Original Article

CT characteristics of recurrent acute pancreatitis and acute pancreatitis in different stages—a retrospective cross-sectional study

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Background: Acute pancreatitis (AP), recurrent acute pancreatitis (RAP), and chronic pancreatitis (CP) are a continuum of the same disease. The course of RAP and AP is a dynamic process. Previous studies are contradictory regarding the severity of RAP and AP. We conducted this study to investigate the computed tomography (CT) characteristics of RAP and AP in the early and late stages; respectively.

Methods: Patients who underwent contrast-enhanced computed tomography for symptoms during RAP or AP episodes were retrospectively collected from three tertiary hospitals in Sichuan Province, China from January 2015 to December 2019. The patients were categorized into RAP and AP groups based on recurrence and initial events. Both the RAP and AP groups were divided into early (first week) and late stages (after the first week) based on the 2012 revised Atlanta classification (RAC). Patient demographic data, RAC, CT findings, CT severity index (CTSI) scores, and extrapancreatic inflammation on CT scores in the early and late phases were analyzed between the two groups. The Wilcoxon signed-rank test, χ^2 test, and Fisher's exact test were used to compare continuous and categorical variables between the two groups respectively.

Results: In 683 RAP and 1,829 AP patients, the most common etiologies were hypertriglyceridemia and cholelithiasis, respectively. The RAP group had lower extrapancreatic inflammation on CT scores and Acute Physiology and Chronic Health Evaluation II scores than the AP group in the early stage (both $P<0.001$). The RAP group had higher CTSI scores than the AP group in the late stage ($P=0.022$).

Conclusions: Compared with AP patients, the most common cause of RAP patients was hypertriglyceridemia in China, and the severity of RAP was lower than that of initial AP in the early stage and higher than that of initial AP in the late stage.

Keywords: Recurrent acute pancreatitis (RAP); acute pancreatitis (AP); CT characteristics; different stages

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Introduction

Acute pancreatitis (AP) is a common acute gastrointestinal disease. Recurrent acute pancreatitis (RAP) refers to the occurrence of two or more well-documented and separate AP episodes with a complete resolution period between events that exceeds 3 months (1,2). The recurrence rate of AP has been reported to be approximately 22%, and approximately 36% of RAP patients will progress to chronic pancreatitis (CP) (3). Previous studies have indicated that AP, RAP, and CP are a continuum of the same disease, and the course of RAP and AP is a dynamic process (3-6). Recognizing the differences in computed tomography (CT) manifestations between RAP and AP at different phases can help clinicians provide timely and effective clinical interventions, improve patient prognosis and thus reduce the occurrence of CP.

Lee *et al.* (7) and Song *et al.* (8) reported that the clinical severity of RAP was lower than that of AP in the early stage. However, Yang *et al.* (9) and Boumezrag *et al.* (10) showed that RAP patients were more severe on CT than AP patients. Earlier studies also showed that the majority (95%) of RAP patients had mild disease, and approximately 62.5% of patients with severe AP were also severe at the second attack (11,12). The above studies are contradictory regarding the severity of RAP and AP and do not provide a specific analysis of RAP and AP severity at different stages. Following the criteria of AP, both RAP and AP can be categorized into two phases referring to the 2012 revised Atlanta classification (RAC) (4)—namely, the early stage (first week) and the late stage (after the first week).

CT is recommended after the first 3–5 days of illness in AP patients with suspected complications, due to its fast scanning speed, high tissue resolution, and clear visualization of pancreatic and peripancreatic tissues. 2012 RAC highlights the importance of contrast-enhanced computed tomography (CECT) in the diagnosis and assessment of AP severity (4,13). Guda *et al.* (2) also reported that CT scanning is recommended for RAP, typically at least 48–72 h after presentation, for severe episodes, to allow any necrosis to develop. Furthermore, the CT severity index (CTSI) score based on CECT and the CT Extrapancreatic Inflammation (EPIC) score based on inflammation around the pancreas are important scoring systems for predicting AP severity (14,15). All the above AP grading systems based on CT have great potential to assess RAP and AP severity and compare the differences between the two in different stages. However, currently, no reports exist regarding this.

We conducted this study to investigate the CT characteristics of RAP and AP (only those who had CT) in different stages, including demographic data, AP types, necrosis subtypes, local complications, and severity on CT. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1172/rc).

Methods

Patients and study design

This retrospective cross-sectional study will evaluate the CT characteristics of RAP and initial AP in the early and late stages, respectively. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College [No. 2019ER(R)064-01], and individual consent for this retrospective analysis was waived. This study was conducted in three tertiary hospitals in Sichuan Province, China (Affiliated Hospital of North Sichuan Medical College, Chinese People's Liberation Army Western Theater General Hospital, and Suining Central Hospital) from January 2015 to December 2019. A total of 896 patients with RAP and 2,421 patients with AP were included in the study by finding all patients with AP according to the International Code of Diseases (ICD) codes in the hospital information system. All enrolled patients were treated according to the IAP/APA evidence-based guidelines (16). The diagnostic criteria for AP were based on two of the following three criteria: (I) upper abdominal pain; (II) amylase (or lipase) levels 3 times the upper limit of normal; and (III) typical AP imaging features (4). The diagnostic criteria for RAP were defined as two or more separate AP episodes, complete remission for at least 3 months between episodes, and no morphological changes in CP (1,2).

Given that RAP and AP are dynamic disease courses, the severity of AP varies between episodes in the same patient (7,17-19). If the same patient has both RAP and AP and if

the same RAP patient has multiple RAPs, any episode of AP that meets the inclusion criteria can be included.

The inclusion criteria for RAP patients in this study were as follows: (I) adults ≥18 years of age; (II) patients for whom CECT was performed for symptoms during episodes of RAP; (III) patients with an interval of ≤3 days between laboratory examinations and CT examinations; (IV) if a RAP patient had only one CT scan in the early or late stages that met the inclusion criteria, the CT scan would be selected; (V) if a patient with RAP had both an early and a late stages CT scan that met the inclusion criteria, both would be included; (VI) if a patient with RAP had multiple CT scans in both early and late stages of a single episode that met the inclusion criteria, the most severe of the early and late ones would be selected, respectively; (VII) if multiple RAPs were collected for a patient, the inclusion criteria for each episode of the RAP were the same as described in (I)–(VI) above. The exclusion criteria for RAP patients were as follows: (I) patients with complications of tumors or severe chronic wasting disease; (II) pregnant patients; and (III) patients with unsatisfactory CECT images or incomplete medical records.

The inclusion criteria for patients with AP in this study were as follows: (I) adults ≥18 years of age; (II) patients for whom CECT was performed for symptoms during an episode of AP; (III) patients with an interval of ≤3 days between laboratory examinations and CT examinations; (IV) if an AP patient had only one CT scan in the early or late stages that met the inclusion criteria, the CT scan would be selected; (V) if a patient with AP had both an early and a late stages CT scan that met the inclusion criteria, both would be included; (VI) if a patient with AP had multiple CT scans in both early and late stages of a single episode that met the inclusion criteria, the most severe of the early and late ones would be selected, respectively. The exclusion criteria for AP patients were as follows: (I) patients with an acute exacerbation of CP; (II) patients with complications of tumors or severe chronic wasting disease; (III) pregnant patients; and (IV) patients with unsatisfactory CECT images or incomplete medical records.

The diagnostic criteria for the etiology of RAP and AP were as follows: (I) alcoholism, with a daily alcohol intake of more than 60 g for more than 5 years (20); (II) cholelithiasis, with any imaging method that found gallstones in the gallbladder and/or bile duct (21); (III) hypertriglyceridemia (hyperlipidemia), with admission triglyceride levels that were higher than 11.3 mmol/L or previous triglyceride levels that fluctuated at 5.65–11.3 mmol/L, excluding other triggers (20-22); (IV) multiple causes, with two or more causes (2,23,24); and (V) other/idiopathic causes include endoscopic retrograde cholangiopancreatography (ERCP), pancreas divisum, genetics, polymorphisms, drugs, and so on. We grouped the other etiologies and idiopathic etiologies into a subgroup.

Patients were categorized into the RAP and AP groups based on relapse and initial events. Both the RAP and AP groups were categorized into the early stage (1st week) and the late stage (after the 1st week) based on the 2012 RAC. Finally, 683 out of a total of 896 RAP patients and 1,829 out of a total of 2,421 AP patients had a CT within 3 days, for a total of 2,512 patients being recruited in this study. Four categories of patients were included in this study: (I) patients with only a single RAP were collected (n=481); (II) patients with only a single AP were collected (n=1,625); (III) patients with both RAP and AP were collected (n=77); (IV) patients with only multiple RAPs were collected (n=40); and (V) patients with both early and late stages CT scans (43 RAP and 135 AP). Of the 77 patients with both RAP and AP collected, 2 had collected RAP twice, 2 had collected RAP three times and 73 had collected RAP once, the total number of relapses collected from this group of RAP patients was 83. Of the 77 patients with both RAP and AP collected, 4 patients with RAP and 8 patients with AP had both early and late stages CT examinations. Of the 40 patients with only multiple RAPs were collected, 4 collected RAP three times, and 36 collected RAP twice, the total number of relapses collected in this group of RAP patients was 84. Of these 40 patients with only multiple RAPs collections, 4 RAP patients had both early and late stages CT examinations. There were 8 RAP patients and 8 AP patients in this study who was recorded repeatedly once. Therefore, the total number of patients in the RAP group should be 481+83+84+43−8=683. The total number of CT examinations in the RAP group should be 683+43=726. The total number of patients in the AP group should be 1,625+77+135−8=1,829. The total number of CT examinations in the AP group should be 1,829+135=1,964. Overall, the number of CT examinations for the RAP and AP patients was 726 and 1,964, respectively. Of them, there were 1,670 examinations (RAP *vs.* AP=529:1,141) in the early phase and 1,020 examinations (RAP *vs.* AP=197:823) in the late phase. The study flowchart is presented in *Figure 1*.

CT technology

CECT with abdominal imaging was conducted for all

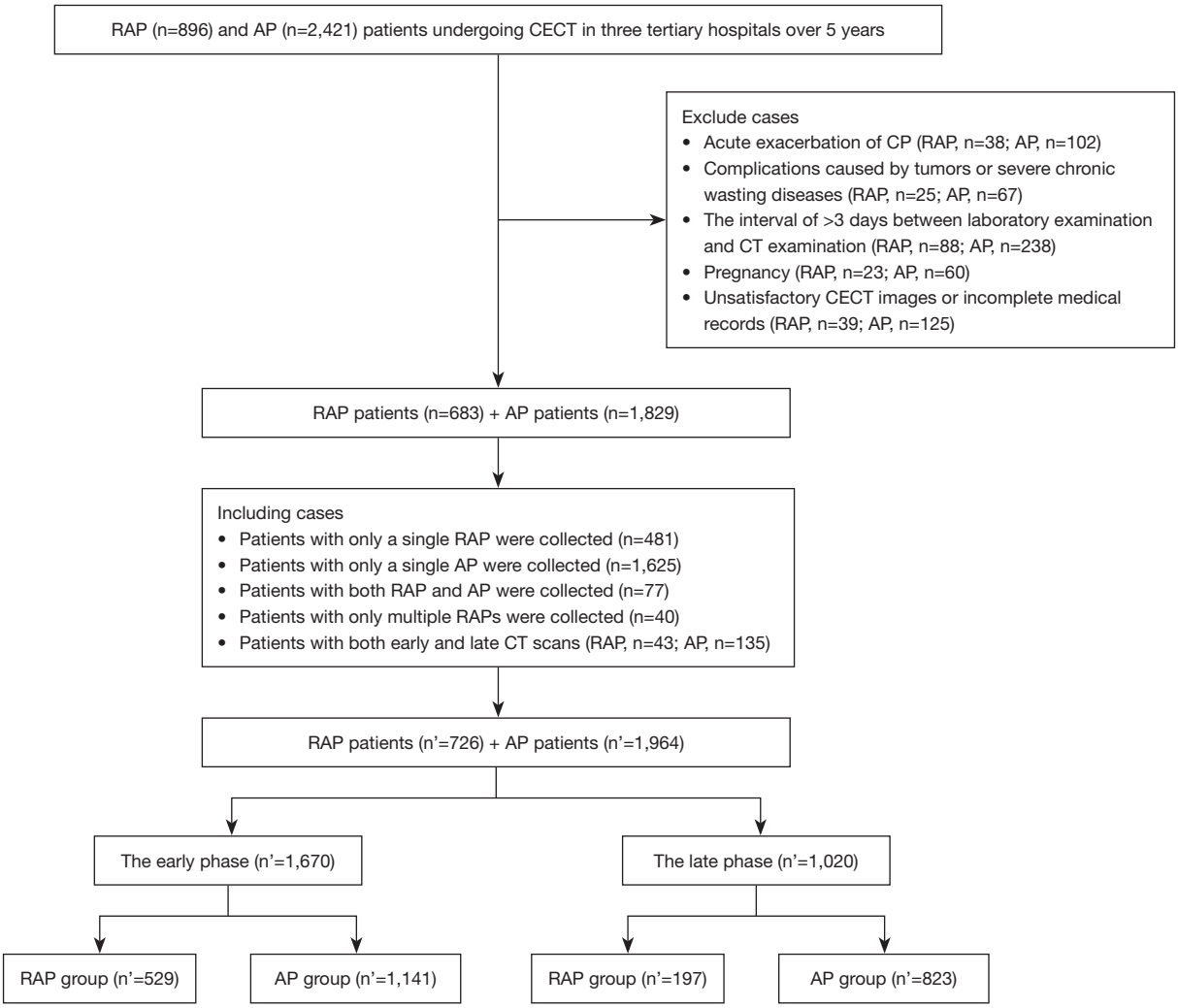

Figure 1 Flow chart illustrating patient recruitment in the present study. RAP, recurrent acute pancreatitis; AP, acute pancreatitis; CECT, contrast-enhanced computed tomography; CP, chronic pancreatitis; CT, computed tomography; n, number of patients; n', number of CT examinations.

RAP and AP patients using one of the following five multidetector CT systems: SOMATOM Definition AS + 128 (Siemens Healthineers, Germany), LightSpeed VCT 128 (GE Healthcare, Boston, USA), Brilliance 64 (Philips Healthcare, Netherlands), Toshiba Aquilion ONE 320 (Toshiba Medical Systems, Japan), and SOMATOM Definition Flash (Siemens Healthineers, Germany). Detailed CT image acquisition is provided in Appendix 1 and Table S1.

Image analysis

CT image data of all patients were retrieved from the picture archiving and communication system (PACS). Two abdominal radiologists with at least 5 years of experience independently reviewed the CT images without the knowledge of patient outcomes. RAP and AP were classified as either interstitial edematous pancreatitis (IEP) or necrotizing pancreatitis (NP) according to the 2012 RAC (4). NP was determined as uneven perfusion of the pancreatic parenchyma or heterogeneous enhancement after contrast injection in the early phase; the area of pancreatic perfusion injury can evolve into necrosis and shows no enhancement of the pancreatic parenchymal necrotic area, mostly after one week of onset (4). Subsequently, NP was divided into

three subtypes: extrapancreatic necrosis alone (EXPN), pancreatic parenchymal necrosis alone (PN), and both pancreatic parenchymal and peripancreatic necrosis (BN). Local complications included acute peripancreatic fluid collections (APFCs), acute necrotic collections (ANCs), pancreatic pseudocysts (PPCs), and walled-off necrosis (WON). The two radiologists reviewed the CT images and determined the CTSI scores (15) and EPIC scores (14) for RAP and AP severity assessments. In case of differences, a consensus was reached through discussion.

Laboratory and clinical data

The medical records of 2,512 patients who underwent 2,690 CT scans were reviewed. Age, sex, etiology, length of hospital stay, AP type and necrotic subtype on CT were recorded according to the number of patients. The CTSI scores, EPIC scores, Acute Physiology and Chronic Health Evaluation (APACHE) II scores, RAC and local complications at different time periods were recorded based on the number of CT examinations. With respect to severity, both RAP and AP were classified as mild, moderately severe, or severe based on the 2012 RAC (4).

Interrater reliability

The intraclass correlation coefficient (ICC) for the CTSI and EPIC scores was calculated to assess the consistency between the two observers, with an ICC of >0.75 considered indicative of satisfactory consistency. Additionally, the kappa coefficient for necrosis, necrosis type, and local complications and the weighted kappa coefficient for the RAC were calculated to evaluate the consistency between the two observers, with a κ value of >0.80 for consistency regarded as indicative of a perfect match.

Statistical analysis

The Kolmogorov-Smirnov (K-S) test was used to evaluate the distribution of continuous variables. Continuous variables (age, hospital stay, APACHE II score, CTSI score, EPIC score) that did not follow a normal distribution are described by the median and interquartile range and were compared with the Wilcoxon signed-rank test. Categorical variables and grade variables (sex, etiology, necrosis, local complications, and RAC) are expressed as frequencies and proportions and were compared by the χ^2 test and Fisher's exact test. The correlation between CTSI/EPIC scores with RAC was assessed by the Spearman rank correlation test. The Spearman correlation coefficients were defined as follows: absolute values between 0.00 and 0.30 were considered negligible correlations; weak correlations between 0.30 and 0.50, moderate correlations between 0.50 and 0.70, strong correlations between 0.70 and 0.90, and very strong correlations between 0.90 and 1.00 (25). All statistical analyses were conducted by SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Differences were considered significant at $P<0.05$.

Results

Demographic and clinical characteristics of the RAP and AP patients

A total of 683 RAP patients and 1,829 AP patients were enrolled in this study. Among the 683 RAP patients, 449 (65.74%) were male, whereas 234 (34.26%) were female, and the median age was 45 (range, 39–52) years. RAP was due to cholelithiasis in 13.03% (89/683), alcoholism in 9.37% (64/683), hypertriglyceridemia in 38.07% (260/683), multiple causes in 20.79% (142/683), and other/idiopathic causes in 18.74% (128/683) of the patients. Of the 1,829 AP patients, 1,071 (58.56%) were male, whereas 758 (41.44%) were female, and the median age was 48 (range, 40–61) years. AP was due to cholelithiasis in 30.56% (559/1,829), alcoholism in 11.54% (211/1,829), hypertriglyceridemia in 17.77% (325/1,829), multiple causes in 14.76% (270/1,829), and other/idiopathic causes in 25.37% (464/1,829) of the patients. The median hospital stays for RAP and AP groups were 11 (range, 8–15) and 13 (range, 9–18), respectively. There were significant differences in sex, age, etiology, and length of stay between the RAP and AP groups (sex, $P=0.001$, others $P<0.001$; *Table 1*).

CT findings of RAP and AP

In the 683 RAP patients, IEP and NP accounted for 61.64% (421/683) and 38.36% (262/683) of the patients, respectively. In the 262 RAP patients with NP, EXPN, PN, and BN accounted for 17.56% (46/262), 4.20% (11/262), and 78.24% (205/262) of the patients, respectively. Of the 1,829 AP patients, IEP and NP accounted for 64.95% (1,188/1,829) and 35.05% (641/1,829) of the patients, respectively. In the 641 AP patients with NP, EXPN, PN and BN accounted for 19.81% (127/641), 4.99% (32/641),

Table 1 Demographic and clinical characteristics of recurrent acute pancreatitis and initial acute pancreatitis patients

Characteristics	RAP (n=683)	AP (n=1,829)	P
Sex, n (%)			0.001
Male	449 (65.74)	1,071 (58.56)	
Female	234 (34.26)	758 (41.44)	
Age (years)†	45 [39, 52]	48 [40, 61]	<0.001
Etiology, n (%)			<0.001
Alcoholism	64 (9.37)	211 (11.54)	
Cholelithiasis	89 (13.03)	559 (30.56)	
Hypertriglyceridemia	260 (38.07)	325 (17.77)	
Multiple causes	142 (20.79)	270 (14.76)	
Other/Idiopathic causes	128 (18.74)	464 (25.37)	
Length of hospital stay (days)†	11 [8, 15]	13 [9, 18]	<0.001

†, data are the medians [interquartile ranges]. RAP, recurrent acute pancreatitis; AP, acute pancreatitis; n, number of patients.

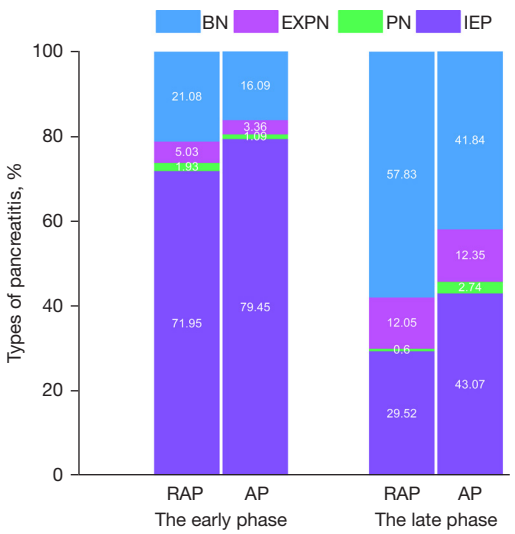

Figure 2 Types of the pancreatitis of recurrent acute pancreatitis and initial acute pancreatitis on computed tomography (n, number of patients). BN, both pancreatic parenchymal and peripancreatic necrosis; EXPN, extrapancreatic necrosis alone; PN, pancreatic parenchymal necrosis alone; IEP, interstitial edematous pancreatitis; RAP, recurrent acute pancreatitis; AP, acute pancreatitis.

and 75.20% (482/641) of the patients, respectively. No significant difference was found between the RAP and AP patients in the type of pancreatitis and subtype of necrosis (P_1=0.13; P_2=0.34). Among the 683 RAP and 1,829 AP patients, the number of CT examinations was 726 and 1,964, respectively, and the percentage of NP in the RAP and AP groups was 28.36% and 20.95% in the early phase, respectively. The percentages of NP in the RAP and AP groups were 68.53% and 56.99% in the late phase, respectively. The RAP group had a higher proportion of NP and BN than the AP group in both the early and late stages (the early phase; P_1=0.001; P_2=0.006; the late phase; P_3=0.003; P_4=0.02; *Figure 2*; Tables S2,S3).

Local complications of the RAP and AP groups on CT

In the 683 RAP patients and 1,829 AP patients, the prevalence of local complications in all RAP and AP patients was 64.57% (441/683) and 65.77% (1,203/1,829), respectively. Among the 726 CT examinations of RAP patients, the proportion of local complications was as follows: 26.58% (193/726) for APFCs, 0.14% (1/726) for PPCs, 31.82% (231/726) for ANCs, and 5.92% (43/726) for WON. Among the 1,964 CT examinations of AP patients, the proportion of local complications was as follows: 32.13% (631/1,964) for APFCs, 0.15% (3/1,964) for PPCs, 28.56% (561/1,964) for ANCs, and 5.60% (110/1,964) for WON.

Among the 726 CT examinations for the RAP group and the 1,964 CT examinations for the AP group, compared to the AP group, the RAP group had a lower percentage of APFCs in the early stage (P<0.001); the RAP group had a higher proportion of ANCs in both the early and late stages (P_1=0.03; P_2=0.004); and the RAP group had a higher proportion of WON in the early

stage (P<0.001). The proportion of PPCs throughout the courses of RAP and AP was extremely low, and no significant difference was found between the two groups (P_1=0.32; P_2=0.40; *Figure 3*, Table S4).

RAP and AP severity at different stages on CT

The median CTSI scores for the early and late phases were 3 (range, 2–4) points and 5 (range, 3–6) points, respectively, in the 726 CT examinations of the RAP group. The median CTSI scores for the early and late phases were 3 (range, 2–4) points and 4 (range, 3–6) points, respectively, in the 1,964 CT examinations of the AP group. The RAP group had a higher median CTSI score than the AP group in the late stage (P=0.02), but no significant difference was observed between the two in the early stage (P=0.44). The median EPIC scores for the early and late phases were 3 (range, 2–5) points and 4 (range, 3–6) points, respectively, in the 726 CT examinations of the RAP group. The median EPIC scores for the early and late phases were 4 (range, 2–5) points and 4 (range, 3–6) points, respectively, in the 1,964 CT examinations of the AP group. The median EPIC score of the RAP group in the early stage was lower than that of the AP group (P<0.001), and the EPIC score did not significantly differ between the two groups in the late stage (P=0.79; *Table 2*).

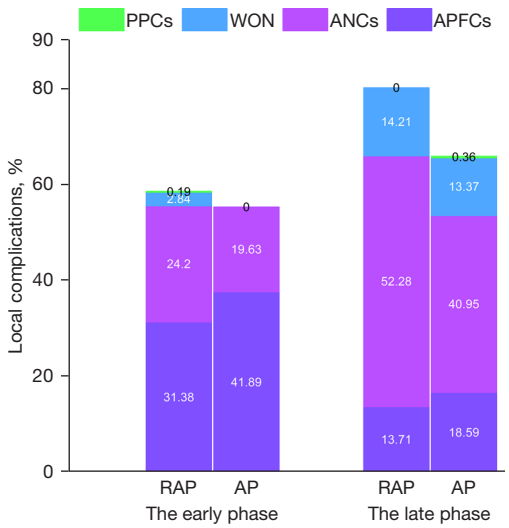

Figure 3 Local complications of recurrent acute pancreatitis and initial acute pancreatitis on computed tomography (n', number of CT examinations). PPCs, pancreatic pseudocysts; WON, walled-off necrosis; ANCs, acute necrotic collections; APFCs, acute peripancreatic fluid collections; RAP, recurrent acute pancreatitis; AP, acute pancreatitis.

RAP and AP severity at different stages on clinical scoring systems

The median APACHE II scores for the early and late phases were 4 (range, 2–6) points and 4 (range, 2–7) points, respectively, in the 726 CT examinations of the RAP group. The median APACHE II scores for the early and late phases were 4 (range, 2–7) points and 5 (range, 2–7) points, respectively, in the 1,964 CT examinations of the AP group. The median APACHE II score of the RAP group was lower than that of the AP group in both the early and late stages (P_1<0.001; P_2=0.007). For the 726 CT examinations of the

Table 2 Recurrent acute pancreatitis and initial acute pancreatitis severity on both computed tomography and clinical scoring systems

Severity	The early phase			The late phase		
	RAP (n'=529)	AP (n'=1,141)	P	RAP (n'=197)	AP (n'=823)	P
CTSI score†	3 [2, 4]	3 [2, 4]	0.44	5 [3, 6]	4 [3, 6]	0.02
EPIC score†	3 [2, 5]	4 [2, 5]	<0.001	4 [3, 6]	4 [3, 6]	0.79
APACHE II score†	4 [2, 6]	4 [2, 7]	<0.001	4 [2, 7]	5 [2, 7]	0.007
RAC, n' (%)			0.12			0.41
Mild	190 (35.92)	364 (31.90)		36 (18.27)	170 (20.66)	
Moderately severe	309 (58.41)	688 (60.30)		140 (71.07)	545 (66.22)	
Severe	30 (5.67)	89 (7.80)		21 (10.66)	108 (13.12)	

†, data are the medians [interquartile ranges]. RAP, recurrent acute pancreatitis; AP, acute pancreatitis; n', number of CT examinations; CTSI, CT severity index; EPIC, extrapancreatic inflammation on CT; APACHE II, Acute Physiology and Chronic Health Evaluation II; RAC, 2012 revised Atlanta classification; CT, computed tomography.

Table 3 Computed tomography severity index for recurrent acute pancreatitis and initial acute pancreatitis of different etiologies

Etiology	The early phase			The late phase		
	RAP (n'=529)	AP (n'=1,141)	P	RAP (n'=197)	AP (n'=823)	P
Alcoholism†	4 [2, 4.75]	3 [2, 4]	0.38	6 [5, 7.5]	4 [4, 6]	0.006
Cholelithiasis†	4 [2, 6]	3 [2, 4]	0.02	4 [4, 6]	4 [2, 6]	0.27
Hypertriglyceridemia†	3 [2, 4]	3 [3, 4]	0.14	4 [3, 6]	4 [3, 6]	0.48
Multiple causes†	3 [2, 4]	3 [2, 4]	0.91	5.5 [3, 6]	4 [3, 6]	0.16
Other/idiopathic causes†	3 [2, 4]	3 [2, 4]	0.47	6 [3, 6]	4 [3, 6]	0.19

†, data are the medians [interquartile ranges]. RAP, recurrent acute pancreatitis; AP, acute pancreatitis; n', number of CT examinations.

RAP group, the proportions of mild, moderately severe, and severe RAP based on the 2012 RAC of RAP were 35.92% (190/529), 58.41% (309/529), and 5.67% (30/529), respectively, in the early phase and 18.27% (36/197), 71.07% (140/197), and 10.66% (21/197), respectively, in the late phase. For the 1,964 CT examinations of the AP group, the proportions of mild, moderately severe, and severe AP based on the 2012 RAC of AP were 31.90% (364/1,141), 60.30% (688/1,141), and 7.80% (89/1,141), respectively, in the early phase and 20.66% (170/823), 66.22% (545/823), and 13.12% (108/832), respectively, in the late phase. The RAC did not significantly differ between the RAP and AP groups throughout the disease course (P_1=0.12; P_2=0.41; *Table 2*).

CTSI for RAP and AP of different etiologies

The CTSI scores for different etiologies of RAP and AP at early and late stages are shown in *Table 3*.

The CTSI score of alcohol RAP in the late stage is higher than that of AP (P=0.006), and no significance was found in the early phase (P=0.38). The CTSI score of cholelithiasis RAP in the early stage is higher than that of AP (P=0.02), no significance was observed in the late phase (P=0.27). No significant differences were found in CTSI of hyperlipidemia; multiple causes and other/idiopathic causes of RAP and AP in both the early and late phases (hyperlipidemia; P_1=0.14; P_2=0.48; multiple causes; P_3=0.91; P_4=0.16; other/idiopathic causes; P_5=0.47; P_6=0.19; *Table 3*).

Correlation of CTSI/EPIC scores with RAC

According to Spearman's rank correlation, the CTSI and EPIC scores of RAP were all positively correlated with RAC in both the early and late phases. In the early stage, the CTSI and EPIC scores with RAC were moderately correlated (r_1=0.643, r_2=0.545; both P<0.001). In the late stage, the CTSI score and RAC were moderately correlated (r=0.683; P=0.003); the EPIC score and RAC were weakly correlated (r=0.466; P<0.001).

According to Spearman's rank correlation, the CTSI scores in the early phase of AP and the EPIC scores in both the early and late phases of AP were positively correlated with RAC. In the early stage, the CTSI and EPIC scores with RAC were moderately correlated (r=0.646, r=0.518; both P<0.001). In the late stage, the CTSI score and RAC did not correlate (r=0.97; P=0.64); the EPIC score and RAC were weakly correlated (r=0.450; P<0.001).

Interobserver agreement

The ICC for the CTSI score between the two observers was 0.928 [95% confidence interval (CI), 0.924–0.931; P<0.001]. The Cohen kappa coefficient for NP, necrosis type, and local complications between the two observers was 0.869 (95% CI, 0.861–0.877; P<0.001), and the weighted kappa coefficient for the RAC between the two observers was 0.931 (95% CI, 0.918–0.944; P<0.001), all of which showed strong consistency.

Discussion

The study yielded the following major findings. First, compared with the AP group, the RAP group had a higher proportion of males and younger patients, and the most common cause of RAP was hypertriglyceridemia. Second, the RAP group had higher NP ratios than the AP group in both the early and late stages, and the proportion of NP in the late stage of RAP was as high as 70.48%. Third, the

RAP group had lower EPIC and APACHE II scores than the AP group in the early phase, while the RAP group had a higher CTSI score than the AP group in the late phase. Our results indicated that RAP patients and AP patients exhibited different demographic characteristics and CT findings, and the severity of RAP was lower than that of AP in the early stage and higher than that of AP in the late stage. This suggests that physicians should conduct personalized management at different stages of RAP to improve patients' prognoses, thereby reducing the occurrence of CP.

Earlier studies have shown that compared to the AP patients, the RAP patients had younger patients and a higher proportion of males, and the most common cause of RAP in China was hypertriglyceridemia (7,9,18,26,27). Our researchers obtained the same results. Previous studies (9,17,18,28) have reported that the proportion of NP patients in RAP patients was as high as 48–72.06%, and among NP patients, BN, EXPN, and PN accounted for the first, second, and third, respectively, in both the RAP and AP patients. Our research obtained similar results.

Previous reports indicated that local complications of RAP and AP were significantly different; local complications of PPCs and WON occurred in the early phase of RAP, and the incidence of PPCs in RAP and AP was extremely low (7,26). Our study obtained the same results.

Song *et al.* (8) reported that no statistical difference was observed in CT Balthazar grades between RAP and AP in the early stage, our study achieved the similar results. AP mainly manifests as early inflammation within and around the pancreas during the first week. With treatment, peripancreatic inflammation was absorbed, AP patients with mild severity and lower CTSI scores were discharged within the first week, and the NP and severe AP rates increased in the late phase (17,20). Our study obtained the same results for RAP and AP. In our study, the proportion of NP, BN, and ANCs and the CTSI score of the RAP group were higher than those of the AP group in the late phase. The reason may be that severe cases with pancreatic necrosis were irreversible (29). NP of RAP in the late phase may include two parts, uncured NP in a previous episode and newly occurring NP, but NP in AP only includes newly occurring NP. Our findings suggest that the CTSI cannot accurately assess the severity of RAP and AP in the early phase, while it can better assess the severity of RAP and AP in the late stage. Moreover, the severity of RAP was higher than that of AP in the late stage.

Earlier studies (30,31) reported that the milder the disease in alcoholic AP the more likely it is to recur and patients with mild first episodes based on RAC had fewer chronic changes in the pancreas over the long term. However, in our study, alcoholic RAP was more severe than AP in the late stage of CTSI. Alcoholic RAP may be morphologically more severe than AP in the late phase, but the specific mechanism is unclear and further study may be needed. In our study, cholelithiasis RAP was more severe than AP in the early stage of the CTSI, However, early CT imaging may underestimate the severity of AP, and the severity initially recorded based on the CTSI score did not correlate strongly with AP outcome (13).

Avanesov *et al.* (18) reported that the EPIC score of RAP was lower than that of AP in the early stage. Our study obtained the same results. Therefore, the severity of RAP was lower than that of AP in the early stage, demonstrating the role of the EPIC score in the early assessment of RAP and AP severity.

Song *et al.* (8) reported that the APACHE II scores were lower in the RAP group than in the AP group in the early phase, our study obtained the same result in the early phase. However, the proportion of NP in RAP and AP was as high as 70.48–56.96% in the late phase, but the APACHE II score was not reliable for diagnosing NP (32,33). Therefore, the severity of RAP was lower than that of AP in the early phase.

Du *et al.* (34) showed that the MCTSI was moderately correlated with the RAC in the early stage of AP and moderately to weakly correlated in the late stage. Bollen *et al.* (35) showed no significant differences between CTSI and MCTSI in assessing the severity of AP. Our study yielded the same results throughout the course of RAP and in the early stage of AP. De Waele *et al.* (14) reported that the EPIC score could predict AP severity and was superior to the CTSI score for the prediction of AP severity in the early phase. In our study, both EPIC and CTSI of RAP and AP were moderately correlated with RAC in the early stage. This may be due to differences in inclusion criteria, as we included patients who underwent CT within the first week of onset, whereas the study by De Waele *et al.* (14) included patients who underwent CT within 24 hours after admission. EPIC and RAC of RAP and AP were weakly correlated in the late phase, as EPIC is mainly used for early assessment of AP severity (14,36).

This study has some limitations. First, this is a retrospective study, some patients were unable to collect clinical and CT characteristics at the same time, which may lead to data loss and affect the results. Secondly, it is an

ideal state to divide all patients into two stages and compare the RAP and AP patients in each group. Therefore, it is worth conducting a case-control study to investigate the differences in CT manifestation between RAP and AP in the same patient. Third, the study included only a subgroup of patients with RAP and AP (only those who had CT), which affected the percentage of mild/moderate severe and severe AP, therefore a prospective cohort study may therefore be warranted.

Conclusions

Compared with AP patients, RAP patients were more likely to be males and younger, with the most common cause being hypertriglyceridemia in China. Patients with RAP had a higher proportion of NP in both the early and late phases than those with AP, with up to 70.48% of NP in the late phase of RAP, and the severity of RAP was lower than that of AP in the early stage and higher than that of AP in the late stage. These findings suggest that physicians should conduct personalized management at different stages of RAP to improve patients' prognoses, thereby reducing the occurrence of CP.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1172/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Affiliated Hospital of North Sichuan Medical College [No. 2019ER(R)064-01], and individual consent for this retrospective analysis was waived.

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Appendix 1: Text, Supplemental Digital Content

For the first four CT scanners, a nonenhanced scan was performed first, and 1.5 mL/kg of an iodinated contrast medium (Ultravist 370; Bayer Schering Pharma, Guangzhou, China) was subsequently injected into the vein at a rate of 3.5–4 mL/s using a motorized syringe pump (Ulrich CT Plus 150; Ulrich Medical, Boston, USA). Arterial and portal vein phase CECT scans were obtained with delays of 25–30 and 65–70 s, respectively, after contrast material injection.

For the SOMATOM Definition Flash system, the conventional unenhanced phase scan was performed in the single-energy mode, whereas the arterial and portal vein phase scans were carried out in the dual-energy mode. The A tube and B tube data were simultaneously obtained. Dual-energy scanning was conducted using an automatic exposure control system (CARE Dose 4D; Siemens Medical Solutions, Germany) to simultaneously obtain a collimation of 128×0.6 mm, a pitch of 0.9, a field of view of 33 cm, and a B30f reconstruction kernel. For routine nonenhanced scans, a pump sampler (MEDRAD; Stellant, USA) was used to intravenously inject 1.5 mL/kg of an iodinated contrast agent (300 mg I/mL, Omnipaque; GE Healthcare, Boston, USA) at a flow rate of 3.5 mL/s. Bolus tracking (CARE Bolus; Siemens Medical Solutions) was conducted for timing in each phase. A nonlinear data combination algorithm was used to reconstruct the images acquired at 140 and 80–120 kV.

Table S1 Specific computed tomography scanners and parameters

CT parameters	Tube voltage (kV)	Tube current (Ma)	FOV (cm)	Matrix	Reconstruction kernels	Collimation (mm)	Pitch (mm)	Slice thickness (mm)
SOMATOM Definition AS + 128	120	200	35×35	512×512	B30f	128×0.6	1.0	5
LightSpeed VCT 128	120	200	35×35	512×512	B30f	64×0.6	0.9	5
Brilliance 64	120	200	35×35	512×512	B30f	64×0.6	0.8	5
Toshiba Aquilion ONE 320	120	250	35×35	256×256	B30f	64×0.6	0.5	5
SOMATOM Definition Flash	140/80	200/155	50×50/33×33	512×512	B30f	2×128×0.6	0.9	5

CT, computed tomography.

Table S2 Types of the pancreatitis of recurrent acute pancreatitis and initial acute pancreatitis in all patients on CT

Types of pancreatitis	All			The early phase			The late phase		
	RAP (n=683)	AP (n=1,829)	P	RAP (n=517)	AP (n=1,100)	P	RAP (n=166)	AP (n=729)	P
NP, n (%)	262 (38.36)	641 (35.05)	0.13	145 (28.05)	226 (20.55)	0.001	117 (70.48)	415 (56.93)	0.001
Types of pancreatitis, n (%)			0.34			0.008			0.001
IEP	421 (61.64)	1,188 (64.95)		372 (71.95)	874 (79.45)		49 (29.52)	314 (43.07)	
PN	11 (1.61)	32 (1.75)		10 (1.93)	12 (1.09)		1 (0.60)	20 (2.74)	
EXPN	46 (6.73)	127 (6.94)		26 (5.03)	37 (3.36)		20 (12.05)	90 (12.35)	
BN	205 (30.01)	482 (26.35)		109 (21.08)	177 (16.09)		96 (57.83)	305 (41.84)	

CT, computed tomography; RAP, recurrent acute pancreatitis; AP, acute pancreatitis; n, number of patients; IEP, interstitial edematous pancreatitis; NP, necrotizing pancreatitis; PN, pancreatic parenchymal necrosis alone; EXPN, extrapancreatic necrosis alone; BN, both pancreatic parenchymal and peripancreatic necrosis.

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Table S3 Types of the pancreatitis of recurrent acute pancreatitis and initial acute pancreatitis in the number of CT examinations of all patients

Types of pancreatitis	All			The early phase			The late phase		
	RAP (n'=726)	AP (n'=1,964)	P	RAP (n'=529)	AP (n'=1,141)	P	RAP (n'=197)	AP (n'=823)	P
NP, n' (%)	285 (39.26)	707 (35.60)	0.12	150 (28.36)	239 (20.95)	0.001	135 (68.53)	469 (56.99)	0.003
Types of pancreatitis, n' (%)			0.41			0.006			0.02
IEP	441 (60.74)	1,257 (64.00)		379 (71.64)	903 (79.14)		62 (31.47)	354 (43.01)	
PN	15 (2.07)	36 (1.83)		10 (1.89)	12 (1.05)		5 (2.54)	24 (2.92)	
EXPN	52 (7.16)	142 (7.23)		27 (5.10)	37 (3.24)		25 (12.69)	105 (12.76)	
BN	218 (30.03)	529 (26.93)		113 (21.36)	189 (16.56)		105 (53.30)	340 (41.31)	

CT, computed tomography; RAP, recurrent acute pancreatitis; AP, acute pancreatitis; n', number of CT examinations of all patients; IEP, interstitial edematous pancreatitis; NP, necrotizing pancreatitis; PN, pancreatic parenchymal necrosis alone; EXPN, extrapancreatic necrosis alone; BN, both pancreatic parenchymal and peripancreatic necrosis.

Table S4 Local complications of recurrent acute pancreatitis and initial acute pancreatitis on computed tomography

Local complications, n' (%)	All			The early phase			The late phase		
	RAP (n'=726)	AP (n'=1,964)	P	RAP (n'=529)	AP (n'=1,141)	P	RAP (n'=197)	AP (n'=823)	P
APFCs	193 (26.58)	631 (32.13)	0.006	166 (31.38)	478 (41.89)	<0.001	27 (13.71)	153 (18.59)	0.11
ANCs	231 (31.82)	561 (28.56)	0.10	128 (24.20)	224 (19.63)	0.03	103 (52.28)	337 (40.95)	0.004
WON	43 (5.92)	110 (5.60)	0.87	15 (2.84)	0	<0.001	28 (14.21)	110 (13.37)	0.76
PPCs	1 (0.14)	3 (0.15)	0.93	1 (0.19)	0	0.32	0	3 (0.36)	0.40

RAP, recurrent acute pancreatitis; AP, acute pancreatitis; n', number of CT examinations; APFCs, acute peripancreatic fluid collections; ANCs, acute necrotic collections; WON, walled-off necrosis; PPCs, pancreatic pseudocysts.

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