu S: **Acute Pancreatitis Due to Hypertriglyceridaemia in Pregnancy**. *Turk J Anaesthesiol Reanim* 2015, **43**(2):116-118.
43. Halonen KI, Pettila V, Leppaniemi AK, Kemppainen EA, Puolakkainen PA, Haapiainen RK: **Multiple organ dysfunction associated with severe acute pancreatitis**. *Crit Care Med* 2002, **30**(6):1274-1279.
44. Schepers NJ, Bakker OJ, Besselink MG, Ahmed Ali U, Bollen TL, Gooszen HG, van Santvoort HC, Bruno MJ, Dutch Pancreatitis Study G: **Impact of characteristics of organ failure and infected necrosis on mortality in necrotising pancreatitis**. *Gut* 2019, **68**(6):1044-1051.

45. Zhu GL, Chen SH, Fan XD, Fan JC, Men XL, Zhang YM, Sun Q, Zhang B, Ji RG, Wang S *et al*: **[A prospective cohort study on BMI levels and risk of acute pancreatitis]**. *Zhonghua Liu Xing Bing Xue Za Zhi* 2021, **42**(12):2131-2137.
46. Hong S, Qiwen B, Ying J, Wei A, Chaoyang T: **Body mass index and the risk and prognosis of acute pancreatitis: a meta-analysis**. *Eur J Gastroenterol Hepatol* 2011, **23**(12):1136-1143.
47. Buter A, Imrie CW, Carter CR, Evans S, McKay CJ: **Dynamic nature of early organ dysfunction determines outcome in acute pancreatitis**. *Br J Surg* 2002, **89**(3):298-302.
48. Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA: **Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis**. *Gastroenterology* 2010, **139**(3):813-820.
49. Komolafe O, Pereira SP, Davidson BR, Gurusamy KS: **Serum C-reactive protein, procalcitonin, and lactate dehydrogenase for the diagnosis of pancreatic necrosis**. *Cochrane Database Syst Rev* 2017, **4**:CD012645.
50. Bollen TL, Singh VK, Maurer R, Repas K, van Es HW, Banks PA, Mortele KJ: **A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis**. *Am J Gastroenterol* 2012, **107**(4):612-619.
51. Rau BM, Kemppainen EA, Gumbs AA, Buchler MW, Wegscheider K, Bassi C, Puolakkainen PA, Beger HG: **Early assessment of pancreatic infections and overall prognosis in severe acute pancreatitis by procalcitonin (PCT): a prospective international multicenter study**. *Ann Surg* 2007, **245**(5):745-754.
52. Sheng C, Xu Z, Wang J: **Nomogram for Predicting Persistent Organ Failure With Acute Pancreatitis in Pregnancy**. *Front Endocrinol (Lausanne)* 2022, **13**:863037.
53. Yang DJ, Lu HM, Liu Y, Li M, Hu WM, Zhou ZG: **Development and validation of a prediction model for moderately severe and severe acute pancreatitis in pregnancy**. *World J Gastroenterol* 2022, **28**(15):1588-1600.
54. Valdivielso P, Ramirez-Bueno A, Ewald N: **Current knowledge of hypertriglyceridemic pancreatitis**. *Eur J Intern Med* 2014, **25**(8):689-694.
55. Kiss L, Fur G, Matrai P, Hegyi P, Ivany E, Cazacu IM, Szabo I, Habon T, Alizadeh H, Gyongyi Z *et al*: **The effect of serum triglyceride concentration on the outcome of acute pancreatitis: systematic review and meta-analysis**. *Sci Rep* 2018, **8**(1):14096.
56. Nawaz H, Koutroumpakis E, Easler J, Slivka A, Whitcomb DC, Singh VP, Yadav D, Papachristou GI: **Elevated serum triglycerides are independently associated with persistent organ failure in acute pancreatitis**. *Am J Gastroenterol* 2015, **110**(10):1497-1503.
57. Pascual I, Sanahuja A, Garcia N, Vazquez P, Moreno O, Tosca J, Pena A, Garayoa A, Lluch P, Mora F: **Association of elevated serum triglyceride levels with a more severe course of acute pancreatitis: Cohort analysis of 1457 patients**. *Pancreatology* 2019, **19**(5):623-629.
58. Zeng L, Cai X, Chen J, Jin G, Zheng Y: **Role of mean platelet volume in hypertriglyceridemia-induced acute pancreatitis during pregnancy**. *BMC Pregnancy Childbirth* 2020, **20**(1):592.

59. Cao L, Zhou J, Chen M, Chen T, Liu M, Mao W, Lin J, Hong D, Yao W, Sun Y *et al*: **The Effect of Plasma Triglyceride-Lowering Therapy on the Evolution of Organ Function in Early Hypertriglyceridemia-Induced Acute Pancreatitis Patients With Worrisome Features (PERFORM Study): Rationale and Design of a Multicenter, Prospective, Observational, Cohort Study**. *Front Med (Lausanne)* 2021, **8**:756337.
60. Twilla JD, Mancell J: **Hypertriglyceridemia-induced acute pancreatitis treated with insulin and heparin**. *Am J Health Syst Pharm* 2012, **69**(3):213-216.
61. Adiamah A, Psaltis E, Crook M, Lobo DN: **A systematic review of the epidemiology, pathophysiology and current management of hyperlipidaemic pancreatitis**. *Clin Nutr* 2018, **37**(6 Pt A):1810-1822.
62. Gupta M, Liti B, Barrett C, Thompson PD, Fernandez AB: **Prevention and Management of Hypertriglyceridemia-Induced Acute Pancreatitis During Pregnancy: A Systematic Review**. *Am J Med* 2022, **135**(6):709-714.
63. Hong W, Zimmer V, Stock S, Zippi M, Omoshoro-Jones JA, Zhou M: **Relationship between low-density lipoprotein cholesterol and severe acute pancreatitis ("the lipid paradox")**. *Ther Clin Risk Manag* 2018, **14**:981-989.
64. Sanyour HJ, Rickel AP, Hong Z: **The interplay of membrane cholesterol and substrate on vascular smooth muscle biomechanics**. *Curr Top Membr* 2020, **86**:279-299.
65. Awan S, Lambert M, Imtiaz A, Alpy F, Tomasetto C, Oulad-Abdelghani M, Schaeffer C, Moritz C, Julien-David D, Najib S *et al*: **Wnt5a Promotes Lysosomal Cholesterol Egress and Protects Against Atherosclerosis**. *Circ Res* 2022, **130**(2):184-199.
66. Tall AR, Yvan-Charvet L: **Cholesterol, inflammation and innate immunity**. *Nat Rev Immunol* 2015, **15**(2):104-116.
67. Sah RP, Saluja A: **Molecular mechanisms of pancreatic injury**. *Curr Opin Gastroenterol* 2011, **27**(5):444-451.
68. Booth DM, Murphy JA, Mukherjee R, Awais M, Neoptolemos JP, Gerasimenko OV, Tepikin AV, Petersen OH, Sutton R, Criddle DN: **Reactive oxygen species induced by bile acid induce apoptosis and protect against necrosis in pancreatic acinar cells**. *Gastroenterology* 2011, **140**(7):2116-2125.
69. Hermida N, Balligand JL: **Low-density lipoprotein-cholesterol-induced endothelial dysfunction and oxidative stress: the role of statins**. *Antioxid Redox Signal* 2014, **20**(8):1216-1237.
70. Leung PS, Chan YC: **Role of oxidative stress in pancreatic inflammation**. *Antioxid Redox Signal* 2009, **11**(1):135-165.
71. Peng YS, Chen YC, Tian YC, Yang CW, Lien JM, Fang JT, Wu CS, Hung CF, Hwang TL, Tsai YH *et al*: **Serum levels of apolipoprotein A-I and high-density lipoprotein can predict organ failure in acute pancreatitis**. *Crit Care* 2015, **19**:88.
72. Hong W, Zimmer V, Basharat Z, Zippi M, Stock S, Geng W, Bao X, Dong J, Pan J, Zhou M: **Association of total cholesterol with severe acute pancreatitis: A U-shaped relationship**. *Clin Nutr* 2020, **39**(1):250-257.

73. Hong W, Lin S, Zippi M, Geng W, Stock S, Basharat Z, Cheng B, Pan J, Zhou M: **Serum Albumin Is Independently Associated with Persistent Organ Failure in Acute Pancreatitis**. *Can J Gastroenterol Hepatol* 2017, **2017**:5297143.
74. Liu Y, Coresh J, Eustace JA, Longenecker JC, Jaar B, Fink NE, Tracy RP, Powe NR, Klag MJ: **Association between cholesterol level and mortality in dialysis patients: role of inflammation and malnutrition**. *JAMA* 2004, **291**(4):451-459.
75. Wu BU, Johannes RS, Sun X, Conwell DL, Banks PA: **Early changes in blood urea nitrogen predict mortality in acute pancreatitis**. *Gastroenterology* 2009, **137**(1):129-135.
76. Quiros JA, Marcin JP, Kuppermann N, Nasrollahzadeh F, Rewers A, DiCarlo J, Neely EK, Glaser N: **Elevated serum amylase and lipase in pediatric diabetic ketoacidosis**. *Pediatr Crit Care Med* 2008, **9**(4):418-422.
77. Dickerson RN, Vehe KL, Mullen JL, Feurer ID: **Resting energy expenditure in patients with pancreatitis**. *Crit Care Med* 1991, **19**(4):484-490.
78. Spitzer AL, Barcia AM, Schell MT, Barber A, Norman J, Grendell J, Harris HW: **Applying Ockham's razor to pancreatitis prognostication: a four-variable predictive model**. *Ann Surg* 2006, **243**(3):380-388.
79. Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA: **The early prediction of mortality in acute pancreatitis: a large population-based study**. *Gut* 2008, **57**(12):1698-1703.
80. Faisst M, Wellner UF, Utzolino S, Hopt UT, Keck T: **Elevated blood urea nitrogen is an independent risk factor of prolonged intensive care unit stay due to acute necrotizing pancreatitis**. *J Crit Care* 2010, **25**(1):105-111.
81. Ranson JH, Rifkind KM, Roses DF, Fink SD, Eng K, Localio SA: **Objective early identification of severe acute pancreatitis**. *Am J Gastroenterol* 1974, **61**(6):443-451.
82. Liu N, He J, Hu X, Xu SF, Su W, Luo JF, Wang QF, Guo F: **Acute necrotising pancreatitis: measurements of necrosis volume and mean CT attenuation help early prediction of organ failure and need for intervention**. *Eur Radiol* 2021, **31**(10):7705-7714.
83. Oh SE, Seo SW, Choi MG, Sohn TS, Bae JM, Kim S: **Prediction of Overall Survival and Novel Classification of Patients with Gastric Cancer Using the Survival Recurrent Network**. *Ann Surg Oncol* 2018, **25**(5):1153-1159.
84. Yadav D, Pitchumoni CS: **Issues in hyperlipidemic pancreatitis**. *J Clin Gastroenterol* 2003, **36**(1):54-62.
85. Fortson MR, Freedman SN, Webster PD, 3rd: **Clinical assessment of hyperlipidemic pancreatitis**. *Am J Gastroenterol* 1995, **90**(12):2134-2139.
86. Jin D, Tan J, Jiang J, Philips D, Liu L: **The early predictive value of routine laboratory tests on the severity of acute pancreatitis patients in pregnancy: a retrospective study**. *Sci Rep* 2020, **10**(1):10087.
87. Yang Z, Guo G, Li H: **Predicting fetal loss in severe acute pancreatitis during pregnancy: a 5-year single-tertiary-center retrospective analysis**. *Postgrad Med* 2020, **132**(5):473-478.

88. Haiyan Z, Na P, Jialin H, Qingjian L, Jianying B, Xiumei B: **Acute Pancreatitis in Pregnancy: A Ten-Year Noninterventional, Retrospective Cohort Experience**. *Gastroenterol Res Pract* 2022, **2022**:3663079.

Tables

Table 1. Clinical characteristics of AP patients between non-pregnant and pregnant groups

	All patients(n=233)	Pregnant =49(21.0%)	Non-pregnant =184(79.0%)	P values
Age, years	37.9±8.6	29.0±5.6	40.4±7.7	0.000*
BMI, kg/m2	24.3±3.7	25.3±3.7	24.1±2.9	0.000*
Severity of AP				0.320‡
MAP	73(31.3%)	11(22.4%)	62(33.7%)	
MSAP	114(48.9%)	27(55.1%)	87(47.3%)	
SAP	46(19.7%)	11(22.4%)	35(19.0%)	
Etiology of AP				0.001†
Biliary	85(36.5%)	8(16.3%)	77(41.8%)	
HTG	115 (49.4%)	29(59.2%)	86(46.7%)	
Alcohol	4(1.7%)	0	4(2.2%)	
Other	29(12.4%)	12(24.5%)	17(9.2%)	
Pre-existent Hypertension	17(7.3%)	0	17(9.2%)	0.027†
Pre-existent Diabetes	21(9.0%)	1(2.0%)	20(10.9%)	0.087†
Smoking	2(0.9%)	0	2(1.1%)	1.000†
Drinking	11(4.7%)	1(2.0%)	10(5.4%)	0.466†
Organ failure				
Respiratory failure	72(30.9%)	23(46.9%)	49(26.6%)	0.006‡
Renal failure	10(4.3%)	0	10(5.4%)	0.126‡
Circulatory failure	2(0.9%)	0	2(1.1%)	1.000‡
Persistent failure	44(18.9%)	10(20.4%)	34(18.5%)	0.759‡
Multiple organ failure （MOF）	11(4.7%)	0	11(6.0%)	0.126†
Complication	37(15.9%)	6(12.2%)	31(16.8%)	0.953‡
Pancreatic necrosis	55(23.6%)	9(18.4%)	46(25.0%)	0.331‡
Infected Pancreatic Necrosis	20(8.6%)	3(6.1%)	17(9.2%)	0.774†
shock	8(3.4%)	0	8(4.3%)	0.209‡
ICU admission	69(29.6%)	26(53.1%)	43(23.4%)	0.000‡

LOS, days	11.9±13.5	16.9±20.5	10.5±10.6	0.038*
Death	8(3.4%)	1(2.0%)	7(3.8%)	1.000†

Continuous variables are presented as the mean (standard deviation). Categorical variables are presented as number (percentage). *Student's t test. ‡ Pearson Chi-Square test. †Fisher's exact test.

Abbreviations: Acute pancreatitis=AP. Body mass index = BMI. Mild acute pancreatitis=MAP. Moderately severe acute pancreatitis=MSAP. Severe acute pancreatitis=SAP. Hypertriglyceridemia=HTG. intensive care unit= ICU. Length of stay= LOS. Acute pancreatitis in pregnancy= APIP.

Table 2. Comparison of laboratory parameters between AP patients in the non-pregnant and pregnant groups

	mean	Pregnant =49(21.0%)	Non-pregnant =184(79.0%)	P values
WBC (*10⁹/L*)	12.7(9.8 16.8)	15.0(9.3 19.2)	12.2(9.9 15.9)	0.059#
NEU (*10⁹/L*)	87.6(82.9 91.1)	89.3(82.2 91.7)	87.4(82.9 91.1)	0.362#
Hb, g/L	124.0(111.0 141.0)	113.0(106.0 127.0)	127.0(114.3 143.0)	0.001#
HCT, %	37.5±5.8	34.5±4.2	38.6±5.9	0.000*
PLT(*10⁹/L*)	225.0(170.0 285.5)	229.0(176.0 300.0)	224.5(169.0 282.0)	0.731#
ALT, IU/L	20.0(11.0 51.5)	17.0(8.0 23.0)	22.5(11.1 62.5)	0.006#
AST, U/L	26.0(18.0 50.4)	21.0(16.5 46.5)	27.0(19.0 51.8)	0.106#
AKP, U/L	78.0(61.6 120.5)	82.0(60.5 123.0)	78.0(61.4 121.3)	0.728#
CK, U/L	59.0(35.0 95.2)	60.0(30.5 85.0)	58.5(35.3 98.8)	0.497#
Cr. umol/L	46.6(40.3 56.3)	44.2(37.6 50.6)	47.6(41.2 58.3)	0.025#
BUN, mmol/L	3.5(2.5 5.2)	2.5(1.9 3.6)	3.7(2.8 5.4)	0.000#
TBIL, umol/L	12.4(8.0 18.9)	11.5(7.8 17.1)	12.4(8.4 19.7)	0.435#
DBIL, umol/L	3.7(2.3 6.7)	3.9(2.2 6.7)	3.7(2.3 6.7)	0.773#
ALB, umol/L	36.2±5.5	34.7±5.2	36.6±5.7	0.033*
TG, mmol/L	7.3±11.1	10.7±14.1	6.5±10.0	0.018*
TC, mmol/L	4.9(3.7 8.6)	5.5(4.2 11.2)	4.7(3.6 7.7)	0.013#
AMY, U/L	242.0(83.7 624.5)	266.0(72.0 373.0)	237.0(92.2 650.8)	0.348#
GLU, mmol/L	7.74(5.9 10.8)	7.0(6.1 9.4)	8.0(5.9 11.9)	0.183#
K^+, mmol/L	3.9(3.6 4.3)	3.9(3.5 4.3)	3.9(3.6 4.3)	0.530#
Na^+, mmol/L	137.2(134.1 139.8)	135.4(130.7 139.9)	137.4(134.6 139.8)	0.032#
Ca^{2+}, mmol/L	2.04(1.8 2.2)	1.9(1.8 2.2)	2.1(1.9 2.2)	0.131#
PT, s	12.1(11.5 12.9)	12.1(11.4 13.3)	12.1(11.5 12.9)	0.975#
APTT, s	26.9(24.5 29.7)	26.5(24.5 29.4)	27.2(24.4 29.9)	0.292#
DD, ug/ml	2.4(1.2 4.9)	2.9(1.6 5.5)	2.2(1.1 4.7)	0.072#

Continuous variables are presented as the mean (standard deviation). Categorical variables are presented as number (percentage). * Student's t test. # Mann-Whitney Test.

Abbreviations: Acute pancreatitis = AP. White blood cell= WBC. Neutrophil count= NEU. Hemoglobin= Hb. Hematocrit= HCT. Platelet count= PLT. Aminotransferase= ALT. Aspartate Transaminase= AST. Alkaline phosphatase= AKP. Creatine Kinase= CK. Creatinine= Cr. Blood urea nitrogen= BUN. Total bilirubin= TBIL. Direct Bilirubin= DBIL. Albumin= ALB. Triglyceride= TG. Total cholesterol= TC. Amylase= AMY. Glucose= GLU. Potassium ion = K^+. Sodium ion= Na^+. Calcium ion= Ca^{2+}. Prothrombin Time= PT. Activated partial thromboplastin time= APTT. D-Dimer= DD.

Table 3. Characteristics of APIP patients with or without organ failure

	All patients(n=49)	Organ failure=23(46.9%)	Non-Organ failure=26(53.1%)	P values
Age, years	29.0±5.6	29.9±6.0	28.2±5.1	0.268*
BMI, kg/m2	24.3±3.7	25.3±3.7	24.1±2.9	0.014*
Severity of AP				0.000†
MAP	11(22.4%)	0	11(42.3%)	
MSAP	27(55.1%)	12(52.2%)	15(57.7%)	
SAP	11(22.4%)	11(47.8%)	0	
Etiology of AP				0.147†
Biliary	8(16.3%)	2(8.7%)	6(23.1%)	
HTG	29 (59.2%)	17(73.9%)	12(46.2%)	
Alcohol	0	0	0	
Other	12(24.5%)	4(17.4%)	8(30.8%)	
Pre-existent Hypertension	0			
Pre-existent Diabetes	1(2.0%)	1(4.3%)	0	0.469†
Smoking	0			
Drinking	1(2.0%)	1(4.3%)	0	0.469†
Complication	28(57.1%)	17(73.9%)	11(42.3%)	0.026‡
Pancreatic necrosis	9(18.4%)	7(30.4%)	2(7.7%)	0.064†
Infected Pancreatic Necrosis	3(6.1%)	3(13.0%)	0	0.096†
shock	0			
ICU admission	26(53.1%)	20(87.0%)	6(23.1%)	0.000‡
LOS, days	16.0±19.1	22.3±25.3	10.4±8.3	0.041*
Death	1(2.0%)	0	1(3.8%)	1.000†

Continuous variables are presented as the mean (standard deviation). Categorical variables are presented as number (percentage). *Student's t test. ‡ Pearson Chi-Square test. †Fisher's exact test.

Abbreviations: Acute pancreatitis in pregnancy= APIP. Acute pancreatitis=AP. Body mass index = BMI. Mild acute pancreatitis=MAP. Moderately severe acute pancreatitis=MSAP. Severe acute pancreatitis=SAP.

Hypertriglyceridemia=HTG. intensive care unit= ICU. Length of stay= LOS.

Table 4. Comparison of laboratory parameters between APIP patients with or without organ failure

	mean	Organ failure=23(46.9%)	Non-Organ failure =26(53.1%)	P values
WBC(*10⁹/L*)	15.2±6.5	16.5±6.0	13.9±6.7	0.178*
NEU(*10⁹/L*)	89.3(82.2 91.7)	90.0(86.4 92.1)	86.9(76.3 90.8)	0.118#
Hb, g/L	113.0(106.0 127.0)	120.0(107.0 141.0)	110.5(103.8 122.3)	0.056#
HCT, %	34.8(31.7 37.9)	36.9(33.1 39.0)	33.9(30.7 36.8)	0.012#
PLT(*10⁹/L*)	238.6±89.0	212.6±83.8	261.6±88.7	0.024*
ALT, IU/L	17.0(8.0 23.0)	17.0(9.0 20.0)	14.0 (7.5 33.3)	0.896#
AST, U/L	21.0(16.5 46.5)	21.0(14.0 47.0)	22.0(17.0 48.0)	0.810#
AKP, U/L	82.0(60.5 123.0)	82.0(58.0 107.9)	82.5(61.3 143.8)	0.336#
CK, U/L	60.0(30.5 85.0)	74.0(35.0 97.0)	48.5(27.8 68.5)	0.138#
Cr. umol/L	44.2(37.6 50.6)	45.8(37.2 53.7)	41.8(37.6 48.9)	0.331#
BUN, mmol/L	2.5(1.9 3.6)	3.4(2.3 5.5)	2.4(1.5 3.0)	0.003#
TBIL, umol/L	11.5(7.8 17.1)	11.5(7.8 15.7)	10.9(7.7 17.6)	0.711#
DBIL, umol/L	3.9(2.2 6.7)	4.3(2.4 6.3)	3.0(2.2 7.2)	0.452#
ALB, umol/L	34.7±5.2	33.9±5.3	35.3±5.2	0.349*
TG, mmol/L	3.1(1.5 17.8)	14.7(2.4 29.1)	1.7(1.1 6.1)	0.002#
TC, mmol/L	5.5(4.2 11.2)	11.1(4.9 15.8)	4.7(3.9 7.4)	0.001#
AMY, U/L	266.0(72.0 373.0)	284.0(67.0 482.0)	177.5(79.8 303.8)	0.667#
GLU, mmol/L	7.0(6.1 9.4)	8.3(6.6 14.5)	6.6(5.3 8.7)	0.020#
K^+, mmol/L	3.9(3.5 4.3)	3.9(3.5 4.4)	3.9(3.5 4.1)	0.638#
Na^+, mmol/L	135.4(130.7 139.9)	132.7(128.5 139.0)	136.4(131.7 140.8)	0.130#
Ca^{2+}, mmol/L	1.9(1.7 2.2)	1.9(1.7 2.1)	2.0(1.6 2.5)	0.288#
PT, s	12.1(11.4 13.3)	12.8(11.5 14.4)	11.9(11.2 12.2)	0.012#
APTT, s	26.9±4.4	26.5±5.0	27.2±3.9	0.592*
DD, ug/ml	2.9(1.6 5.5)	3.4(1.6 5.3)	2.9(1.2 5.8)	0.541#

Continuous variables are presented as the mean (standard deviation). Categorical variables are presented as number (percentage). * Student's t test. # Mann-Whitney Test.

Abbreviations: Acute pancreatitis in pregnancy= APIP. White blood cell= WBC. Neutrophil count= NEU. Hemoglobin= Hb. Hematocrit= HCT. Platelet count= PLT. Aminotransferase= ALT. Aspartate Transaminase= AST. Alkaline phosphatase= AKP. Creatine Kinase= CK. Creatinine= Cr. Blood urea nitrogen= BUN. Total bilirubin= TBIL. Direct Bilirubin= DBIL. Albumin= ALB. Triglyceride= TG. Total cholesterol= TC. Amylase= AMY. Glucose= GLU. Potassium ion = K^+. Sodium ion= Na^+. Calcium ion= Ca^{2+}. Prothrombin Time= PT. Activated partial thromboplastin time= APTT. D-Dimer= DD

Table 5. Univariate and multivariate logistic regression analysis of risk factors associated with organ failure

Variable	Univariate analyses		Multivariate analyses	
	OR (95% CI)	P	OR (95% CI)	P
BMI, kg/m2	1.23(1.03-1.47)	0.022	1.13(0.84-1.53)	0.426
HCT, %	1.22(1.03-1.43)	0.021	1.19(0.90-1.57)	0.221
PLT(*10⁹/L*)	0.99(0.99-1.00)	0.061		
BUN, mmol/L	2.08(1.17-3.69)	0.012	8.6(1.19-61.7)	0.032
TG, mmol/L	1.09(1.03-1.17)	0.007	1.18(1.00-1.38)	0.046
TC, mmol/L	1.33(1.11-1.59)	0.002	1.68(1.02-2.76)	0.041
GLU, mmol/L	1.25(1.03-1.51)	0.021	1.03(0.72-1.47)	0.870
PT, s	1.81(1.13-2.92)	0.014	0.76(0.28-2.09)	0.601

Abbreviations: odds ratio=OR. 95% confidence interval=95% CI. Body mass index = BMI. Hematocrit= HCT. Platelet count= PLT. Blood urea nitrogen= BUN. Triglyceride= TG. Total cholesterol= TC. Glucose= GLU. Prothrombin Time= PT.

Table 6. Parameters of biomarker's receiver operating characteristic curves

Biomarkers	AUC	95%CI	S.E	cut-off value	*P*
BUN	0.751	0.615 0.887	0.069	2.550	0.003
TG	0.763	0.630 0.896	0.068	13.865	0.002
TC	0.788	0.656 0.920	0.067	9.215	0.001

Abbreviations: area under the curve = AUC. 95% confidence interval = 95% CI. Standard Error = S.E. Blood urea nitrogen= BUN. Triglyceride= TG. Total cholesterol= TC.

Table 7. Comparison of predictive efficacy of BUN, TG and TC

Biomarkers	Sensitivity (%)	Specificity (%)	YDI	PPV	NPV	+LR	-LR
BUN	69.6	69.2	0.388	0.693	0.759	2.259	0.439
TG	52.2	92.3	0.575	0.871	0.659	6.779	0.518
TC	65.2	92.3	0.575	0.894	0.726	8.468	0.377

Abbreviations: Youden index = YDI. Positive predict value = PPV. Negative predict value = NPV. Positive likelihood ratio = +LR. Negative likelihood ratio =-LR. Blood urea nitrogen= BUN. Triglyceride= TG. Total cholesterol= TC.

Table 8. Joint detection of serum markers（%）

Joint detection	In series		In parallel	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
BUN+TG	30.4	96.2	91.3	65.4
BUN+TC	43.5	100.0	91.3	61.5
TG+TC	43.5	100.0	73.9	84.6
BUN+TG+TC	30.4	100.0	100.0	57.5

Abbreviations: Blood urea nitrogen= BUN. Triglyceride= TG. Total cholesterol= TC.

Figures

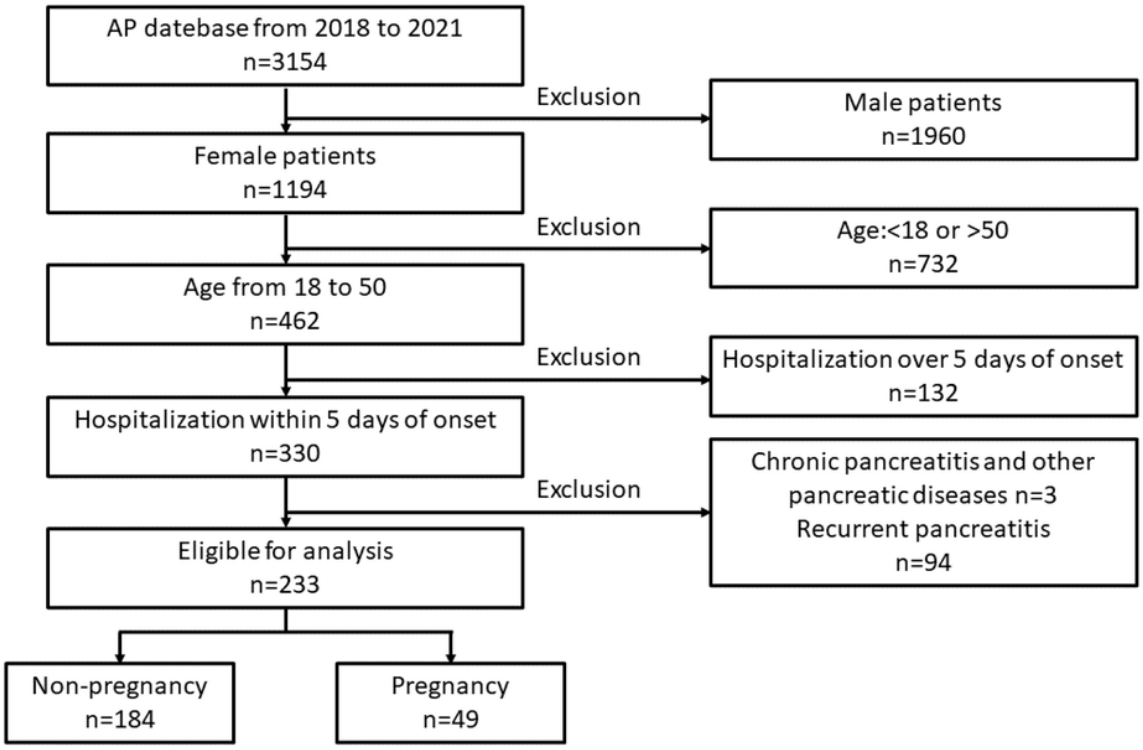

Figure 1

Flow chart of study participants

Abbreviations: Acute pancreatitis = AP.

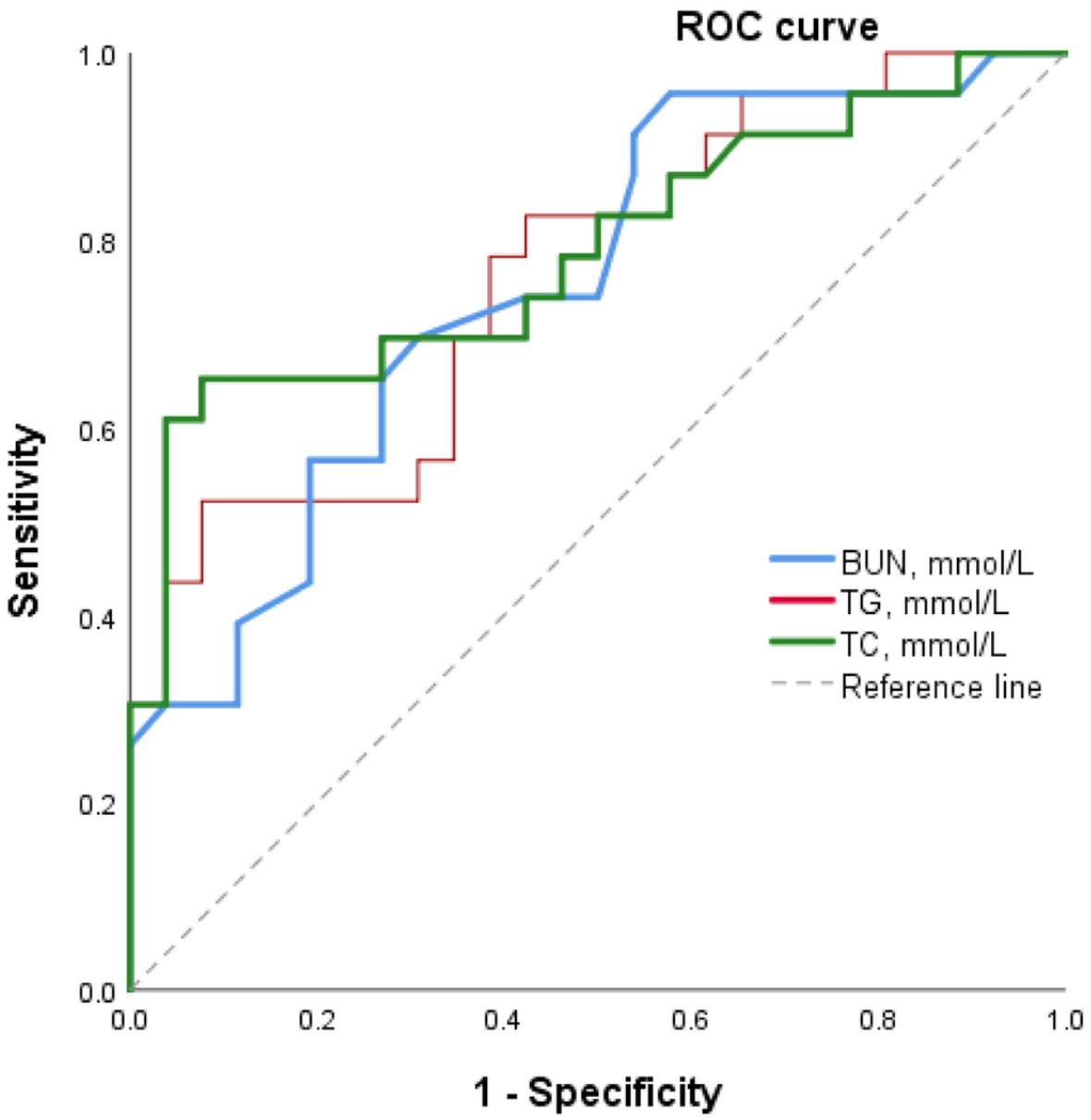

Figure 2

Receiver operating characteristic curve of BUN, TG and TC for predicting organ failure in pregnant acute pancreatitis

Abbreviations: Acute pancreatitis = AP. Receiver operating characteristic= ROC. Blood urea nitrogen= BUN. Triglyceride= TG. Total cholesterol= TC.

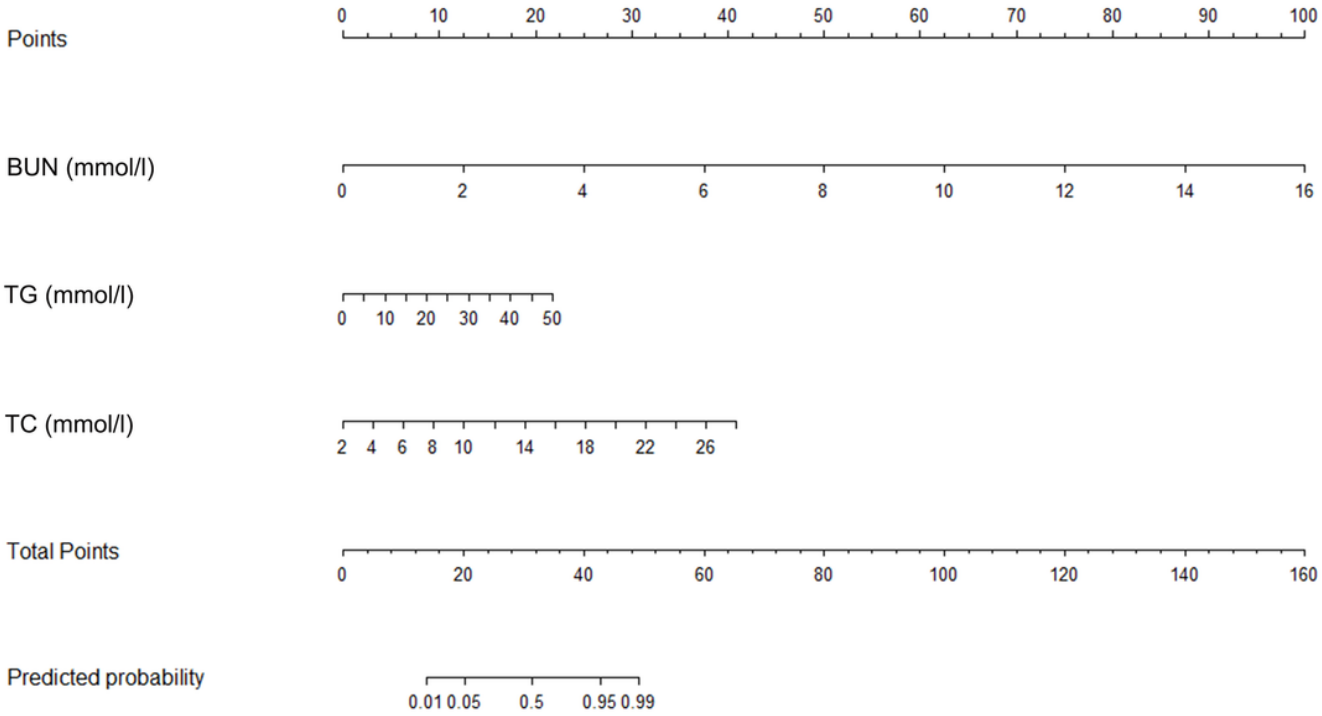

Figure 3

The nomogram for predicting organ failure among the acute pancreatitis in pregnancy

For example, a patient whose blood urea nitrogen (BUN) was 2 mmol/L, triglyceride (TG) was 20 mmol/L, total cholesterol (TC) was 8 mmol/L, total points scored was 31.25, and organ failure probability was approximately 50%.

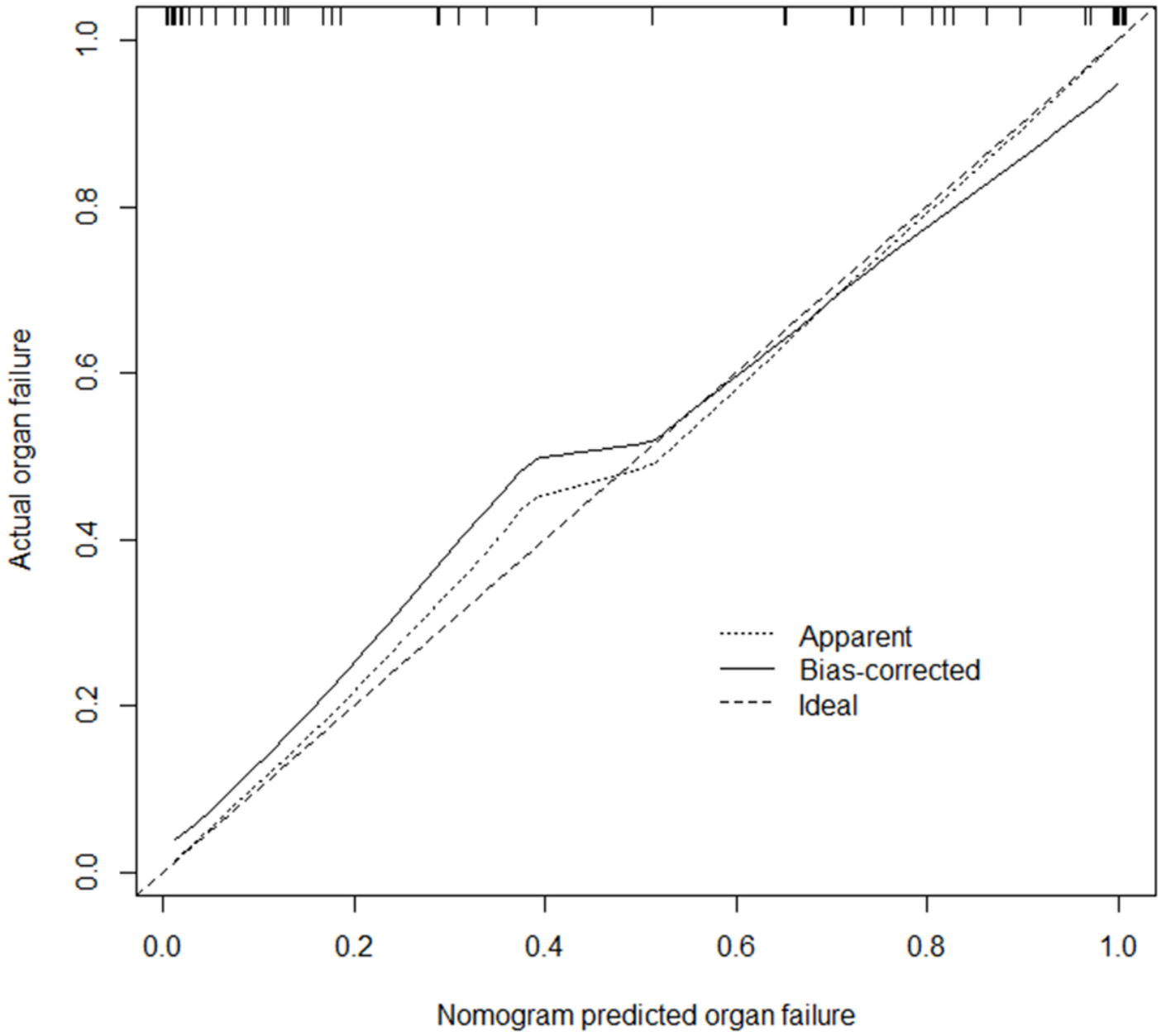

Figure 4

The calibration curves for the nomogram

Nomogram-predicted probability of organ failure is represented on the x-axis, and the actual probability is represented on the y-axis. The 45°dashed diagonal line would correspond to the perfect prediction and the other dashed line represents the entire cohort (n=49). The closer the dotted line is to the ideal line, the better the prediction accuracy of Nomogram is. Moreover, the solid line is bias-corrected through bootstrapping B=1000 repetitions), indicating the performance of the nomogram.

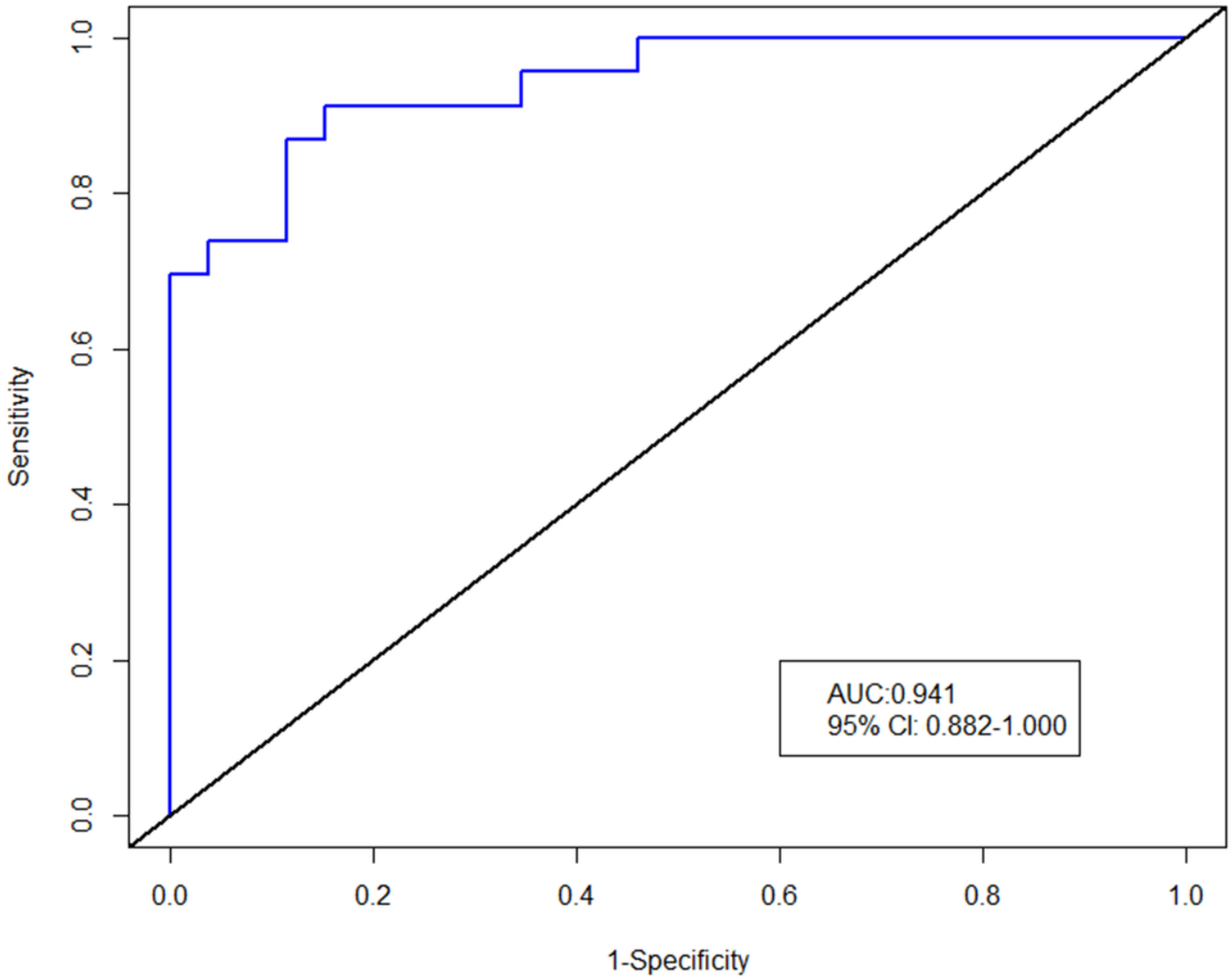

Figure 5

The receiver operating characteristic curve for the predictive model

Area under the curve (AUC)=0.941; 95% confidence interval (CI): 0.882 – 1.000

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial.docx