Original Article

Different clinical characteristics between recurrent and non-recurrent acute pancreatitis: A retrospective cohort study from a tertiary hospital

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Abstract

Background: Acute pancreatitis (AP) is a common digestive disorder with different clinical outcomes, some of which develop into recurrent acute pancreatitis (RAP). This study aimed to explore the differences between AP and RAP.

Methods: All patients with AP admitted to Changsha Central Hospital between January 2015 and December 2020 were included. Characteristics between RAP and non-RAP groups were compared. Independent factors associated with RAP were identified by multivariate logistic regression analyses.

Results: This was a retrospective study. A total of 1567 patients, including 262 patients in the RAP group and 1305 patients in the non-RAP group, were enrolled. Compared to the non-RAP group, results indicated that the RAP group was younger ($P < 0.001$), had a male predominance ($P < 0.001$), and had higher incidences of diabetes ($P < 0.001$) and hypertriglyceridemia (HTG) ($P < 0.001$). Lower incidences of cholelithiasis ($P < 0.001$) and acute liver injury ($P < 0.001$) were also noted in the RAP group. Scores of Ranson, BISAP, SOFA, and APACHE II were significantly higher in the non-RAP group ($P < 0.001$ for all). Three independent factors associated with RAP, including male gender ($P = 0.006$), diabetes ($P < 0.001$), and HTG ($P < 0.001$), were identified by multivariate logistic regression.

Conclusion: Compared to the non-RAP, the incidence of cholelithiasis and acute liver injury was lower in RAP. Three independent factors associated with RAP, namely male, diabetes, and HTG, were identified.

Keywords: Diabetes, hypertriglyceridemia, male, recurrent acute pancreatitis

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INTRODUCTION

Acute pancreatitis (AP), as a common digestive disorder, has different clinical outcomes, some of which develop into recurrent acute pancreatitis (RAP).[1] Epidemiological studies have shown that the incidence rate of RAP varies from 11% to 32% in AP patients,[2,3] some of which may develop chronic pancreatitis, resulting in a reduction in physical and mental components of quality of life and an increase in socioeconomic burden.[4]

Increasing studies have been done on the epidemiology and clinical characteristics in AP,[5,6] while few have focused

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on RAP. In addition, the differences between AP and RAP has also varied in different regions and cohorts. Recent research on RAP from European countries observed that in AP patients, 27% experienced one or more AP attacks. The most frequent factor (57%) was alcohol, and the majority (78.8%) were men with a mean age of 43 years.[7] Another study with 1471 AP patients in China verified that 157 (10.7%) had RAP with younger age and higher incidence of complications compared with those without recurrent attacks; the most frequent causes were alcohol (20.4%) and cholelithiasis (20.4%).[8] In addition, in one study investigating RAP in children, the study illuminated that the main differences in etiologies between children and adults were anatomical (29.6%) and pharmacological, (19.2%) and no significant difference was found in severity and complications between RAP and AP.[9] One recent review concluded that alcoholic pancreatitis was the most common RAP type. In alcohol-induced acute pancreatitis, 46% of the patients developed RAP within more than a 10-year follow-up.[10]

In this study, clinical data including clinical features, complications, and outcomes of AP and RAP patients for 5 years were retrospectively analyzed and compared. The purpose of our research was to investigate the clinical characteristics of RAP and the difference between RAP and AP, to develop preventive strategies before the irreversible features of RAP appear.

METHODS

Patients and database

This study was a retrospective study. In our study, all patients with AP admitted to Changsha Central Hospital between January 2015 and December 2020 were included. The clinical data of all the patients were retrospectively collected and analyzed. Ethics approval for the conduction of the study was provided by the Medical Ethics Committee of Changsha central Hospital. Due to the retrospective nature of the study, informed patient consent was waived. Inclusion criteria were defined as follows: age ≥18 and confirmed diagnosis of AP. Patients with the following criteria were excluded: more than 72 h after onset of symptoms, age <18, malignant tumor, pregnant, and data missing >5%.

Patient follow-up was performed by means of medical record review until death or the end of 2020. The median follow-up time of all patients was 24.6 months.

Definition

AP was confirmed when the patient possessed at least two of the following: abdominal symptoms relating to AP, serum levels of lipase or amylase elevated at least three times, image of AP confirmed by abdominal ultrasongraphy and/or CT scan.[11] CT scan usually shows diffuse enlargement of the pancreas and relatively homogeneous enhancement. Peripancreatic fat usually shows some inflammatory changes of haziness or mild stranding. There may also be some peripancreatic fluid and even pancreatic necrosis.[11]

When a participant experienced two or more episodes of documented AP separated by at least 3 months, RAP was diagnosed.[12]

Three main etiologies, including cholelithiasis, alcohol, and hypertriglyceridemia (HTG), were included in this study. Cholelithiasis was confirmed by image examination. Alcohol was defined as an etiological factor with AP when at least 80 g/day had been consumed for more than 5 years, or regularly drinking during social occasions or weekends had been continued for at least the same number of years. HTG associated with AP was defined as follows: triglyceride ≥11.3 mmol/L or ≥5.65 mmol/L accompanied with milky serum.[13]

Data collection

Baseline characteristics, including age, gender, etiologies including cholelithiasis, alcohol, and HTG, were collected. Comorbidities, including diabetes, hypertension, coronary heart disease, and chronic obstructive pulmonary disease (COPD), were recorded. Past medical history of biliary surgery was also collected.

CT images were also recorded, including CT grades, pleural effusion, abdominal effusion, and lung infection. Based on the clinical and laboratory variables, the scores of sequential organ failure assessment (SOFA), bedside index of severity in acute pancreatitis (BISAP), Ranson, and acute physiology and chronic health evaluation (APACHE II) were calculated for each patient after admission.

Clinical management data including mechanical ventilation and continuous renal replacement therapy (CRRT) were collected. In-hospital complications including acute respiratory distress syndrome (ARDS), acute kidney injury, acute liver injury, and cardiac insufficiency were recorded. Clinical outcomes including ICU admission and length of stay (LOS) in ICU and hospital were collected.

Statistical analysis

Statistical results were presented as mean ± standard deviation for normal data, and interquartile range (IQR) and median were used for non-normal data. Categorical

data were presented as percentages and numbers. Chi-squared test or Mann–Whitney U-test were utilized for the comparison between two groups. A two-sided $P < 0.05$ was considered statistically significant.

RESULTS

Comparison baseline characteristics between RAP and non-RAP groups

At the beginning of the study, a total of 1668 patients with AP were included in our research. Based on the exclusion criteria, 1567 patients, including 262 patients in the RAP group and 1305 patients in the non-RAP group, were enrolled in the study [Figure 1].

The distribution of numbers of recurrent attacks in patients with RAP is presented in Figure 2. In the RAP group, most patients (177, 67.56%) experienced one recurrent attack. The number of patients who experienced recurrent attacks two, three, four and ≥five times were 39 (14.88%), 27 (10.31%), 4 (1.52%), and 15 (5.73%), respectively.

Baseline characteristics between the two groups are listed and compared in Table 1. The mean age in the RAP and non-RAP groups were 41 and 47, respectively ($P < 0.001$). In the RAP group, the proportion of males was significantly higher (79.39% vs. 66.05%, $P < 0.001$). Compared to different etiologies, hypertriglyceridemia accounted for 58.01% in the RAP group and only 31.57% in the non-RAP group ($P < 0.001$). Significant differences were also noted in alcohol (20.61% vs. 16.32%, $P = 0.012$) and cholelithiasis (4.19% vs. 17.08%, $P < 0.001$) between the two groups. Idiopathic showed no significant difference between the two groups (16.03% vs. 16.85%, $P = 0.618$). Among comorbidities, the RAP group had a higher incidence of diabetes (20.99% vs. 13.56%, $P < 0.001$). No significant differences were noted in coronary heart disease ($P = 0.568$), COPD ($P = 0.300$), and history of biliary surgery ($P = 0.066$) between the two groups.

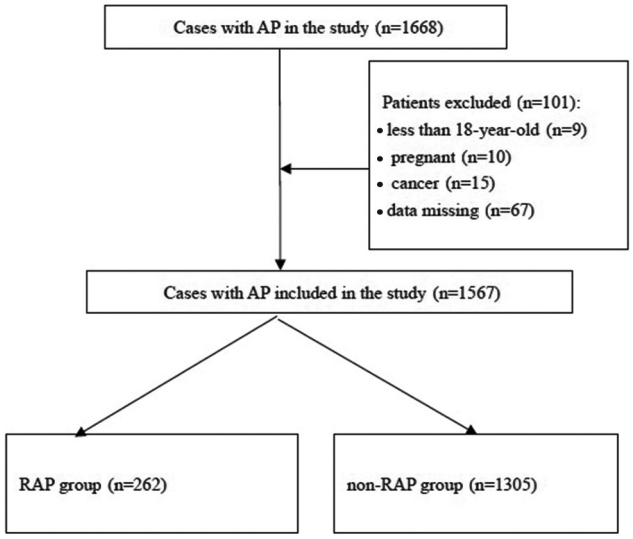

Figure 1: Flowchart for patients enrollment and study design
Abbreviations: AP: Acute pancreatitis, RAP: Recurrent acute pancreatitis

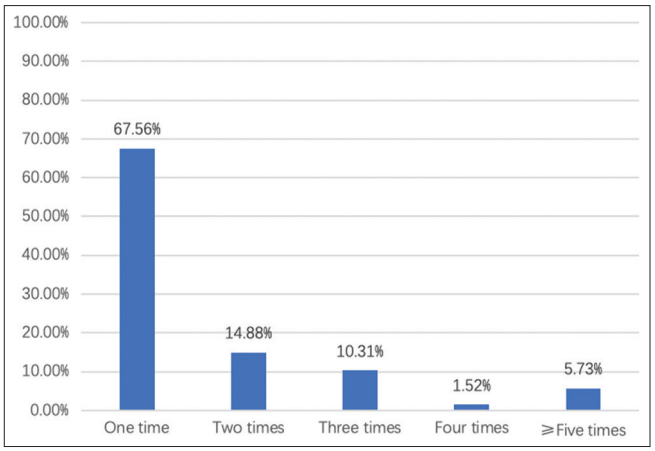

Figure 2: Distribution of numbers of recurrent attacks in patients with RAP Abbreviation: RAP: Recurrent acute pancreatitis

Clinical characteristics between RAP group and non-RAP group

In Table 2, when comparing CT images between RAP and non-RAP groups, CT grade (D, E) showed no significant differences (5.72% vs. 7.74%, $P = 0.172$). In the RAP group, the number of pleural effusion and abdominal effusion was 29 (11.07%) and 30 (11.45%), respectively, and 175 (13.41%) and 158 (12.11%) in the non-RAP group, respectively. Lung infection showed a significant difference between the two groups (27 (10.30%) vs. 185 (14.18%)), $P = 0.018$).

Table 1: Comparison of baseline characteristics between RAP and non-RAP groups

Baseline Variables	RAP (*n*=262)	Non-RAP (*n*=1305)	*P*
Age (years)	41.00 (33.75, 51.00)	47.00 (37.00, 60.00)	<0.001
Gender			<0.001
Male (*n*,%)	208 (79.39%)	862 (66.05%)	
Female (*n*,%)	54 (20.61%)	443 (33.95%)	
Etiologies (*n*,%)			
Cholelithiasis	11 (4.19%)	223 (17.08%)	<0.001
Alcohol	54 (20.61%)	213 (16.32%)	0.012
HTG	152 (58.01%)	412 (31.57%)	<0.001
Idiopathic	42 (16.03%)	220 (16.85%)	0.618
Comorbidities (*n*,%)			
Diabetes	55 (20.99%)	177 (13.56%)	<0.001
Hypertension	37 (14.12%)	263 (20.15%)	0.001
Coronary heart disease	8 (3.05%)	47 (3.61%)	0.568
COPD	3 (1.15%)	9 (0.69%)	0.300
History of biliary surgery	4 (1.53%)	23 (1.76%)	0.066

RAP: Recurrent acute pancreatitis, HTG: Hypertriglyceridemia, COPD: Chronic obstructive pulmonary disease

Compared to the management between the two groups, the incidence of mechanical ventilation in the two groups was 1.53% and 1.91%, respectively ($P = 0.250$). Moreover, there was no significant difference in CRRT (6.11% vs. 7.05%, $P = 0.486$).

In-hospital incidence of organ dysfunction, including ARDS (4.96% vs. 5.90%, $P = 0.309$), acute kidney injury (1.14% vs. 1.91%, $P = 0.187$), and cardiac insufficiency (0.07% vs. 0.53%, $P = 0.179$), showed no significant differences in the two groups. In the non-RAP group, the patients had significantly higher incidences of acute liver injury (149 [11.42%] vs. 14 [5.34%], $P < 0.001$).

Severity and outcomes between RAP group and non-RAP group

Scores of Ranson, BISAP, SOFA, and APACHE II were all significantly higher in the non-RAP groups ($P < 0.001$ for all) [Table 3].

The in-hospital incidence of ICU admission in the two groups was 9.16% and 11.34%, respectively ($P = 0.095$). LOS in ICU had no significant differences between the two groups ($P = 0.120$). In non-RAP group, LOS in hospital was longer ($P < 0.001$) [Table 3].

Table 2: Clinical characteristics between RAP group and non-RAP group

Characteristics	RAP (*n*=262)	Non-RAP (*n*=1305)	*P*
Image findings			
CT grade (*n*,%)			0.172
D E grade	15 (5.72%)	101 (7.74%)	
A B C grade	247 (94.28%)	1204 (92.26%)	
Pleural effusion (*n*,%)			0.153
Yes	29 (11.07%)	175 (13.41%)	
No	233 (88.93%)	1130 (86.59%)	
Abdominal effusion (*n*,%)			0.607
Yes	30 (11.45%)	158 (12.11%)	
No	232 (88.55%)	1043 (87.89%)	
Lung infection (*n*,%)			0.018
Yes	27 (10.30%)	185 (14.18%)	
No	235 (89.70%)	1120 (85.82%)	
Managements			
Mechanical ventilation (*n*, %)			0.250
Yes	4 (1.53%)	25 (1.91%)	
No	258 (98.47%)	1280 (98.09%)	
CRRT (*n*, %)			0.486
Yes	16 (6.11%)	92 (7.05%)	
No	246 (93.89)	1213 (92.95%)	
Organ dysfunction (*n*, %)			
ARDS	13 (4.96%)	77 (5.90%)	0.309
Acute liver injury	14 (5.34%)	149 (11.42%)	<0.001
Acute kidney injury	3 (1.14%)	25 (1.91%)	0.187
Cardiac insufficiency	2 (0.07%)	7 (0.53%)	0.179

RAP=recurrent acute pancreatitis, CRRT=continuous renal replacement therapy, ARDS=acute respiratory distress syndrome

Multivariate logistic regression analysis for factors associated with RAP

All variables that were significantly different between the two groups were utilized in multivariate logistic regression, and three independent factors were identified: male gender (Odds Ratio [OR] = 1.699, 95% CI: 1.541–1.902, $P = 0.006$), hypertriglyceridemia (HTG) (OR = 2.534, 95%CI: 2.021–3.176, $P < 0.001$), and diabetes (OR = 1.838, 95%CI: 1.385–2.439, $P < 0.001$) [Table 4].

DISCUSSION

In this study, the RAP patients that possessed higher incidences of diabetes and HTG tended to be both younger and male. Compared to the non-RAP group, the incidence of cholelithiasis and acute liver injury was lower in the RAP group. In addition, LOS in hospital and lower scores including Ranson, BISAP, SOFA, and APACHE II were found in the RAP group. Three independent factors associated with RAP, namely male gender, diabetes, and hypertriglyceridemia, were identified.

In our study, the results demonstrated that 262 (16.71%) of 1567 AP patients experienced one or more attacks of RAP. Different incidences of RAP were reported in previous studies. A study conducted by a team in India with over 8 years of observation found that 12.7% of AP patients had at least one relapse.[14] In Japan, the incidence of RAP was 19% according to a 35-year follow-up with AP patients,[15] while a higher incidence was noted in European countries.[7] Different occurrence rates of RAP might be due to various proportions of etiologies, different geographical locations, and socioeconomic statuses in different populations.

In the RAP group, the mean age was 41, and the proportion of males (79.39%) was significantly higher, which was consistent with some other studies. A study by Yang *et al*.[16]

Table 3: Severity and outcomes between RAP group and non-RAP group

Characteristics	RAP (*n*=262)	Non-RAP (*n*=1305)	*P*
Scoring systems			
Ranson	1 (1, 3)	2 (1, 3)	<0.001
BISAP	1 (1, 2)	2 (1, 2)	<0.001
SOFA	0 (0, 1)	0 (0, 2)	<0.001
APACHE II	9 (6, 12)	11 (8, 14)	<0.001
Outcomes			
ICU admission (*n*, %)	24 (9.16%)	148 (11.34%)	0.095
LOS in ICU (days)	3.00 (2.00, 5.00)	3.00 (2.00, 5.00)	0.120
LOS in hospital (days)	9.00 (6.50, 13.50)	10.00 (7.00, 15.00)	<0.001

RAP: Recurrent acute pancreatitis, SOFA: Sequential organ failure assessment, BISAP: Bedside index of severity in acute pancreatitis, APACHE II: Acute physiology and chronic health evaluation, ICU: Intensive medical care, LOS: Length of stay

Table 4: Multivariate logistic regression analysis for factors associated with RAP

Variables	*B*	SE	Wald	*P*	OR	95%CI for OR	
						Lower	Upper
Age	0.003	0.005	0.442	0.506	1.003	0.994	1.103
Gender, male	0.759	0.131	17.538	0.006*	1.699	1.541	1.902
Cholelithiasis	−0.248	0.176	1.981	0.159	0.780	0.553	1.102
Alcohol	−0.121	0.144	0.710	0.399	0.886	0.668	1.174
HTG	0.930	0.115	64.982	<0.001*	2.534	2.021	3.176
Hypertension	0.003	0.012	0.071	0.790	1.003	0.979	1.028
Lung infection	−0.071	0.201	0.125	0.723	0.931	0.628	1.131
Acute liver injury	−0.030	0.230	0.017	0.897	0.971	0.618	1.525
Diabetes	0.609	0.144	17.794	<0.001*	1.838	1.385	2.439

RAP: Recurrent acute pancreatitis, HTG: Hypertriglyceridemia, OR: odds ratio. *$P<0.05$

concluded that the median age was 42 years and that males accounted for 76.47% of RAP patients. Another study by Yu *et al*.[17] demonstrated that 56 of the 522 patients (10.7%) developed RAP and the mean age in RAP was 47.8 years, while the male gender was a risk factor for RAP (Hazard Ratio [HR] = 2.486, 95%CI: 1.042–5.932), which matched our study's results as well. In a study conducted in Korea, with a median follow-up of 3.2 years in RAP, age <60 years (HR = 1.602, 95%CI: 1.029–2.493) and male gender (HR = 1.927, 95%CI: 1.127–3.295) were significant risk factors for RAP development.[18]

Diabetes as a risk factor was associated with AP occurrence and disease severity, which was demonstrated in previous studies. Diabetes and younger age were potential risk factors in patients with HTG to develop AP.[19] Moreover, AP with diabetes was more likely to be moderate-to-severe pancreatitis, and the incidence of image characteristics, including hemorrhage, abdominal wall, and infected collections, was also higher, which may lead to RAP.[20] Our previous research concluded that AP patients with DM were prone to having higher levels of organ function indicators and a higher incidence of recurrence of AP.[21] A meta-analysis that included eight cohort studies with 14,124 cases of 5.7 million participants substantiated that diabetes was associated with a 74% increase in the risk of AP and a significant 40% increase in risk for chronic pancreatitis.[22] Patients with diabetes were prone to having a higher body weight, higher incidence of dyslipidemia, and lower levels of physical activity, which were significant risk factors for AP.[21]

HTG, as the most frequent factor both in RAP (58.01%) and AP (31.57%) groups, was associated with RAP in our study. Most studies in western countries proved that the incidence of alcoholic AP was higher than HTG associated AP.[6] A study from Sweden with 1457 AP cases concluded that the risk for recurrence was significantly higher in patients with alcohol-associated AP (HR = 1.58; 95% CI: 1.250 − 2.230).[23] Differences in AP etiologies may be due to the different lifestyles and socioeconomic statuses in different regions. In China, the incidence of AP due to HTG has been increasing.[13] A retrospective study from a tertiary center found that more than 40% of AP patients were affected by HTG.[24] In addition, AP patients with severe HTG had more persistent organ failure and poorer prognosis.[25] One recent research also confirmed that HTG was linked with an increased risk of relapse of clinical AP events.[26] For patients with HTG, long-term management includes dietary intervention, long-term medications, and lifestyle modifications. Some of these individuals may not follow certain pieces of lifestyle modification advice, which then may lead to RAP occurrences.

In this study, the RAP group had a significantly lower percentage of cholelithiasis pancreatitis (4.19% vs. 17.08%, $P < 0.001$) and acute liver injury (5.34% vs. 11.42%, $P < 0.001$). It can be partly explained by the fact that the probability of recurrence after an episode of cholelithiasis-related AP was related to whether and how long after an attack an appropriate procedure such as ERCP or cholecystectomy was done, and the risk of recurrence and acute liver injury was eliminated if an operation had been done.[17]

Interestingly, scores including Ranson, BISAP, SOFA, and APACHE II were lower in the RAP group. A recent study from the Cleveland Clinic found that patients with recurrent AP may be at a decreased risk of a severe course as well as decreased mortality. With episodes of AP increasing, the adjusted odds of severe AP, organ dysfunction, and ICU stay decreased by 55%, 86%, and 76% for each additional episode of AP, respectively.[27] Some have speculated that the increasing burden of parenchymal fibrosis and protective immunological mechanisms up-regulated due to recurrent attacks of AP, which in turn may be protective against the inflammatory cascade.[28] Further study needs to be done for exploring this phenomenon.

However, several limitations should be stated. First, due to some missing data, not all clinical characteristics, such as smoking, marital, and socioeconomic status, were included in our study. Moreover, due to its retrospective nature, unknown confounders between the two groups could not be confirmed. Second, HTG was the most frequent factor, which differed from some other studies. Therefore, one should be aware when considering applying our results to other regions and populations. Third, clinical data of patients was only from a single center, and the follow-up duration was not as long compared to other large-scale clinical studies. In addition,

due to the lack of some data such as pancreatic exocrine function tests, we mainly excluded chronic pancreatitis patients based on typical imaging findings and special symptoms. Further study with multiple centers and longer follow-ups should be conducted for validating our results. In our future studies, we will include more clinical and laboratory variables and focus on finding effective treatments such as drugs and interventions for RAP patients with different etiologies.

In conclusion, compared to non-RAP, shorter LOS in hospitals and lower scores including Ranson, BISAP, SOFA, and APACHEII were found in RAP patients. Three independent factors associated with RAP, namely male gender, diabetes, and HTG, were identified. Further studies with more clinical features and a larger population should be conducted to explore effective management of RAP occurrences.

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Conflicts of interest

There are no conflicts of interest.

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