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ORIGINAL RESEARCH

The Effect of Admission Serum Triglyceride Level on the Prediction of Severity of Acute Pancreatitis in Pregnancy

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Purpose: Previous studies indicated that the serum triglyceride level in patients with acute pancreatitis positively correlated with the severity of the disease among the general population. Despite the physiological hypertriglyceridemia in pregnant women, there are no reports on the relationship between serum triglyceride level and the severity of acute pancreatitis in pregnant (APIP) women. This study explores the relationship between serum triglyceride levels and the severity of APIP.

Patients and Methods: Clinical information of APIP patients admitted to the Shengjing Affiliated Hospital of China Medical University was gathered from January 2012 to December 2020 to conduct retrospective research. The participating patients were divided into mild, moderately severe, and severe acute pancreatitis. The clinical outcomes of patients with different serum triglyceride levels (0–2.3 mmol/L, 2.23–5.65 mmol/L, 5.65–11.2 mmol/l, ≥11.2 mmol/L) were analyzed by performing ordinal logistic regression analysis. Receiver operating curve analysis was used to calculate the threshold value of serum triglyceride concentration that can effectively predict the occurrence of severe acute pancreatitis (SAP).

Results: Hypertriglyceridemic acute pancreatitis (HTG-AP) occurred in 47% of APIP patients within the group, with a high prevalence among the Han population. In the present study, the serum triglyceride concentration correlated positively with the severity of APIP (r=0.403, $P < 0.05$). The adjusted logistic model demonstrated that relative to nominal triglyceride levels, the OR value of SAP were 1.036 (95% CI: 0.401–2.677), 3.429 (95% CI: 1.269–9265), 8.329 (95% CI: 3.713–18.682) with triglyceride at the level of 2.23–5.65 mmol/L, 5.65–11.2 mmol/l and ≥11.2 mmol/L. In APIP patients, a triglyceride concentration of 10.7mmol/L or more upon admission was a predictive value for the occurrence of SAP, with a sensitivity of 0.72 and a specificity of 0.65, AUC: 0.708 (95% CI: 0.620–0.796).

Conclusion: As the serum triglyceride level upon admission increased, the frequency of local and systemic complications increased significantly.

Keywords: gestation, hypertriglyceridemia, acute pancreatitis, organ failure

Introduction

Acute pancreatitis (AP) is a common acute abdominal condition. The incidence of AP is about 13–45/100,000 among the general population.[1,2] In most patients, the course is self-limiting, 20~30% of patients face a perilous clinical experience, and the overall mortality rate is 5~10%.[1,3] The incidence of acute pancreatitis in pregnancy (APIP) is higher than the prevalence among the general population, which is about 1/1000–1/12,000.[3,4] Different studies report different statistics regarding the incidence of HTG-AP in pregnant

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women, accounting for around 4–32.2% and higher than that in the general population.[7–10]

Studies involving the general population report that the clinical outcome of HTG-AP was worse than that of the AP with other causes, and the probability of organ failure was also higher.[5–7] Up to date, no study shows a threshold concentration of serum triglycerides (TG) that triggers AP.[8] Clinical practitioners believed that the higher the serum TG concentration, the higher the risk of AP.[9,10] Studies found that the incidence of AP was in the range of 15–20% when the TG concentration was higher than 1000 mg/dL (11.2 mmol/L).[11,12]

During pregnancies, the enlarged uterus changes the anatomical position of abdominal organs, and it is common for contractions induced by inflammation and exudation to mask the symptoms of pancreatitis. It is often challenging to diagnose APIP early because of the atypical location and nature of abdominal pain. APIP is a condition that progresses rapidly, and the maternal and child mortality rate is remarkably high.[13]

Prolactin and Chorionic gonadotropin are specific hormones that have insulin resistance effects in pregnancy. Therefore, they can interfere with lipid hydrolysis, leading to a rise in TG concentration. Compared to pre-pregnancy, the TG concentration is around 2–3 times higher in late pregnancy.[14] There are few reports on the relationship between serum triglyceride level and the severity of APIP. Our study collected the clinical data of APIP patients hospitalized in the Shengjing Affiliated Hospital of China Medical University from January 1, 2012, to December 31, 2020. The study explores the probability of evaluating the clinical characteristics and prognosis of APIP patients based on serum TG concentration within 24 hours of admission.

Patients and Methods

Patients Selection

This study gained access to search the electronic medical records of Shengjing Affiliated Hospital of China Medical University by logging into its HIS system. The keywords "acute pancreatitis" and "pregnancy" helped to search and collect 253 cases of APIP patients onset within 72 hours from January 1, 2012, to December 31, 2020.

In total, 53 cases were excluded, including 45 cases of pancreatic cancer, endoscopic retrograde cholangiopancreatography, or traumatic pancreatitis, history of pancreatic surgery, chronic nephritis, cirrhosis, and hepatitis, 6 cases were twins, and 2 cases were lost in follow-up. A total of 200 cases were identified to have both complete data and meeting the diagnostic criteria for APIP were enrolled (Figure 1).

Data Collection

This study collected the clinical data of selected patients from the electronic medical record database of the Shengjing Affiliated Hospital of China Medical University. The study participants gave consent to have their data published. The data includes the age of onset, gestational age, gestation times, parity, demographic characteristics, clinical presentation, causes of pancreatitis (biliary, hypertriglyceridemia, and idiopathic), serum amylase and lipase levels at admission, the first blood lipid series result within 24 hours of admission [TG, total cholesterol (TC), apolipoprotein-A (Apo-A), apolipoprotein-B (Apo-B), etc.], imaging examinations [including ultrasound, computed tomography (CT) and magnetic resonance imaging (MRI)] during the hospitalization period, hospital costs, days receiving intensive care unit (ICU) treatment and maternal as well as the outcomes of children.

Relevant Definitions

The APIP diagnosis was based on revised Atlanta criteria. Patients who satisfy ≥2 of the following criteria were diagnosed with APIP: ① abdominal pain characteristic of AP; ② serum amylase or lipase higher than thrice the upper normal limit; ③ cross-sectional abdominal imaging findings are consistent with acute pancreatitis.[15]

The severity of APIP was classified according to the 2012 revision of the Atlanta criteria. Mild acute pancreatitis (MAP) is referred to as pancreatitis without organ dysfunction or generalized complications; AP patients were diagnosed as moderately severe acute pancreatitis (MSAP) if they had at least one of the following features: TOF (OF <48 h), deterioration of previous comorbid disease or local complications, including acute peripancreatic fluid collections, pseudocysts, acute necrotic collections, and walled-off necrosis; patients were diagnosed with SAP if they experienced POF (OF ≥48 h).[15]

OF was defined according to the modified Marshall scoring: circulatory failure, systolic blood pressure <90 mmHg with no fluid response; respiratory failure, PaO_2/FiO_2 ≤300; renal failure, and blood serum creatinine (SCr) ≥170/L.[16] Persistent organ failure (POF) is defined when OF occurs for more than 48 hours.[15]

Biliary pancreatitis: alanine aminotransferase (ALT) >150 U/L within 48 h of admission and biliary lesions on abdominal ultrasonography or magnetic resonance

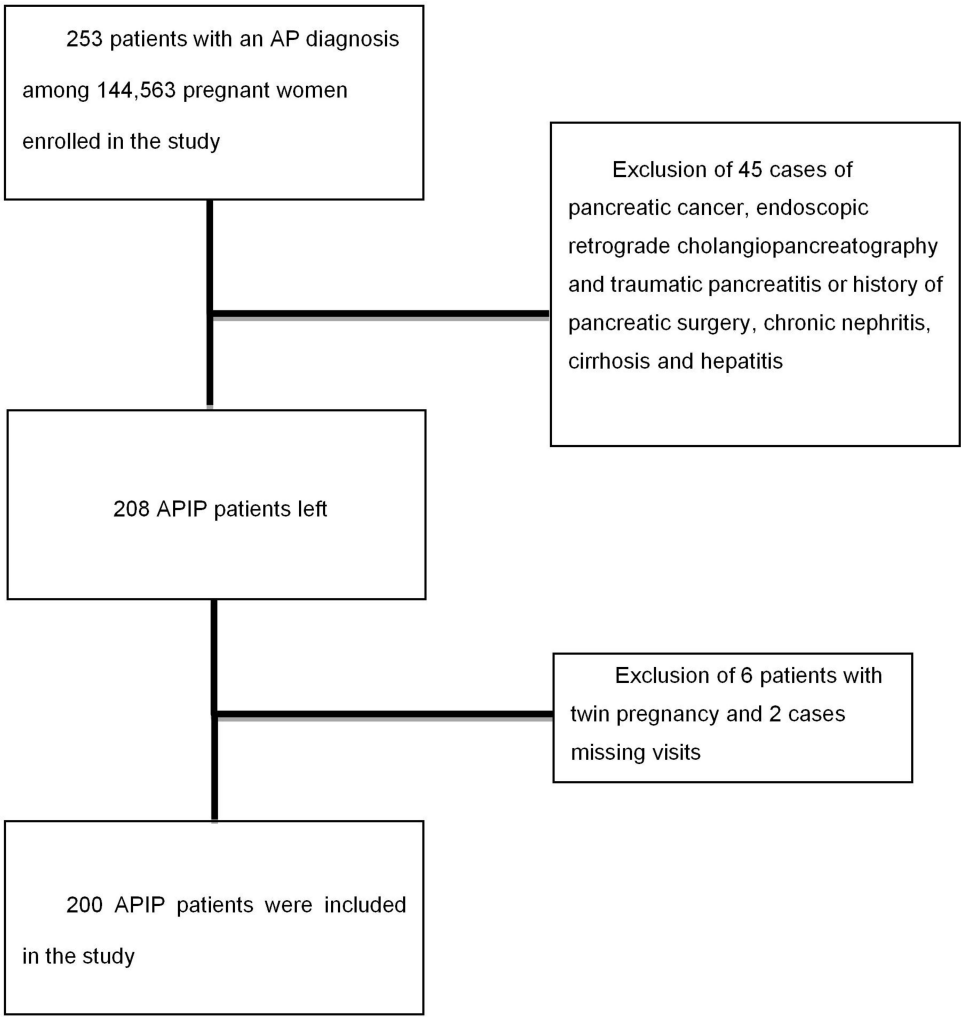

Figure 1 The selection process for patients in a flow chart.

cholangiopancreatography.[13] Hypertriglyceridemic pancreatitis (HTGP): serum triglycerides (TG) ≥11.3 mmol/L or between 5.65 and 11.3 mmol/L with lipid turbidity after excluding biliary, alcohol, or medication factors.[17] Idiopathic pancreatitis was defined as a form of a disease with a similar presentation to SAPIP based on a radiological diagnosis after excluding biliary, alcohol, hypertriglyceridemia (HTG), medication, trauma, autoimmune, and surgical factors.[17]

Satisfying all the following criteria confirms Diabetic Ketoacidosis (DKA): (1) blood glucose >13.9 mmol/L, arterial blood pH <7.25; (2) serum HCO_3 ≤18mmol /L; (3) presence of urine ketones; (4) anion gap ≥10mmol/L.[18]

Statistics

SPSS 26.0 software was used to perform statistical processing and graph analysis of the data, and adopt a retrospective case-control study. The sample size was >100. Moreover, the data distribution was assessed using the Kolmogorov–Smirnov test for normality. Normally distributed data are expressed as mean ± standard deviation (ie, mean ±SD), and non-normally distributed data are expressed as median (interquartile range). Non-parametric tests were used for comparative studies between groups. Count data adopt a Chi-square test of the linear association of ordering grouped data. Kendall's tau-b correlation analysis was used to calculate the correlation between two variables. Moreover, the association between TG levels and SAP probability was investigated using unconditional multivariable logistic regression models and the models adjusted for age, TC, APO-A, and parity, to evaluate the potentially confounding effects among risk factor variables. In addition, Multivariable-adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Locally weighted scatter plot smoothing (Lowess) fitting curve describes the association of continuous variables. Receiver operating characteristic (ROC) curve analyses were carried to calculate the threshold values, the area under the curve

(AUC), and 95% CIs. The sensitivity and specificity of predictive parameters were estimated using ROC curves, where $P<0.05$ indicated statistical significance.

Results

General Features of APIP Patients

This study involved 200 patients with APIP ranging from 17 to 42 years in age, with an average age of 29. Among them, 192 were of Han nationality (94%), 124 were primiparas (62%), and 76 were multiparas (38%). Moreover, 12 cases were in the first trimester (6%), 34 cases were in the second trimester (17%), and 154 cases were in the third trimester (77%). In addition, 24 cases had diabetes (12%), and 66 cases had a combination of hypertension in pregnancy (33%). According to the etiology, 40 cases (20%) were biliary, 94 cases (47%) were hypertriglyceridemic, and 66 cases (33%) were idiopathic. Depending on the severity of the disease, 92 cases were MAP (46%), 65 cases were MSAP (32.5%), and 43 cases were SAP (21.5%). Also, 7 cases of perinatal maternal deaths (3.5%) were recorded during hospitalization, all of whom had HTG as the etiology. Table 1 shows the details of the fatalities.

Twenty patients were discharged to continue the pregnancy after the symptoms subsided upon obtaining hospitalization treatment (10%). One hundred and eighty patients terminated their pregnancy during this hospitalization (90%). By the time of discharge, 55 perinatal deaths occurred (27.5%). Among which 4 cases (7.5%) were due to biliary, 37 cases (67.5%) were HTP-AP, and 14 cases (25.4%) were idiopathic.

The levels of amylase and lipase on the admission of different etiologies APIP patients varied a lot. The HTG-AP group has a significantly lower amylase and lipase level than those in pregnant women with biliary and idiopathic pancreatitis ($P = 0.079$) ($P = 0.026$), respectively (Figures 2 and 3).

Comparison of General Conditions of APIP Patients of Different Severity

In the present study, the 200 recruited APIP patients were divided into three groups according to the severity of the disease, namely MAP, MSAP, and SAP. The comparative analysis included the general conditions of the three groups of patients at the time of admission. There were no significant differences in BMI, the onset of pregnancy, and gravidity. The age of onset and parity of patients in the SAP group and MSAP group were significantly higher compared to the MAP group, and the difference was statistically significant ($P<0.05$). The rate of MSAP or SAP group combined with gestational diabetes or hypertension in pregnancy was higher than that of MAP group. However, there was no significant difference ($P=0.061$, $P=0.081$). The etiology composition of the three groups was also significantly different. HTG-AP accounted for 64.6% and 74.4% of MSAP and SAP patients, respectively, which was significantly higher than 21.7% in the MAP group ($P<0.05$) (Table 2).

Comparison of Blood Lipid Test results of Patients with Different Severity of APIP Within 24 Hours After Admission

A comparative study analyzed the blood lipid test results of patients with different severity levels were compared. Evidently, the TG concentrations on the admission of SAP and MSAP groups were 17.8 (4.30–40.17) mmol/L and 24.98 (6.49–45.00) mmol/L, respectively, these results are much higher than MAP Group with 3.08 (1.82–7.97) mmol/L ($P<0.05$). Moreover, significant differences existed in concentrations of the admission serum TC and APO-A with different severity of APIP patients ($P<0.05$) (Table 3).

Table 1 Situation Analysis of Maternal Deaths

	Gestational Age, Weeks (n=81)	Etiology of AP	Cause of Maternal Death	TG Level at Admission, mmol/L	Fetal Outcomes
Case 1	34	HTG	MOF	46	Fetal death in the uterus
Case 2	23	HTG	MOF	10.54	Abortion
Case 3	25	HTG	Encephalopathy	36.35	Abortion
Case 4	33	HTG	Cardiac sudden death	35.22	Fetal death in the uterus
Case 5	34	HTG	MOF	41.3	Fetal death in the uterus
Case 6	32	HTG	Cardiac sudden death	88.4	Premature birth
Case 7	30	HTG	Hemorrhagic shock	45.86	Fetal death in the uterus

Abbreviations: HTG, hypertriglyceridemia; MOF, multiple organ failure; TG, triglycerides.

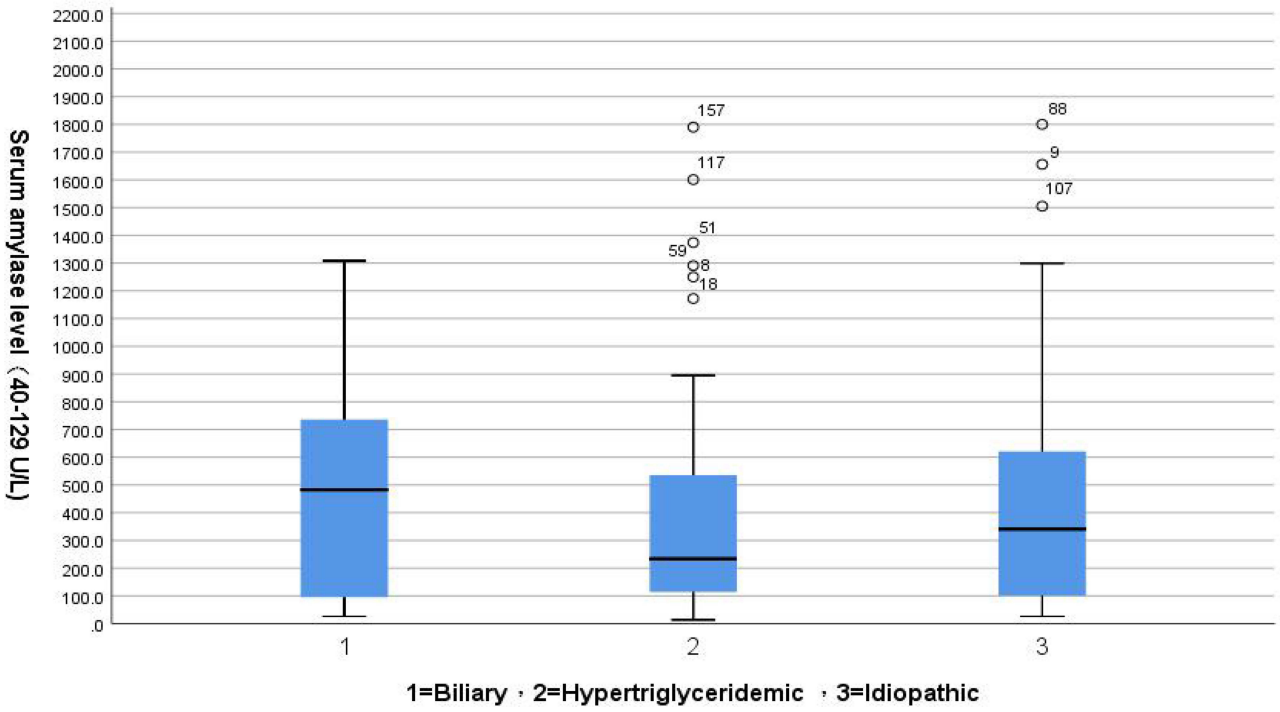

Figure 2 Comparison of serum amylase levels under different etiological factors. *P*=0.079.

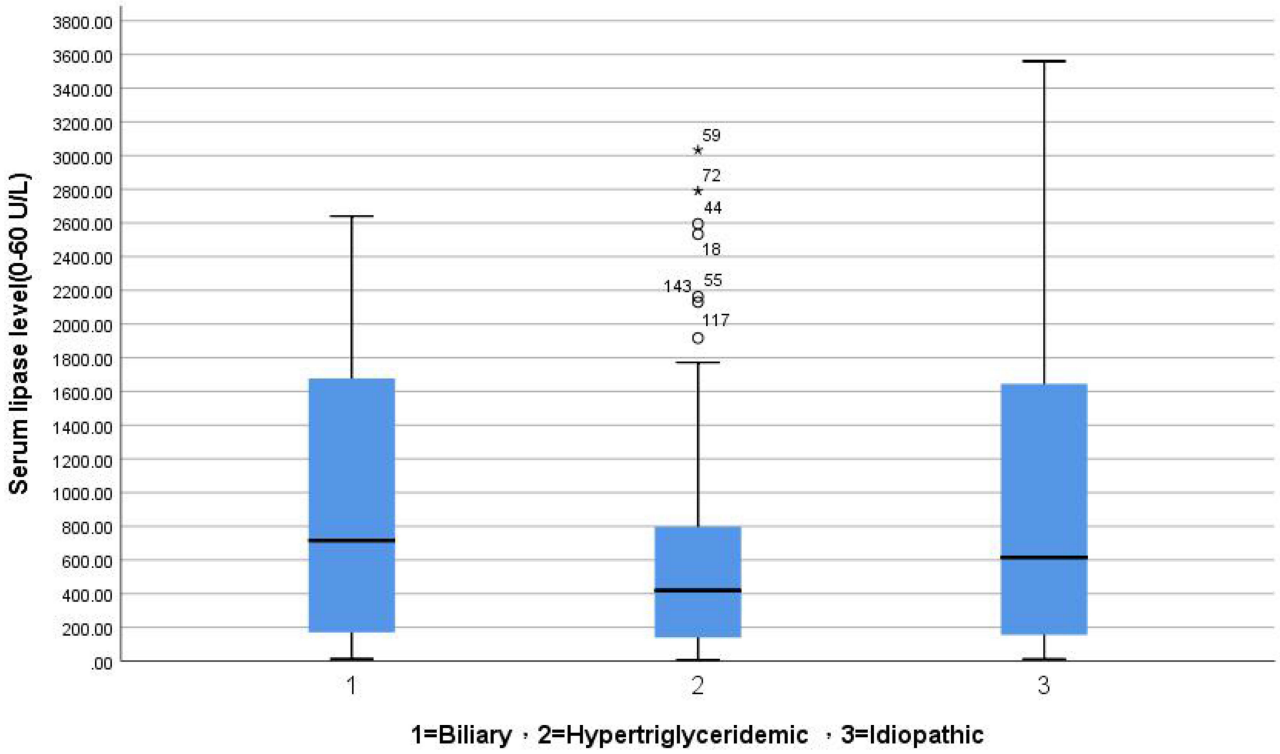

Figure 3 Comparison of serum lipase levels distribution under different etiological factors. *P*=0.026.

Table 2 Comparison of General Conditions in Acute Pancreatitis Patients with Different Severity of Pregnancy

	MAP (n=92)	MSAP (n=65)	SAP (n=43)	*P*
Age, years, mean±SD	27.52±4.75	29.89±5.24	30.65±5.10	0.001#
Trimester of pregnancy, n (%)				
First (before 14 weeks)	10 (10.9%)	1 (1.5%)	1 (2.3%)	0.132
Second (14–27^{+6} weeks)	14 (15.2%)	11 (16.9%)	9 (20.5%)	
Third (after 28 weeks)	68 (73.9%)	53 (81.5%)	33 (76.7%)	
*Gravidity	2 (1–3)	2 (1–3)	2 (1–3)	0.384
Parity				
0	65 (75.3%)	31 (47.7%)	26 (60.5%)	0.008#
1	21 (23.6%)	30 (46.2%)	16 (37.2%)	
2 times or more	1 (1.1%)	4 (6.2%)	1 (2.3%)	
*BMI	27.22 (23.88–28.93)	27.61 (24.73–31.25)	27.39 (23.66–31.25)	0.417
Diabetes, n (%)				
Diabetes in pregnancy	2 (2.2%)	2 (3.1%)	1 (2.3%)	0.061
Gestational diabetes	22 (23.9%)	22 (33.8%)	17 (39.5%)	
Hypertensive disorders, n (%)				
Gestational hypertension	4 (4.3%)	8 (12.3%)	5 (11.6%)	0.081
Preeclampsia	3 (3.3%)	5 (7.7%)	4 (9.3%)	
Eclampsia	1 (1.1%)	2 (3.1%)	0 (0.0%)	
Etiology, n (%)				
Biliary	29 (31.5%)	9 (13.8%)	2 (4.7%)	<0.05#
HTG	20 (21.7%)	42 (64.6%)	32 (74.4%)	
Idiopathic	43 (46.7%)	14 (21.5%)	9 (20.9%)	

Notes: *Indicates that data were not normally distributed and were expressed as median (interquartile range), M(Q); #Indicates *P*<0.05, indicating that the difference was statistically significant.
Abbreviations: BMI, body mass index; HTG, hypertriglyceridemia; MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis.

Table 3 Comparison of Blood Lipids Levels Within 24 Hours After Admission in APIP Patients with Different Severity

	MAP (n=92)	MSAP (n=65)	SAP (n=43)	*P*
*TG, mmol/L	3.08 (1.82–7.97)	17.8 (4.30–40.17)	24.98 (6.49–45.00)	<0.05#
*TC, mmol/L	5.30 (4.24–7.03)	11.62 (5.51–18.17)	15.62 (6.01–20.69)	<0.05#
*HDL, mmol/L	1.34 (0.97–1.66)	1.37 (1.02–1.77)	1.24 (0.79–1.68)	0.682
*LDL, mmol/L	2.43 (1.73–3.37)	2.29 (1.55–4.02)	1.79 (1.14–3.38)	0.234
APO-A, g/L,mean±SD	1.61±0.58	1.35±0.54	1.12±0.62	<0.05#
APO-B, g/L,mean±SD	1.09±0.39	1.03±0.57	0.88±0.62	0.062

Notes: *Indicates that data were not normally distributed and are expressed as median (interquartile range), M(Q); #Indicates *P*<0.05, indicating that the difference was statistically significant.
Abbreviations: APO, apolipoprotein; HDL, high density lipoprotein; LDL, low density lipoprotein; MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; TC, total cholesterol; TG, triglycerides.

Analysis of the Relationship Between the General Condition of APIP Patients, The Results of 24-Hour Blood Lipid Test and the Severity of APIP Disease

Tables 1 and 2 show that there were significant differences among the three groups in age of onset, parity, etiology, and 24-hour serum TG, TC, APO-A concentrations. The correlation analysis of Kendall's tau-b was used to analyze the relationship between the above five indexes and the severity of APIP. These results showed that there was a significant positive correlation between serum TG, TC concentration and the severity of pancreatitis, and

Table 4 Correlation Coefficients Between the Statistically Significant Indicators in Tables 1 and 2 and the Severity of Disease in APIP Patients

	Age, Years	TG, mmol/L	TC, mmol/L	APO-A, g/L	Parity, n
P	<0.05#	<0.05#	<0.05#	<0.05#	0.011
Correlation coefficient, *r*	0.255	0.489	0.403	−0.322	0.169

Notes: #Indicates *P*<0.05, indicating that the difference was statistically significant.
Abbreviations: APO, apolipoprotein; TC, total cholesterol; TG, triglycerides.

a significant negative correlation between APO-A concentration and the severity of pancreatitis ($P<0.05$) (Table 4).

Comparison of Clinical Characteristics of Different Triglyceride Levels with Acute Severe Pancreatitis

This study graded concentrations of serum TG at 24 hours of admission to further explore the relationship between TG levels and APIP severity. Specifically, the comparative analysis included the clinical characteristics of APIP patients with different TG levels.

Due to the current lack of grading standards for serum TG levels in pregnant females, this study referred to the "NCEP ATP III",[19] which defines TG concentrations at 1.7–2.3mmol/L as marginal increase, 2.3mmol/L–5.65mmol/L as an increase, TG≥5.65mmol/L as a severe increase. In accordance with the "The Endocrine Society 2010", TG at 1.7–2.3mmol/L is defined as mildly high HTG, 2.3mmol/L- 5.65mmol/L as moderate HTG, and TG≥11.2mmol/L as severe HTG. Considering the physiological 2–3 times increase of blood lipids during pregnancy,[4] the marginally elevated TG level and the normal TG level were classified into one grade. Resultantly, the serum TG concentrations were divided into four levels: 0–2.3mmol/L, 2.3–5.65mmol/L, 5.65–11.2mmol/L, and ≥11.2mmol/L. As indicated in Table 5, with increasing of the serum TG level, the indicators reflecting the severity of the disease increase significantly. These indicators contain the mortality rate during hospitalization, perinatal mortality, respiratory and circulatory system failure, persistent organ failure, pleural effusion, ascites, pelvic effusion, systemic inflammatory response syndrome (SIRS), and DKA.

Relationship Between TG Level and APIP Severity Under Ordered Logistic Regression Analysis

In order to verify the association between different TG levels and the severity of disease in APIP patients, the present study classified the serum TG levels according to the four levels stated above and proceeded and performed an ordered logistic regression analysis.

Table 6 indicates the results from the univariate and multivariate ordinal logistic regression analysis. TG level was considered to be the only covariant. Patients who had a TG level of 0–2.3 mmol/L were set as the control group. According to the unadjusted single factor logistic regression model, the OR of the TG group with 2.3–5.65mmol/L is 1.112 (95% CI=0.449–2.753, P=0.819), the OR of the TG group with 5.65–11.2mmol/L is 3.631 (95% CI=1.379–9.561, P=0.009), and the OR of the TG group with ≥11.2mmol/L is 9.365 (95% CI=4.196–20.904, P<0.05).

Upon adjusting the effects of age, parity, TC and APO-A, the multivariate ordinal logistic regression analysis showed that the OR values of SAP at different TG levels were 1.036 (95% CI = 0.401–2.677, P = 0.941) at the 2.3–5.65 mmol/L level, 3.429 (95% CI = 1.269–9265, P = 0.015) at the 5.65–11.2 mmol/L level, and 8.329 (95% CI = 3.713–18.682, P< 0.05) at the ≥11.2 mmol/L level, respectively. Despite the reduction in the association of TG classification with SAP justification and sequential adjustments, TG showed a significant and clear gradient from the lowest to the highest level (Table 6).

The Relationship Between Different Triglyceride Levels and the Severity of Acute Pancreatitis During Pregnancy

The adjusted multivariate ordinal logistic regression analysis model is used to gain the predicted probability of SAP. Figure 4 shows a scatter plot of serum the TG and SAP prediction probabilities. Lowess fitting curves are used to describe the relationship. A non-linear relationship exists between TG level and SAP probability. APIP patients with serum TG concentrations in the range of 6–7 mmol/L at hospital admission

Table 5 Comparison of Clinical Characteristics of APIP Patients with Different Triglyceride Levels

	TG< 2.3mmol/L	TG≥ 2.3mmol/L and < 5.65mmol/L	TG ≥ 5.65mmol/L and <11.2mmol/L	TG≥ 11.2mmol/L	*P*
n	45	46	29	80	
*BMI	26.98 (23.55–30.30)	27.06 (24.12–28.96)	26.56 (23.44–29.06)	28.33 (25.02–30.94)	0.534
*Length of ICU stay, days	0 (0–3)	2 (1–3)	3 (1–6)	4 (3–7)	<0.05#
*Total costs, ¥	27,626 (16,318–54,105)	27,477 (14,942–59,305)	54,945 (26,929–102,829)	77,907 (49,273–117,044)	<0.05#
Maternal deaths, n (%)	0 (0%)	0 (0%)	1 (3.4%)	6 (7.5%)	0.011#
Fetal loss, n (%)	10 (22.2%)	5 (10.9%)	8 (27.6%)	32 (40.0%)	0.010#
OF, n(%)					
Respiratory failure	4 (8.9%)	4 (8.7%)	6 (20.7%)	31 (38.8%)	<0.05#
Renal failure	5 (11.1%)	6 (13.6%)	5 (17.2%)	11 (13.8%)	0.667
Circulatory failure	3 (6.7%)	3 (6.7%)	4 (13.8%)	20 (25.0%)	0.001#
POF, n (%)	5 (11.1%)	3 (6.5%)	7 (24.1%)	28 (35.0%)	<0.05#
Pleural effusion, n (%)	11 (24.4%)	15 (32.6%)	16 (55.2%)	47 (58.8%)	<0.05#
Peritoneal effusion, n (%)	15 (33.3%)	17 (37.8%)	17 (58.6%)	42 (52.5%)	0.013#
Pelvic effusion, n (%)	7 (16.3%)	8 (17.4%)	10 (34.5%)	27 –(34.2%)	0.008#
SIRS, n (%)	15 (33.3%)	13 (28.3%)	12 (41.4%)	48 (60%)	0.009#
DKA, n (%)	1 (2.2%)	1 (2.2%)	3 (10.3%)	15 (18.75%)	0.001#
Localized complications, n (%)					
Acute peri-pancreatic fluid collection	10 (22.2%)	13 (28.3%)	7 (24.1%)	33 (41.3%)	0.004#
Pseudocyst	2 (4.4%)	4 (8.7%)	2 (6.9%)	4 (5.0%)	
Walled-off necrosis	0 (0%)	0 (0%)	0 (0%)	2 (2.5%)	
Acute necrotic collections	0 (0%)	1 (2.2%)	1 (3.4%)	3 (3.6%)	

Notes: *Indicates that data were not normally distributed and are expressed as median (interquartile range), M(Q); #Indicates P<0.05, indicating that the difference was statistically significant.

Abbreviations: BMI, body mass index; DKA, diabetic ketoacidosis; MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; OF, organ failure; POF, persistent organ failure; SAP, severe acute pancreatitis; SIRS, systemic inflammatory response syndrome; TG, triglycerides.

have the lowest probability of SAP. Moreover, the probability of developing SAP is less than 0.2 in patients with a TG concentration of less than 6mmol/L. Lastly, in patients with a TG concentration higher than 7mmol/L, the predicted probability of SAP gradually increases as the TG concentration increases (Figure 4).

ROC Curve Calculation Predicts the Critical Value of TG Level Within 24 Hours of Admission to the Occurrence of SAP

The ROC curve analysis also included the TG concentrations and SAP occurrence within 24 h of admission. The cut-off value of the admission triglyceride concentration for predicting the occurrence of SAP is 10.7mmol/L, the sensitivity is 0.72, the specificity is 0.65, and the area under the curve (AUC) is 0.708, $P<0.05$, 95% CI: 0.620 −0.796 (Figure 5 and Table 7).

Discussion

Besides being extremely challenging to diagnose early, APIP is a disease that also progresses rapidly. APIP escalates to severe acute pancreatitis, which is detrimental to the health of both mothers and fetuses.[20–22] Finding the etiology and the primary influencing factors of APIP, particularly in SAPIP patients is of great significance to prevent and treat the disease. The present study conducted a retrospective analysis of APIP patients admitted to a regional medical center in Northeast China over the past eight years.

Table 6 Logistic Regression Analysis of the Relationship Between Triglyceride Level and Severity of APIP

Model Adjustment	TG Classification	SE	Wald	*P*	OR (95% CI)
Univariate Analysis	<2.3mmol/L	–	–	–	–
	2.3mmol/L~	0.463	0.52	0.819	1.112 (0.449–2.753)
	5.65mmol/L~	0.494	6.814	0.009	3.631 (1.379–9.561)
	11.2mmol/L~	0.410	29.818	<0.05#	9.365 (4.196–20.904)
Adjust Model[a]	<2.3mmol/L	–	–	–	–
	2.3mmol/L~	0.484	0.005	0.941	1.036 (0.401–2.677)
	5.65mmol/L~	0.507	5.905	0.015	3.429 (1.269–9265)
	11.2mmol/L~	0.412	26.450	<0.05#	8.329 (3.713–18.682)

Notes: Adjust Model[a]: adjusted for baseline age, Cholesterol, APO-A and parity; #Indicates *P*<0.05, indicating that the difference was statistically significant.
Abbreviations: ORs, odds ratios; TG, triglycerides;.

Reportedly, HTG-AP accounted for 47%, which is the primary cause of this group of cases. In the SAP group, the cause of HTG accounted for 74.4%, which was significantly higher than the rate in the MAP group. All seven perinatal fatalities in the hospital were HTG-AP, and 67.5% of perinatal deaths also occurred in HTG-AP patients.

Previous studies of acute pancreatitis in the general population have found serum amylase and lipase levels are spuriously low in patients with HTG-AP and may be normal in more than 50% patients at the time of admission or during the hospital course.[8,23] Our study found this phenomenon also existed in APIP. The distribution of serum amylase and serum lipase on admission in HTG-AP was significantly lower than that in patients with biliary and idiopathic pancreatitis in the current research.

Unlike serum amylase and lipase, the TG and TC levels in the SAP group within 24 hours of admission

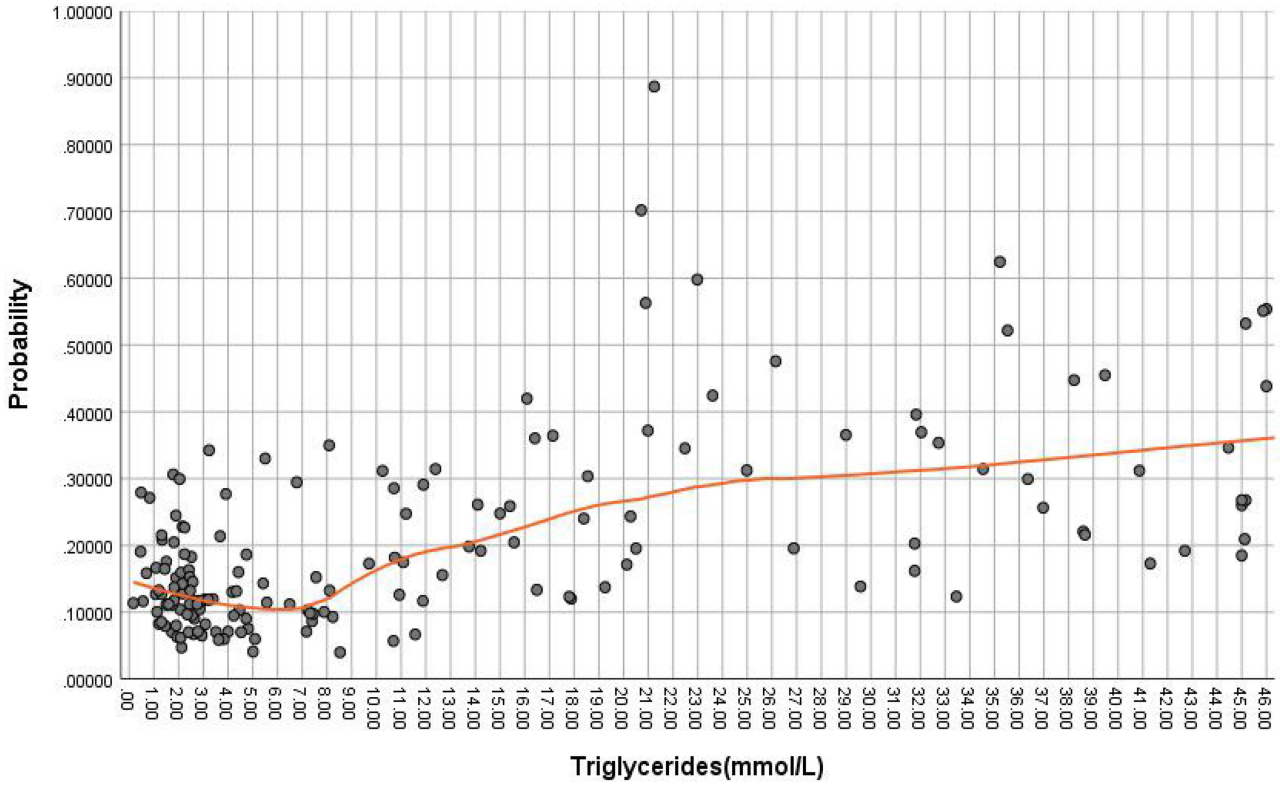

Figure 4 Observed and expected incidence of SAP in patients with different triglycerides concentrations.
Notes: The black circles give the observed incidence of SAP for each patient. The solid curve gives expected incidence of SAP based on restricted cubic spline analysis.
Abbreviation: SAP, severe acute pancreatitis.

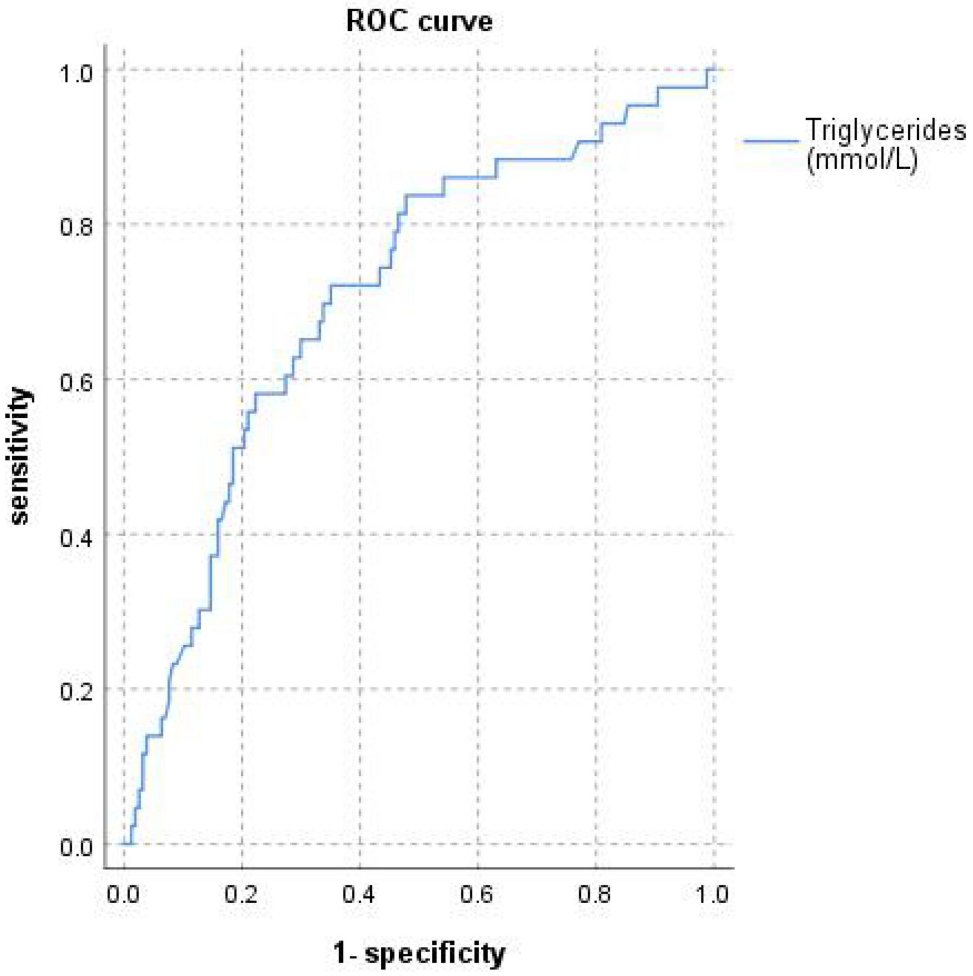

Figure 5 Receiving operator curve of serum TG 24h within admission in predicting SAP.
Abbreviations: ROC, receiving operator curve; SAP, severe acute pancreatitis.

were significantly higher compared to the MSAP and MAP groups. Moreover, the concentration of APO-A was significantly lower compared to the MSAP and MAP groups ($P<0.05$). Correlation analysis demonstrated that the serum TG concentrations and TC concentrations of patients within 24 hours of admission, age, and parity, have a significant positive correlation with the severity of the disease. Meanwhile, the APO-A concentration has a significant negative correlation with the severity.

Observations of AP patients in the general population reveal that compared with other causes, the HTG-AP patients are more severe and have a higher incidence of complications and a higher mortality rate.[5,6,9] A meta-analysis of 16 related trials showed that the incidence of local and systemic complications and mortality in patients with TG ≥11.2 mmol/L were significantly higher compared to those with TG < 11.2 mmol/L.[24] Furthermore, in a Spanish study of 1457 non-pregnant AP patients, the incidences of pancreatitis necrosis and POF increased significantly with the level of HTG within 48 hours of admission progressing (TG < 200 mg/dl, TG=200–749 mg/dl, TG ≥ 750 mg/dl), ($P < 0.05$).[10] In the current study, it was also observed that when admission TG levels increased, local and system complications, POF, and fetus death increased in APIP patients.

Table 7 Receiver Operating Characteristic Curve Analysis of the Predictors of SAP

	AUC (95% CI)	*P* value	Sensitivity	Specificity	Threshold Value
TG, mmol/L	0.708 (0.620–0.796)	<0.05	0.72	0.65	10.7

Abbreviations: AUC, area under curve; TG, triglycerides.

The pathogenesis of AP and severe complications caused by HTG remain unclear. It could be that the high concentration of chylo particles increases blood flow resistance, which leads to pancreatic microcirculation disorders, and even ischemia and necrosis. Meanwhile, TG is hydrolyzed by pancreatic lipase into an excessive quantity of free fatty acid (FFA), which severely damages acinar cells and pancreatic capillary endothelium. Also, the FFA reduces the PH value in the pancreas, and the acidic environment accelerates the activation of trypsinogen, which leads to severe pancreatic self-digestion and activation of inflammatory cells. The release and cascade activation of numerous inflammatory mediators lead to severe systemic inflammation. Inflammatory mediators damage alveoli and cause respiratory failure, which is the most common organ failure associated with SAP.[25] The occurrence of respiratory failure was also observed in the current study. In the group that had an admission TG of over 11.2 mmol/L, the incidence of respiratory failure was as high as 38.8% (Table 5), which was much higher than the cases with TG lower than 11.2 mmol/L ($P<0.05$).

Serious microcirculation disorders, water, electrolyte, and acid-base disorders, could also lead to circulatory disorders.[3] Inadequate correction of fluid deficiency and relatively low blood volume also elevates the risk of pancreatic necrosis.[26] Meanwhile, aggressive fluid resuscitation increases cardiac load and elevates the risk of cardiac insufficiency.[27] Therefore, patients with HTG-AP often have accompanying conditions such as severe respiratory failure, circulatory failure, and other multiple organ dysfunction syndromes. As a result, they are susceptible to early death.[3]

Biliary pancreatitis is the primary etiology cause of AP in general population, accounting for 40–70%, while HTG-AP is only 2–4%.[28] Different from the general population, the incidence of HTG-AP in pregnancy was much higher,[11,29] which reached 29.6–32.2% in several recent studies from East Asia.[13,16,30] In the present study, HTG-AP was the primary cause, accounting for 47%.

During pregnancy, the demand for nutrients increases to meet the needs of fetal growth and development. Prolactin and chorionic gonadotropin alter lipid metabolism, which is mainly manifested in the fat accumulation during early and middle pregnancy and the fat catabolism in late pregnancy. It results in physiological hyperlipidemia in pregnancy, which even reaches 2–3 times that in the late pregnancy.[8] It may partly explain the higher incidence of HTG-AP in pregnant women. The literature reports a different incidence of HTG-APIP between Caucasian and Asian populations, which might be explained by the differences in dietary habits and lifestyle of pregnant women from different regions and cultural backgrounds.[3,31] However, additional research is needed to assess if it is influenced by genetic factors. In pregnant women, congenital hypertriglyceridemia may be associated with a deficiency of lipoprotein lipase or Apolipoprotein C-II.[28]

Considering the higher incidence and harmfulness of HTG-AP in pregnant women, it is crucial to monitor the blood lipid level during pregnancy. The present study found that the severity of APIP increased significantly with the increase of TG levels. So, it was necessary to explore the relationship between TG levels and SAP. The trend of the Lowess fitting curve exhibits a non-linear relationship between TG concentrations and SAP prediction. Only patients with TG concentrations above 7mmol/L have a steadily increasing SAP prediction probability with the increase in TG. The incidence of SAP in patients with TG concentrations below 7 mmol/L fluctuated at a lower level and showed an overall tendency to decline. A plausible explanation is that most of the patients with TG concentrations below 7 mmol/L are non-HTG-AP. In non-HTG-APIP patients, the association between TG level and the incidence of SAP is not obvious.

Due to the increased risk of SAP in patients with high levels of TG, the cut-off value of TG concentrations was calculated to predict the occurrence of SAP through the ROC curve, which was 10.7mmol/L, with a sensitivity of 0.72, a specificity of 0.65, and AUC of 0.78.

APIP is a rapidly developing condition with high maternal and infant mortality. However, there are few reports on large sample studies on HTG-APIP. The two obtainable retrospective studies of APIP in recent years were all from the Chinese population, where the incidence of HTG was 32.2% and 40.7%, respectively.[13,17] In one study, there was a higher risk of fetal distress during pregnancy compared to other causes.[13] The other study observed peripancreatic fluid accumulation in nearly half of the HTG-APIP patients.[17] The current study confirmed these phenomena. The present study also provides evidence that the severity of APIP was associated with elevated TG levels, and the risk of SAP considerably increased when TG was above 10.7 mmol/L.

It is crucial to pay attention to monitoring of blood lipid level of pregnant women, for those with abnormal

blood lipid, a strict low-fat and low-energy diet is ideal, which should be combined with lipid-lowering treatment when necessary.[32] Due to the contraindication of most lipid-lowering drugs in pregnancy, great attention should be paid to weigh the advantages and disadvantages of lipid-lowering treatment. It is crucial to choose the drugs that have less impact on pregnant women and fetus whilst effectively reducing blood lipid, especially TG level, and preventing the occurrence of APIP.[28]

For pregnant women with AP and combined HTG, specialized nutritional support, such as insulin, heparin, and medium-chain triglycerides, are clinically recommended. Plasma exchange is also effective to reduce blood lipid levels urgently.[25,33] Several studies have confirmed that plasma exchange can quickly eliminate harmful cytokines and inflammatory mediators in the circulation to significantly improve clinical symptoms.[33,34] There is no large-scale study of plasma exchange in acute pancreatitis patients with hyperlipidemia. Only a few cases have been reported to be effective.[28] Therefore, whether plasma exchange can effectively improve maternal and infant prognosis in HTG-APIP patients is worthy of future study.

Clinical observations indicate that maternal blood lipid concentrations can reduce by 15–20% within 24 hours after delivery. It returns to normal levels within six weeks after delivery.[33] For APIP patients nearing the term can suffer fetal distress, serious maternal complications, and even organ failure. In such cases, active termination of pregnancy can improve refractory hypertriglyceridemia, reduce abdominal pressure, and relieve peripancreatic edema. Consequently, it improves clinical symptoms and reduces maternal and child mortality.[3,13] In the present study, the maternal mortality rate was 3.5%, and the perinatal mortality rate was 27.5%, both are much lower than those reported in the literature.[3,35] It could most likely be because 90% of the patients actively terminated the pregnancy.

The accompanying disorder of glucose and lipid metabolism accelerates the progress of APIP. AP, DKA, and HTG are often mutually causal and interact with each other to form a "death triangle".[36] The state of high blood sugar, high blood ketones, dehydration, electrolyte disturbances, and metabolic acidosis make patients prone to hyperosmolar coma and eventually life-threatening circumstances.[26] A study of 2.8 million patients with acute pancreatitis indicated that compared with simple HTG-AP patients, DKA and HTG triad had significantly higher mortality, multiple organ failure rate, longer hospitalization periods, and higher costs in AP patients.[36] In the present study, there were 20 cases of DKA (10%). The incidence of DKA in the TG≥11.2 mmol/L group was 18.75%, which was higher than those of the other three groups. Based on the literature and the observation results, it is crucial to monitor the blood glucose, pay attention to correcting hyperglycemia, and avoid DKA in HTG-APIP patients. It is vital to reduce maternal and infant mortality and improving the currently poor prognosis.

According to the experience and observation from this study, early identification, close monitoring, and active treatment are critical for APIP patients. If the patient does not show any sign of improvement after 24–48 hours of active treatment, the pregnancy should be terminated immediately. For those with a small gestational age, repeated plasma exchange is recommended, and then whether to continue the pregnancy should be considered.[28] The ideal scenario is to save both the mother and the child. However, clinical practitioners should inform the mother that blindly prolonging gestational weeks of the fetus drastically reduces the success rate of the rescue of both the mother and the fetus.[3,4,17] Therefore, since the life of the pregnant woman is of priority, it is recommended to not miss out on the window of opportunity to terminate the pregnancy.

Conclusion

A retrospective study of APIP cases in the regional medical center of Northeast China in the past eight years shows that HTG-AP is the primary cause of APIP in this group of people. Moreover, 24 hours after admission, the elevation of serum TG was positively correlated with the severity of AP disease, R = 0.403 ($P < 0.05$). Upon adjusting for age, parity, TC, and APO-A, the TG slightly increased group (2.23–5.65mmol/L) had an OR value of SAP of 1.036 (95% CI = 0.401–2.677), in the TG = 5.65–11.2mmol/L group, the OR value of SAP was 3.429 (95% CI = 1.269–9265), and when TG ≥11.2mmol/L, the OR of SAP was 8.329 (95% CI=3.713–18.682). It was found that the increase of serum TG is related to elevated maternal mortality, perinatal mortality, respiratory system, circulatory system organ dysfunction, pleural effusion, pelvic effusion, and POF. The higher the TG level was, the higher the risk of SAP. Using 10.7 mmol/L as the threshold to predict the occurrence of SAPIP, the sensitivity and specificity were 0.72 and 0.65, respectively.

In conclusion, it is critical to pay attention to the role of triglycerides in the occurrence and development of APIP patients. In patients with suspected APIP, closely monitoring the serum TG levels with the active support of treatment is essential. In the future, more effective treatment will be needed to reduce the mortality and improve the prognosis of HTG-APIP.

Ethics Statement

As a non-interventional retrospective studies, data was kept anonymous. The ethics committee passed our application for exemption from informed consent. We have obtained ethical approval to conduct the study, as well as permission from the electronic medical record database of the Shengjing Affiliated Hospital of China Medical University to use the information for the purpose of the research. Institutional ethical approval was obtained from the ethics committee of Shengjing Affiliated Hospital of China Medical University (Approval No 2019PS683K) on 11 DEC 2019 prior to the study. The study complied with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Guo X, Li Z, Tang C, Yuan Y, Wang Z. Chinese guidelines for the management of acute pancreatitis. *Chin J Pancreatol*. 2019;19(5):321–331.
2. Berger Z, Mancilla C, Tobar E, et al. Acute pancreatitis in Chile: a multicenter study on epidemiology, etiology and clinical outcome. Retrospective analysis of clinical files. *Pancreatology*. 2020;(20):30145–30149.
3. Alnaggar M. Clinical analysis of pregnancy associated with acute pancreatitis. *Int J Adv Med*. 2016;3(4):799–803. doi:10.18203/2349-3933.ijam20163716
4. Mali P. Pancreatitis in pregnancy: etiology, diagnosis, treatment, and outcomes. *Hepatobiliary Pancreat Dis Int*. 2016;15(4):434–438. doi:10.1016/S1499-3872(16)60075-9
5. Wan J, He W, Zhu Y, et al. Stratified analysis and clinical significance of elevated serum triglyceride levels in early acute pancreatitis: a retrospective study. *Lipids Health Dis*. 2017;16(1):124. doi:10.1186/s12944-017-0517-3
6. Nawaz H, Koutroumpakis E, Easler J, et al. Elevated serum triglycerides are independently associated with persistent organ failure in acute pancreatitis. *Am J Gastroenterol*. 2015;110(10):1497–1503. doi:10.1038/ajg.2015.261
7. Garg PK, Singh VP. Organ failure due to systemic injury in acute pancreatitis. *Gastroenterology*. 2019;156(7):2008–2023. doi:10.1053/j.gastro.2018.12.041
8. Yadav D, Pitchumoni CS. Issues in hyperlipidemic pancreatitis. *J Clin Gastroenterol*. 2003;36(1):54–62. doi:10.1097/00004836-200301000-00016
9. Toskes PP. Hyperlipidemic pancreatitis gastroenterol. *Clin North Am*. 1990;19(4):783–791.
10. Pascual I, Sanahuja A, García N, et al. 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. doi:10.1016/j.pan.2019.06.006
11. Valdivielso P, Ramírez-Bueno A, Ewald N. Current knowledge of hypertriglyceridemic pancreatitis. *Eur J Intern Med*. 2014;25(8):689–694.
12. Christian JB, Bourgeois N, Snipes R, Lowe KA. Prevalence of severe (500 to 2000 mg/dl) hypertriglyceridemia in United States adults. *Am J Cardiol*. 2011;107(6):891–897. doi:10.1016/j.amjcard.2010.11.008
13. 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*. 2018;97(7):e9755. doi:10.1097/MD.0000000000009755
14. Ghio A, Bertolotto A, Resi V, Volpe L, Cianni GD. Triglyceride metabolism in pregnancy. *Adv Clin Chem*. 2011;55:133–153.
15. Sarr MG. 2012 revision of the Atlanta classification of acute pancreatitis. *Pol Arch Med Wewn*. 2013;123(3):118–124.
16. Huang CL, Liu J, Lu YY, et al. Clinical features and treatment of hypertriglyceridemia-induced acute pancreatitis during pregnancy: a retrospective study. *J Clin Apher*. 2016;31(6):571–578. doi:10.1002/jca.21453
17. Luo LY, Zen H, Xu HR, et al. Clinical characteristics of acute pancreatitis in pregnancy: experience based on 121 cases. *Arch Gynecol Obstet*. 2018;297(2):333–339. doi:10.1007/s00404-017-4558-7
18. Coutada RS, Cunha SS, Gonçalves ES. Diabetic ketoacidosis in pregnancy. *Int J Reprod Contracept Obstet Gynecol*. 2018;7(7):2945–2947. doi:10.18203/2320-1770.ijrcog20182912
19. Berglund L, Brunzell JD, Goldberg AC, et al. Evaluation and treatment of hypertriglyceridemia: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(9):2969–2989. doi:10.1210/jc.2011-3213
20. Zhang Y, Wu H, Wang C. Serum calcium as an indicator of persistent organ failure in acute pancreatitis. *Am J Emerg Med*. 2017;35(7):978–982. doi:10.1016/j.ajem.2017.02.006
21. Zhou CL, Zhang CH, Zhao XY, et al. Early prediction of persistent organ failure by serum apolipoprotein A-I and high-density lipoprotein cholesterol in patients with acute pancreatitis. *Clin Chim Acta*. 2018;476:139–145. doi:10.1016/j.cca.2017.11.028
22. Shera IA, Shawl MR, Chakravarty S. Does elevated serum levels of procalcitonin potentially correlate with severity of acute pancreatitis: a prospective study. *Pancreat Disord Ther*. 2018;8(2):194–199. doi:10.4172/2165-7092.1000194
23. Fortson MR, Freedman SN, Webster PD III. Clinical assessment of hyperlipidemic pancreatitis. *Am J Gastroenterol*. 1995;90(12):2134–2139.

24. Kiss L, Fűr G, Mátrai P, et al. The effect of serum triglyceride concentration on the outcome of acute pancreatitis: systematic review and meta-analysis. *Sci Rep*. 2018;20(1):14096. doi:10.1038/s41598-018-32337-x
25. 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. doi:10.5152/TJAR.2014.83435
26. Timilsina S, Timilsina S, Mandal A, Paudel R, Gayam V. Triad of diabetic ketoacidosis, hypertriglyceridemia, and acute pancreatitis: severity of acute pancreatitis may correlate with the level of hypertriglyceridemia. *Cureus*. 2019;11(6):e4930.
27. Mao EQ, Fei J, Peng YB, et al. Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis Chin. *Med J*. 2010;123(13):1639–1644.
28. 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. doi:10.1186/s12944-019-1180-7
29. Zhu Y, Pan X, Zeng H, et al. A study on the etiology, severity, and mortality of 3260 patients with acute pancreatitis according to the revised Atlanta classification in Jiangxi, China over an 8-year period. *Pancreas*. 2017;46(4):504–509. doi:10.1097/MPA.0000000000000776
30. Jin J, Yu YH, Zhong M, Zhang GW. Analyzing and identifying risk factors for acute pancreatitis with different etiologies in pregnancy. *J Matern Fetal Neonatal Med*. 2015;28(3):267–271. doi:10.3109/14767058.2014.913132
31. Hu J, Oken E, Aris IM. Dietary patterns during pregnancy are associated with the risk of gestational diabetes mellitus: evidence from a Chinese prospective birth cohort study. *Nutrients*. 2019;11:E405. doi:10.3390/nu11020405
32. Emet T, Ustüner I, Güven SG, et al. Plasma lipids and lipoproteins during pregnancy and related pregnancy outcomes. *Arch Gynecol Obstet*. 2013;288(1):49–55. doi:10.1007/s00404-013-2750-y
33. Jeon HR, Kim SY, Cho YJ, Sj. C. Hypertriglyceridemia-induced acute pancreatitis in pregnancy causing maternal death. *Obstet Gynecol Sci*. 2016;59(2):148–151. doi:10.5468/ogs.2016.59.2.148
34. Rawla P, Sunkara T, Thandra KC, Gaduputi V. Hypertriglyceridemia-induced pancreatitis: updated review of current treatment and preventive strategies. *Clin J Gastroenterol*. 2018;11(6):441–448. doi:10.1007/s12328-018-0881-1
35. Ducarme G, Maire F, Chatel P, Luton D, Hammel P. Acute pancreatitis during pregnancy: a review. *J Perinatol*. 2014;34(2):87–94. doi:10.1038/jp.2013.161
36. Simons-Linares CR, Jang S, Sanaka M, et al. The triad of diabetes ketoacidosis, hypertriglyceridemia and acute pancreatitis. How does it affect mortality and morbidity? A 10-year analysis of the national inpatient sample. *Medicine*. 2019;98(7):e14378. doi:10.1097/MD.0000000000014378