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The clinical characteristic of biliary-hyperlipidemic etiologically complex type of acute pancreatitis: a retrospective study from a tertiary center in China

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Abstract. – OBJECTIVE: Biliary and hyperlipidemic acute pancreatitis (AP) has become the second most common AP in China. Currently, AP is exclusively diagnosed as biliary or hyperlipidemic AP. However, as suggested by some reports, biliary and hyperlipidemic AP might coexist in a single patient. Moreover, acute lipotoxicity was shown to regulate the severity of biliary AP in the mouse model. Thus, whether these two etiologies coexist in AP patients and potentially worsen the clinical course remains unclear. To elucidate the clinical feature of a new complex type of acute pancreatitis with both biliary and hyperlipidemic etiologies.

PATIENTS AND METHODS: This retrospective study included AP patients who were admitted into our department within 7 days after the onset of the disease. 267 AP patients were enrolled in this study and were classified as BAP (biliary acute pancreatitis, n=153), HLAP (hyperlipidemic acute pancreatitis, n=65) and BHAP (biliary-hyperlipidemic acute pancreatitis, n=49). All the enrolled patients met the classification criteria of biliary etiology, hyperlipidemic etiology, and both etiologies, respectively. BHAP was compared with BAP and HLAP in terms of general information, inflammatory biomarkers, organ dysfunction, disease severity and clinical outcomes.

RESULTS: BHAP (41 *vs.* 53) patients were younger than BAP patients. Serum procalcitonin of BHAP patients was higher than BAP and HLAP patients. Serum CRP of BHAP patients was higher than BAP patients. BHAP patients had the highest diagnosis rate of severe acute pancreatitis (SAP) (46.9% vs. 17.6% or 21.5%) compared to BAP and HLAP. Prevalences of persistent respiratory, acute renal, and circulatory failure were highest in BHAP patients (44.9%, 28.6%, 12.2%, respectively). Requirements for mechanical ventilation, renal replacement therapy and vasoactive agents were also highest in BHAP patients (36.7%, 34.7%, 12.2%, respectively). Hospital stay was longer in BHAP patients (33 days) compared with BAP patients (24 days).

CONCLUSIONS: Patients with both biliary and hyperlipidemic etiologies suffer from more severe clinical course of the disease and have worse prognosis than single-etiology BAP or HLAP patients in the early stage of AP (within 7 days). It should be recognized as a new etiological type named biliary-hyperlipidemic acute pancreatitis (BHAP).

Key Words:
Biliary acute pancreatitis, Hyperlipidemic acute pancreatitis, Etiology, Clinical features.

Abbreviations

AP, acute pancreatitis; MAP, mild acute pancreatitis; MSAP, moderately severe acute pancreatitis; SAP, severe acute pancreatitis; BAP, biliary acute pancreatitis; HLAP , hyperlipidemic acute pancreatitis; BHAP , biliary-hyperlipidemic acute pancreatitis; ARDS, acute respiratory distress syndrome; AKI, acute kidney injury; MODS, multiple organ dysfunction syndrome; AUS, abdominal ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; EUS, endoscopic ultrasonography; MRCP, magnetic resonance cholangiopancreatography; ERCP, endoscopic retrograde cholangiopancreatography; APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; BISAP, acute pancreatitis severity bedside index; CTSI, CT severity index; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma glutamyltranspeptidase; WBC, white blood cells; PCT, procalcitonin; CRP, C-reactive protein; ICU, Intensive Care Unit; EICU, Emergency Intensive Care Unit.

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Introduction

Acute pancreatitis (AP) is the most common gastrointestinal disorder in the Emergency Department. While in most of the cases AP has a mild course, 15-20% of patients develop severe AP, which is characterized by systemic inflammatory response and persistent organ failure, resulting in high morbidity and mortality[1].

The most common etiology of AP is gallstones (60%), followed by alcohol abuse (30%) and hyperlipidemia. Accumulating data have shown that biliary and hyperlipidemic AP have become the first two common types of AP in China[2,3]. Etiologic diagnosis of AP in the early phase is important not only for the timely delivery of targeted therapies, but also for the prediction of severity and prognosis. Although several studies compared the severity of various AP, their conclusion remains inconsistent. In the recent study by Li et al[4], of 730 AP patients, patients with hyperlipidemic acute pancreatitis (HLAP) had a more severe clinical course than biliary AP (BAP) patients. HLAP patients also had a higher occurrence of systemic complications, such as acute respiratory distress syndrome (ARDS), acute kidney injury (AKI), deep venous thrombosis and multiple organ dysfunction syndrome (MODS)[4]. However, another study[5] of 177 AP patients reported the opposite outcome, with less MODS observed in HLAP patients as compared to BAP patients.

The most reliable diagnosis of AP is done using the classification proposed by the Atlanta Pancreatitis Classification working Group[1]. However, distinguishing biliary pancreatitis from other AP can be difficult and requires biochemical and radiological evaluations. As shown in Figure 1, Van Geenen et al[6] pointed out that BAP diagnosis should only be considered when the following criteria are fulfilled: confirmation of gallstones or biliary sludge using radiological imaging (including EUS, AUS, CT and MRCP), elevated serum levels of ALT (>1.0 μkat/l) and a BMI <30 kg/m^2. In all other cases another cause of AP should be considered. This suggests that diagnosis of BAP is exclusive from other forms of AP, for example, HLAP.

However, this assumption may need to be re-evaluated. Huang and Raskin[7] reported a case of diabetic hypertriglyceridemia-induced recurrent acute pancreatitis that masquerades as biliary pancreatitis. This finding indicates that biliary and hyperlipidemic etiology of AP might be similar and therefore confusing. Additionally, Durgampudi et al[8] found that acute lipotoxicity may increase the severity of BAP in the mouse model. They also reported that patients with post pancreatitis necrotic collections were obese (BMI, 36±1.8), and 13 of 15 such patients had biliary AP. On the other hand, increasing prevalence of dyslipidemia has become a serious public health problem in China[9]. From 2005 to 2014, the prevalence of dyslipidemia in adults increased from 18.6%[10] to 30.7%[11]. Mao[12] proposed that a portion of APs meets the diagnostic criteria for BAP and HLAP simultaneously, and such patients tend to suffer from more severe clinical manifestations

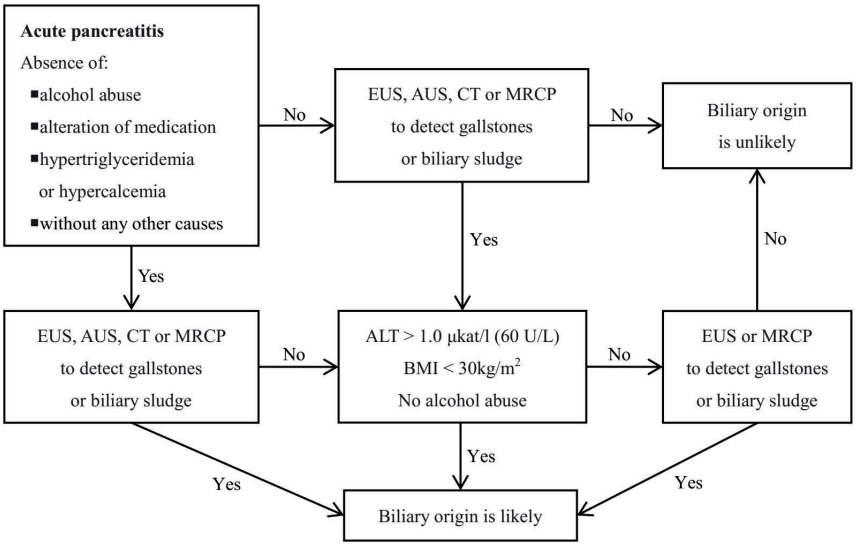

Figure 1. Biliary origin of acute pancreatitis diagnostic flow chart.

of the disease than patients diagnosed with BAP or HLAP alone. Taken together, we hypothesize that biliary and hyperlipidemic AP could coexist in patients, thus leading to a worsening clinical course and outcomes as compared to single-etiologic AP, especially at the early stages (within 7 days after onset of disease) of AP.

In the current review, we conducted a retrospective study to elucidate the clinical features of this complex type of AP with both biliary and hyperlipidemic etiologies, and proposing a new type of AP, a BHAP. We present the following article in accordance with the STROBE reporting checklist.

Patients and Methods

Cohort Subjects

This single center cohort study retrospectively screened 635 AP patients admitted to the Emergency Department and Emergency Intensive Care Unit (EICU) of Ruijin Hospital from January 2016 to June 2019.

Patients who met the following criteria were excluded: 1) aged < 18 years; 2) patients with a history of chronic pancreatitis, known malignancy, and chronic liver disease or hepatic dysfunction; 3) pregnancy or lactation; 4) patients who were admitted > 7 days after the onset of abdominal pain; 5) idiopathic AP.; 6) alcoholic AP, as diagnosed based on drinking history (more than 35 standard drinks per week for a period over 5 years). Eventually, 267 AP patients were enrolled in this study.

Diagnosis

According to 2012 revised Atlanta guideline[1], AP is defined as the presence of at least two out of the following three criteria: 1) pain in the upper abdomen, 2) serum amylase or lipase concentration > 3 times the upper limit of normal, or 3) imaging features of acute pancreatitis on computed tomography (CT) or magnetic resonance imaging (MRI).

The severity of AP was analyzed by the following criteria. Mild acute pancreatitis (MAP) was characterized as AP without organ failure or local/systemic complications. Moderately severe acute pancreatitis (MSAP) was characterized as AP with transient organ failure or local/systemic complications. Severe acute pancreatitis (SAP) was characterized as AP with persistent organ failure (> 48 hours).

The etiology of AP was analyzed by the criteria listed in Table I. BAP was confirmed by the procedure shown in Figure 1, which conclusively identifies gallstones or biliary sludge by CT and magnetic resonance cholangiopancreatography (MRCP), or elevated serum levels of ALT (> 60 U/L) and BMI < 30 kg/m^2 [6]. BAP patients were further subgrouped into BAP and BHAP according to triglyceride levels as listed in Table I. HLAP was confirmed by triglyceride levels > 1000 mg/dL or triglyceride levels between 500 mg/dL to 1000 mg/dL together with emulsion plasma and without other etiologies[13].

Data Collection

General information including age, sex, time between the onset of the disease to admission, hospital unit upon admission (general ward or ICU), diabetes mellitus, hypertension, and smoking history were retrieved from the medical charts. Serum levels of procalcitonin were determined by the VIDAS PCT assay (bioMérieux, Marcy L'Etoile, France) according to the protocol as previously described[14]. Serum levels of C-reactive protein (CRP) were measured using an immuno-turbidimetry assay following the manufacturer's package inserts for Beckman Coulter reagents using the IMMAGE 800 analyzer and the AU5800 analyzer (Beckman Coulter Inc, Brea, CA, USA)[15]. The ratio of SAP and the type of organ support (mechanical ventilation, renal replacement therapy, use of vasoactive agent) were calculated in each group. Several severity

Table I. Diagnostic features of BAP, BHAP and HLAP.

Groups	Biliary etiology diagnosis flowchart shown in Fig. 1	Triglyceride levels	Emulsion plasma
BAP	Yes	< 500 mg/dL	No
BHAP	Yes	> 1000 mg/dL or 500-1000 mg/dL	Yes
HLAP	No	> 1000 mg/dL or 500-1000 mg/dL	Yes

BAP, biliary acute pancreatitis; HLAP, hypertriglyceridemia acute pancreatitis, BHAP, biliary-hypertriglyceridemia acute pancreatitis.

scores including acute physiology and chronic health evaluation II (APACHE II), sequential organ failure assessment (SOFA), acute pancreatitis severity bedside index (BISAP), and CT severity index (BISAP) were collected on admission. The outcome indicators including length of stay (in hospital), surgery and mortality were analyzed.

We used strict criteria to enroll and classify patients, and collected patients' serum samples before treatments to avoid bias. Furthermore, treatment for all patients was conducted by the same clinic team.

Statistical Analysis

We used SPSS 20.0 statistical software package (IBM Analytics, Armonk, NY, USA) for statistical analyses. Nominal data were reported as numbers (percentage of the group). Quantitative data were reported as median, lower and upper quartiles (Q1; Q3), depending on normality of each variable's distribution (as assessed using Shapiro-Wilk's test). The contingency tables were analyzed with Pearson's chi-squared test. In the case of three groups, the whole contingency table was analyzed first, and then the pairwise comparisons were done using Pearson chi-squared test with Bonferroni correction. Due to the non-normal distribution of most quantitative variables, Kruskal-Wallis's analysis of variance (with post-hoc comparisons using Dunn-Bonferroni method) was applied when three groups were compared and Mann-Whitney's test when two groups were compared. The p-value <0.05 is considered significant.

Results

Baseline Characteristics and Clinical Features

A total of 635 AP patients admitted to the Emergency Department and EICU of Ruijin Hospital from January 2016 to June 2019 were screened for this study. As shown in Figure 2, 267 patients were enrolled and diagnosed with BAP (n=202) and HLAP (n=65) according to the Atlanta guideline[1]. Among BAP patients, 49 of the 202 patients had elevated serum triglycerides, meeting the diagnostic criteria of HLAP, and were classified into BHAP subgroup. The classification criteria of BAP, HLAP and BHAP based on the serum triglyceride levels are shown in Table I. All patients were followed up to discharge or death.

As shown in Table II, BAP, HLAP and BHAP patients did not differ significantly in gender, comorbidity of hypertension, the history of smoking and alcohol use (did not meet the diagnostic criteria for alcoholic pancreatitis), duration from disease onset to admission or in receiving ther-

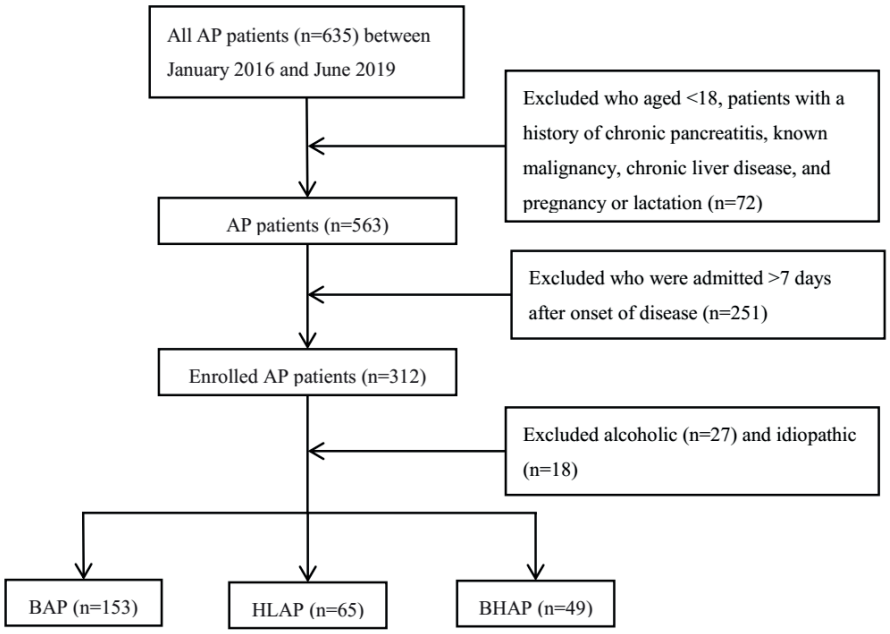

Figure 2. Workflow of patient enrollment and screening in this study.

Table II. DClinical characteristics of the study group according to the etiology of acute pancreatitis (AP).

Characteristic	BAP (n=153)	HLAP (n=65)	BHAP (n=49)	*p*-value
Male, n	93.0 (60.8)	44.0 (67.7)	35.0 (71.4)	0.327
Age, year	53.0 (40.5, 65.5)	39.0 (32.0, 47.0)	41.0 (35.0, 47.0)	<0.001[ac]
Duration since onset to admission, day	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.5, 4.0)	0.196
Amylase, U/L	773.0 (255.5, 1750.0)	254.0 (106.0, 511.5)	421.0 (212, 791.5)	<0.001[ac]
Triglyceride, mmol/L	0.97 (0.54, 1.77)	10.7 (6.8, 20.5)	7.6 (5.8, 21.9)	<0.001[ac]
BMI, kg/m^2	24.2 (22.2, 26.9)	27.0 (24.8, 30.8)	25.7 (24.2, 29.3)	<0.001[ac]
ALT, U/L	38.0 (19.0, 119.5)	26.0 (18.0, 41.0)	25.0 (17.0, 65.5)	0.005[c]
AST, U/L	36.0 (21.0, 76.0)	28.0 (17.5, 38)	42.0 (28.0, 85.0)	<0.001[bc]
γ-GT, U/L	65.0 (22.0, 133.0)	56.0 (33.5, 160.5)	70.0 (29.0, 148.5)	0.611
Total bilirubin, μmol/L	23.5 (17.5, 34.7)	22.8 (14, 33.6)	32.8 (23.7, 42.3)	0.004[ab]
Direct bilirubin, μmol/L	5.5 (2.7, 11.1)	3.5 (1.75, 8.5)	10.6 (4.4, 18.0)	<0.001[abc]
Diabetes, n	21.0 (13.7)	21.0 (32.3)	11.0 (22.4)	0.006[c]
Hypertension, n	48.0 (31.4)	16.0 (24.6)	14.0 (28.6)	0.601
Smoking, n	45.0 (29.4)	26.0 (40.0)	20.0 (40.8)	0.175
Alcohol use, n	50.0 (32.7)	24.0 (36.9)	21.0 (42.9)	0.418
Therapeutic ERCP, n	10.0 (6.5)	0.0 (0.0)	3.0 (6.1)	0.11
Percutaneous transhepatic gallbladder drainage, n	18.0 (11.8)	0.0 (0.0)	6.0 (12.2)	0.014[bc]

ERCP, endoscopic retrograde cholangiopancreatography; BAP, biliary acute pancreatitis; HLAP, hypertriglyceridemia acute pancreatitis, BHAP, biliary-hypertriglyceridemia acute pancreatitis; Categorical variables presented as n (%), number and percentage; Continuous variables presented as median (Q1; Q3), Q1, lower quartile; Q3, upper quartile; p-value is reported for overall comparison between three groups (in Pearson chi-squared test or Kruskal-Wallis ANOVA), the letters in superscript indicate the results of post-hoc tests: a significant difference between the BAP and BHAP groups in post-hoc comparison; b significant difference between the HLAP and BHAP groups in post-hoc comparison; c significant difference between the BAP and HLAP groups in post-hoc comparison.

apeutic ERCP. Both BHAP (41 *vs.* 53, p <0.001) and HLAP (39 *vs.* 53, p <0.001) patients were significantly younger than BAP patients. Serum amylase level was significantly higher in BAP patients (773.0 U/L) than that of HLAP (254.0 U/L) or BHAP (421.0 U/L) patients, respectively. There was no significant difference in serum amylase levels between HLAP and BHAP patients. For the hyperlipidemic parameters, serum triglyceride levels were higher in HLAP (10.7 mmol/L) and BHAP (7.6 mmol/L) patients, compared to BAP (0.97 mmol/L) patients. There was no significant difference between HLAP and BHAP groups, which is consistent with the classification criteria. Similar differences were observed in BMI of BAP, HLAP and BHAP patients (24.2 *vs.* 27.0 or 25.7 kg/m^2 respectively). For the biliary parameters, we detected lower ALT levels in HLAP (26.0 U/L) and BHAP (25.0 U/L) patients compared to BAP (38.0 U/L) group. However, this difference was statistically significant only between HLAP and BAP groups (p=0.005). Of note, AST level was highest in BHAP (42.0 U/L) patients, lowest in HLAP (28.0 U/L) group, while AST levels of BAP patients were in the middle of that range (36.0 U/L). γ-GT level was comparable among three groups, with the highest level in BHAP patients. Total and direct bilirubin levels were significantly higher in BHAP patients (32.8 and 10.6 μmol/L, respectively) compared to other groups. In addition, there was no significant difference in the occurrences of diabetes between BHAP patients and other groups. Occurrence of percutaneous transhepatic gallbladder drainage, the specific therapy for BAP, was higher in BHAP patients than in HLAP patients but comparable with that of the BAP group. Taken together, BHAP, BAP and HLAP patients share comparable clinical features, and biliary and hyperlipidemic parameters.

Comparison of Inflammatory Markers Among Cohorts

Serum procalcitonin, CRP and white blood cell (WBC) levels are reported as inflammatory biomarkers of AP by indicating systemic inflammation and organ failure in the early stage of AP[16-18]. These biomarkers were evaluated and compared among three groups on admission. As shown in

Figure 3, serum procalcitonin levels of BHAP patients were almost 5-fold higher than those of BAP and HLAP patients. There was no significant difference in serum CRP levels between BHAP and HLAP cohorts, but both groups had markedly higher serum CRP than BAP cohort. WBC levels of three groups were comparable. These results show that inflammatory profile of BHAP is more similar to HLAP than to BAP, but elevated serum procalcitonin is likely more specific to BHAP. Underlying mechanism of this effect remains to be explored.

Comparison of Severity and Organ Dysfunctions Among Cohorts

It is important to predict the severity of AP at the very early stage of the disease. We accessed the disease severity of three groups on admission upon SAP diagnosis rate and several scoring systems including APACHEII, SOFA, BISAP and CTSI. As summarized in Table III, 46.9% of BHAP patients were diagnosed as SAP, compared to 17.6% and 21.5% of BAP and HLAP patients, respectively. Similarly, BHAP patients received significantly higher scoring by all four scoring systems compared to BAP and HLAP patients. These results suggest that BHAP has a more severe disease course than the single-etiologic BAP and HLAP.

Organ failure typically develops in the early course of AP, and accounts for approximately 20% AP diagnosed as SAP[19]. We next investigated the occurrence of organ failure, commonly observed in SAP patients, and rates of replacement or support therapy among three groups. As shown in Table III, occurrences of persistent respiratory, acute renal, circulatory failure in BHAP patients were 44.9%, 28.6%, 12.2%, respectively, compared with 17.0%, 7.8%, 3.3% in BAP patients and 23.1%, 4.6%, 1.5% in HLAP patients. Application of mechanical ventilation, renal replacement therapy and vasoactive agent were 36.7%, 34.7%, 12.2% in BHAP patients, respectively, a 11.1%, 9.2%, 2.6% in BAP patients and 10.8%, 7.7%, 1.5% in HLAP patients. These results demonstrate that BHAP patients have higher occurrence of organ failure and require more replacement or support therapy as compared to BAP and HLAP patients, indicative of a more severe damage caused by BHAP.

Comparison of Clinical Outcomes Among Cohorts

Finally, we investigated clinical outcomes of three groups. As shown in Table IV, no significant difference was found in ICU admission, mortality and surgery rates among BAP, HLAP and BHAP patients, although hospital stay was longer in BHAP patients (33.0 days) compared with BAP patients (24.0 days).

Discussion

In this retrospective cohort study, we identified a subgroup of BAP patients with elevated serum triglyceride levels that meets the diagnostic criteria of HLAP, and classified this subgroup as BHAP. We evaluated and compared the patient profiles, clinical features and outcomes of BHAP patients with those of BAP and HLAP patients.

We found that BHAP patients present a combination of clinical features of both BAP and HLAP patients. Compared to BAP patients, BHAP patients are younger and have lower serum amylase and ALT levels, higher serum CRP and BMI as compared to HLAP patients. Our results are in agreement with another study recently conducted in China that reported similar age distribution[4].

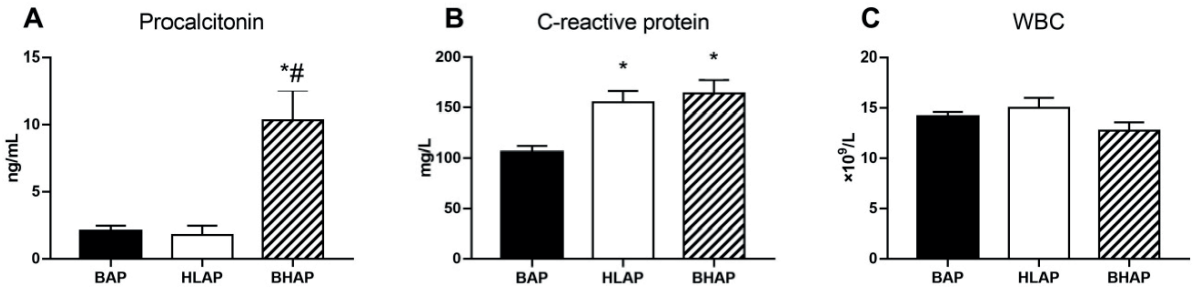

Figure 3. Comparison of inflammatory biomarkers. *higher than BAP $p < 0.05$; # higher than HLAP $p < 0.05$. higher than BAP $p < 0.05$; #higher than HLAP $p < 0.05$.

The previous reports show that serum amylase levels are higher in BAP patients than in other AP patients[20]. Of note, we found that serum AST and occurrence of percutaneous transhepatic gallbladder drainage were higher among BHAP patients but comparable to BAP patients. The underlying mechanism of this effect remains unclear.

We showed that BHAP patients also display several unique characteristics. Total and direct bilirubin levels were significantly higher in BHAP patients compared to other groups, even higher than those in BAP patients. Similarly, BHAP patients also have elevated serum procalcitonin. However, the most significant observation of this study is that, BHAP patients demonstrated the most severe clinical course in the early stages of AP than BAP and HLAP patients. Our results showed that BHAP patients had the highest diagnostic rate of SAP, disease severity scoring, prevalence of organ failure and need for replacement or support therapy compared to other two single-etiologic AP, BAP and HLAP.

Such severe course of BHAP may be associated with the combination of elevated triglyceride levels and biliary etiologies. The previous report has shown that high levels of serum triglyceride are a crucial risk factor associated not only with induction of acute pancreatitis but also with more severe course of the disease and organ dysfunction[21]. It is assumed that the hydrolyzed product of triglyceride, free fatty acid (FFA) may damage the vascular endothelium and acinar cell of pancreas. It may also generate an acidic environment and ischemic injury which triggers systemic inflammatory response and multi-systemic organ failure, especially acute kidney injury[21,22].

Similar to our findings, Zeng et al[23] reported BAP patients with serum triglyceride levels > 500 mg/ml showing higher occurrence of respiratory failure and local complications than those with normal triglyceride level. Cheng et al[24] also reported that BAP patients with high triglyceride levels (6.52 ± 1.52 mmol/L) have higher risk of developing SAP and multiple organ dysfunction compared with those with normal triglyceride level. While both studies are in agreement with our results, triglyceride levels of patients enrolled in these two studies did not strictly meet the hyperlipidemic etiology classification criteria as we did (Table I). Severe hypertriglyceridemia is defined as triglyceride concentrations greater than 1000 mg/dL (11.3 mmol/L). 15-20% of AP patients with severe hypertriglyceridemia will develop HLAP[13]. Current opinion for the diagnosis of HLAP remains controversial, but the classification criteria that serum triglyceride levels > 1000 mg/dl, or 500-1000 mg/dl with emulsion serum is widely accepted and used[25-27].

This study investigates for the first time the potential effect that the combination of biliary and hyperlipidemic etiologies in BAP patients may have on the clinical course of AP. Although other

Table III. Comparison of severity and organ dysfunction among cohorts.

Variable	BAP (n=153)	HLAP (n=65)	BHAP (n=49)	*p*-value
SAP, n	27 (17.6)	14 (21.5)	23 (46.9)	<0.001[ab]
APACHEII score, points	6 (3, 8)	6 (3, 8)	8 (4, 14)	0.002[ab]
SOFA score, points	2 (1, 4)	2 (1, 3)	4 (2, 7)	0.001[ab]
BISAP score, points	2 (1, 2)	2 (1, 2)	2 (2, 3)	0.003[ab]
CTSI score, points	4 (2, 4)	4 (2, 4)	4 (4, 5)	0.008[a]
Persistent (≥48 h) respiratory failure, n	26 (17.0)	15 (23.1)	22 (44.9)	<0.001[ab]
Persistent (≥48 h) acute renal failure, n	12 (7.8)	3 (4.6)	14 (28.6)	<0.001[ab]
Persistent (≥48 h) circulatory failure, n	5 (3.3)	1 (1.5)	6 (12.2)	0.013[ab]
Mechanical ventilation, n	17 (11.1)	7 (10.8)	18 (36.7)	<0.001[ab]
Renal replacement therapy, n	14 (9.2)	5 (7.7)	17 (34.7)	<0.001[ab]
Use of vasoactive agent, n	4 (2.6)	1 (1.5)	6 (12.2)	0.006[ab]

ERCP, endoscopic retrograde cholangiopancreatography; BAP, biliary acute pancreatitis; HLAP, hypertriglyceridemia acute pancreatitis, BHAP, biliary-hypertriglyceridemia acute pancreatitis; Categorical variables presented as n (%), number and percentage; Continuous variables presented as median (Q1; Q3), Q1, lower quartile; Q3, upper quartile; p-value is reported for overall comparison between three groups (in Pearson chi-squared test or Kruskal-Wallis ANOVA), the letters in superscript indicate the results of post-hoc tests: a significant difference between the BAP and BHAP groups in post-hoc comparison; b significant difference between the HLAP and BHAP groups in post-hoc comparison; c significant difference between the BAP and HLAP groups in post-hoc comparison.

Table IV. Comparison of severity and outcome among cohorts.

Characteristic	BAP (n=153)	HLAP (n=65)	BHAP (n=49)	*p*-value
ICU admission, n	73 (47.7)	37 (56.9)	21 (42.9)	0.290
Surgery, n	12 (7.8)	2 (3.1)	4 (8.2)	0.418
Hospital mortality, n	16 (10.5)	1 (1.5)	6 (12.2)	0.060
Length of hospital stay, days	24 (13, 38)	29.4 (18.2, 40)	33 (26, 49.7)	0.003[a]

ICU, Intensive Care Unit. Categorical variables presented as n (%), number and percentage; Continuous variables presented as median (Q1; Q3), Q1, lower quartile; Q3, upper quartile; p-value is reported for overall comparison between three groups (in Kruskal-Wallis ANOVA), the letters in superscript indicate the results of post-hoc tests: a significant difference between the BAP and BHAP groups in post-hoc comparison; b significant difference between the HLAP and BHAP groups in post-hoc comparison; c significant difference between the BAP and HLAP groups in post-hoc comparison.

studies also indicated that biliary and lipidemic etiologies may coexist in BAP patients, the influence of this combination on the disease course was not fully evaluated. For example, Nawaz H et al identified BAP patients with triglyceride levels >1000 mg/dl[27]. Another cohort study[28] enrolled one case of a BAP patient with triglyceride levels > 750 mg/dl. In this study we specifically report the unique characteristics of BHAP patients with a severe clinical course of the disease.

Our study has several limitations. As an observational retrospective report, our study is highly susceptible to different types of bias and confounding. To avoid bias, we used strict criteria to enroll and classify patients, and collected samples of patients' serum before treatments. In addition, our data come from one center and may require validation from external sources. A prospective multicenter study with bigger sample size should be conducted.

Conclusions

The AP patients with both biliary and hyperlipidemic etiologies should be recognized as a new etiological type named biliary-hyperlipidemic acute pancreatitis (BHAP) and should be taken seriously due to distinguishable severe clinical features that they present at the early stages of AP. We propose that the observed severity of this disease might be due to the combined effect of biliary and hyperlipidemic etiologies.

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

Ethical approval and Patients consent
All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Ruijin Hospital, Shanghai Jiao Tong University School of Medicine and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All of the data were obtained from patient records. Formal consent was not required.

Conflict of Interest
The Authors declare that they have no conflict of interests.

Authors' contribution
Yihui Wang (First author) conceived and designed this study, interpreted and analyzed the data, and wrote the manuscript. Zhihong Xu contributed to conception of the study, analyzed the data, and revised the article. Enqiang Mao* (Corresponding author) conceived this study, revised this article critically for important intellectual content, and helped perform the analysis with constructive discussions. Bing Zhao* (Corresponding author): contributed significantly to analysis and manuscript preparation and revised this article critically for important intellectual content. Huiqiu Sheng contributed to analysis and manuscript preparation, revised this article critically for important intellectual content. Zhiwei Xu and Silei Sun helped to design this study, collected the data, contributed analysis tools, and helped to revise this article. Xing Qi, Weijun Zhou and Yuhua Zhou collected the data, and helped perform the analysis. All authors have read and approved the final version of this manuscript, including the authorship.

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