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Original Article

Risk of and factors influencing the progression from acute to recurrent acute to chronic pancreatitis

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ABSTRACT

Objectives & Aims: Acute pancreatitis (AP) recurrence rates range from 11 to 36 % yet accurately predicting recurrent acute pancreatitis (RAP) and its progression to chronic pancreatitis (CP) after an initial episode remains challenging. Thus, this study explored the risk factors contributing to RAP and its progression to CP.

Methods: This retrospective study included patients with AP from three tertiary medical centers between January 2010 and December 2017. The patients were followed up for up to 60 months. The primary endpoint was the incidence of RAP and CP; risk factors influencing these outcomes were also identified.

Results: Overall, 501 patients were included, of which 164 (32.7 %) experienced RAP, and 71 (14.2 %) progressed to CP. The leading causes of AP were alcohol consumption (43.1 %), gallstones (41.5 %) and hypertriglyceridemia (4.4 %). Multivariate Cox regression analysis revealed that smoking (HR, 4.09; 95 % CI, 2.752–6.078, $p < 0.001$), and organ failure after 48 h of hospitalization (HR, 3.52; 95 % CI, 1.22–10.19, $p < 0.02$) were significant risk factors for RAP. Significant risk factors for progression to CP included age over 60 years (HR, 5.29; 95 % CI, 1.25–22.47, $p = 0.024$), smoking (HR, 2.50; 95 % CI, 1.04–6.01, $p = 0.04$), alcohol consumption (HR, 8.79; 95 % CI, 2.06–37.43, $p = 0.003$), computed tomography severity index (CTSI) (HR, 1.22; 95 % CI, 1.04–1.44, $p = 0.015$), and recurrence of AP (HR, 70.69; 95 % CI, 2.61–1914.86, $p = 0.011$). In alcohol-induced RAP patients, ≥3 recurrences (HR, 4.18; 95 % CI, 1.75–9.98, $p = 0.001$) was significant risk factor for progression to CP.

Conclusions: Alcohol consumption was the predominant cause of AP and RAP. The severity of the initial AP episode was the key determinant for RAP, and RAP was the most significant risk factor for the progression to CP. Therefore, smoking and alcohol cessation are important to prevent the development of recurrent AP and CP during long-term follow-up.

1. Introduction

Acute pancreatitis (AP) is a common gastroenterological disease with a steadily increasing incidence rate over the past decades [1,2]. Most patients with AP experience spontaneous improvement and achieve complete recovery within a few weeks [3]. However, 10–20 % of patients develop severe complications, including necrosis, infection, or organ failure, necessitating intensive medical intervention [3,4]. Furthermore, a subset of individuals develop recurrent acute pancreatitis (RAP), defined as two or more episodes of AP with the complete resolution of symptoms between episodes [5,6]. RAP is a concerning clinical scenario because repeated inflammation can lead to cumulative damage to the pancreatic tissue [1,7–9]. Chronic pancreatitis (CP), a progressive fibro-inflammatory disease, results from sustained or recurrent

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pancreatic injury, leading to irreversible structural changes, including fibrosis, calcification, and exocrine and endocrine dysfunction [8,10,11]. Patients with CP often suffer from chronic pain, malabsorption, and diabetes mellitus, significantly impacting their quality of life [10,12,13]. The natural course of AP and risk factors associated with recurrent events are not well known, and previous studies report conflicting findings [9,14–16]. Furthermore, the transition from AP to CP is not well defined, and a debate is ongoing regarding the etiological relationship between these conditions [2,5,9]. The assertion that most patients with CP have an idiopathic etiology implies the potential distinctiveness of CP as a separate disease entity from AP [8]. In contrast, others propose that RAP and CP may represent a single disease continuum [9,17]. The distinction between AP and CP is based on histopathological, morphological, and functional changes within the pancreas [12], and this differentiation is crucial, as CP is indicative of irreversible pancreatic destruction.

Therefore, understanding the factors contributing to the progression from AP to CP is clinically significant for the prevention and early detection of CP. Therefore, this study evaluated the risk factors associated with RAP and the progression to CP in patients following their first AP episode. We aimed to provide insights that could inform clinical practice and improve patient outcomes through targeted interventions and long-term management strategies.

2. Materials and methods

2.1. Patients

The medical records of patients who experienced their first AP attack survived, and were followed up for up to 60 months at three tertiary medical centers between January 2010 and December 2017 were retrospectively reviewed. The exclusion criteria were patients with known CP, those with unexplained abdominal pain before the first AP attack, those who underwent previous abdominal surgery, patients missing alcohol intake data at their first hospitalization, and patients with pancreatitis occurring after endoscopic retrograde cholangiopancreatography. All patients with AP received standardized management based on the guidelines and a consensus, including intravenous fluid resuscitation, nutritional support, and analgesics. For patients with biliary AP with acute cholangitis, endoscopic retrograde cholangiopancreatography was performed during hospitalization as soon as possible.

The Institutional Review Board of Gachon Gil Medical Center, Sanggye Paik Hospital, and Wonju Severance Christian Hospital (GDIRB2020-002, 2023-11-020, and CR315005-002, respectively) approved this study. Informed consent was waived due to the study's retrospective nature.

2.2. Data collection

We collected comprehensive demographic and clinical data from the patients' medical records, including age, sex, AP etiology, comorbidities, smoking habit, alcohol use, the severity of the initial AP episode, and laboratory results. AP severity was assessed using the revised Atlanta classification, Ranson, Bedside Index of Severity in Acute Pancreatitis (i.e., BISAP), Acute Physiology and Chronic Health Evaluation II (i.e., APACHE-II), and computed tomography severity index (CTSI) values.

2.3. Diagnosis and definitions

An AP diagnosis was based on the presence of two of the following three features: 1) abdominal pain (acute onset of a persistent, severe, epigastric pain often radiating to the back); 2) serum amylase or lipase at least three times greater than the upper limit of the normal value; and 3) characteristic manifestations of AP on a contrast-enhanced computed tomography scan [18]. RAP was defined as: 1) one or more recurrent pancreatitis episodes requiring another hospitalization; 2) an interval between attacks greater than 3 months; 3) the first AP episode entirely or near wholly resolved; and 4) no conclusive evidence of underlying CP [6]. CP was defined based on the M-ANNHEIM diagnostic criteria for definite CP as a typical clinical history of CP (e.g., recurrent pancreatitis or abdominal pain) and one or more of the following additional criteria: 1) pancreatic calcifications; 2) moderate or marked ductal lesions (based on the Cambridge classification) [3]; marked and persistent exocrine insufficiency: documented persistent steatorrhea in the medical chart, fecal elastase $\leq$200 μg/g or abnormally increased amount of fat in the feces after 24 h; and [4] typical histology of an adequate tissue specimen [19]. The etiology of AP was classified as: 1) biliary, when gallstones were detected in the gallbladder or the bile ducts; 2) alcoholic, when the patient or the patient's family reported regular consumption of $\geq$40 g of alcohol (Soju $\geq$0.5 bottle or beer $\geq$3 bottles) per day for $\geq$5 years; 3) hypertriglyceridemia (HTG), when the serum triglyceride level at admission was greater than 11.3 mmol/L or greater than 5.65 mmol/L without other causes; 4) hypercalcemia, when a serum ionized calcium level at admission was greater than 2.1 mmol/L without other causes; 5) autoimmune pancreatitis; 6) malignancy; or 7) idiopathic, when no cause was identified [20–24].

2.4. Follow-up

Patients who were followed up for up to 60 months after their first AP episode were included. Patients who were lost to follow-up before 60 months were included in the study by analyzing data up to the last hospitalization or outpatient visit. The primary endpoint was the incidence of RAP and CP, defined by established clinical and radiologic criteria. Follow-up evaluation included a clinical assessment, laboratory tests, and imaging studies to monitor for AP recurrence and the development of CP. For the multivariate analysis of risk factors for progression to CP, the severity of the first episode of AP in patients with RAP was considered as a risk factor.

2.5. Statistical analyses

Data are expressed as means and standard deviations, medians and interquartile ranges, or numbers and percentages, as appropriate. When comparing groups, the chi-square and Fischer's exact test were used for categorical variables. Risk factors for RAP and CP were assessed by univariate analysis with logistic regression for categorical variables and the Student's *t*-test for continuous variables; groups were compared with the log-rank test. A multivariate Cox regression analysis was used to identify independent predictors of RAP and CP after the first AP attack. A Kaplan–Meier analysis showing the cumulative risk over time for progression to CP was also performed. A p-value of 0.05 was used as the threshold for statistical significance. All statistical analyses were conducted using SPSS version 21 (IBM Corp., Armonk, NY, USA).

The proportional hazards (PH) assumption for the Cox regression model was tested using Schoenfeld residuals, calculated and analyzed in SPSS. No significant violations of the PH assumption were observed for any covariates, as confirmed by non-significant global p-values ($p > 0.05$). Additionally, graphical diagnostics of Schoenfeld residuals plotted against time indicated no systematic deviations, supporting the validity of the assumption.

Kaplan-Meier survival curves were also generated and analyzed in SPSS for key categorical variables (e.g., RAP recurrence, CTSI $\geq$4).

The log-rank test results from these analyses confirmed consistent hazard trends across subgroups. For continuous variables, stratification analyses were performed to detect potential non-proportional effects, but no significant deviations were identified. The combined use of SPSS for Cox regression and Kaplan-Meier analysis ensured the accuracy and reliability of the proportional hazards assumption validation and the overall time-to-event analyses.

3. Results

3.1. Patient characteristics

In total, 501 patients from three tertiary hospitals were enrolled from January 2010 to December 2017; 277 (55.3 %) were male and 224 (44.7 %) were female (Table 1). The mean age was 54.6 ± 19.2 years. The AP cause was classified as alcoholic for 216 patients (43.1 %), biliary for 208 patients (41.5 %), HTG for 22 patients (4.4 %), malignancy for 11 patients (2.2 %), autoimmune pancreatitis for 6 patients (1.2 %), hypercalcemia for 2 patients (0.4 %), and idiopathic for 36 patients (7.2 %). Based on the 2012 revised Atlanta classification, 393 (78.2 %) and 109 (21.8 %) patients had mild and moderately severe/severe AP, respectively.

3.2. Clinical outcome comparisons between single-episode AP and RAP

Table 1 presents the clinical outcomes of patients with single-episode AP (n = 337, 67.3 %) and RAP (n = 164, 32.7 %). Overall, 14 patients (4.2 %) in the single-episode group and 57 (34.8 %) in the RAP group progressed to CP (Fig. 1). In the RAP group, the mean number of relapses was 2.3 ± 2.5 (range, 1–19), and the mean time to first relapse was 432.4 ± 512.7 days. Patients with single-episode AP were older on average than those with RAP (57.1 ± 20.0 years vs. 49.4 ± 16.3 years; $p < 0.01$). The incidences of smoking and alcohol consumption were significantly higher in the RAP group than in the single-episode group (32.6/52.8 % vs. 66.5/79.3 %; $p < 0.01$). Patients with single-episode AP had significantly higher aspartate transaminase (AST), alanine transaminase (ALT), and amylase levels than those with RAP (AST: 142.6 ± 219.1 IU/L vs. 92.1 ± 129.9 IU/L, ALT: 118.4 ± 222.3 IU/L vs. 63.6 ± 82.5 IU/L, amylase: 624.2 ± 765.2 IU/L vs. 404.4 ± 534.3 IU/L; $p < 0.01$). The predominant AP cause in the single-episode AP group was biliary, whereas the predominant cause in the RAP group was alcohol (51.0 % and 64.6 %, respectively). The Ranson criteria and APACHE-II scores (severity indicators) were higher in single-episode group than in the RAP group (2.37 ± 1.57 vs. 1.75 ± 1.41 and 5.00 ± 4.09 vs. 3.49 ± 3.03; $p < 0.01$), but the CTSI score was higher in RAP group than in the single-episode group, (2.09 ± 1.72 vs. 2.79 ± 1.83; $p < 0.01$). The hospitalization duration did not differ between the two groups; however, the progression to CP was more pronounced in the RAP group than in the single-episode group (4.2 % vs. 34.8 %; $p < 0.01$).

3.3. RAP risk factors

The univariate analysis identified several variables with

Table 1
Baseline demographics and characteristics of all patients with acute pancreatitis, those with a single episode of acute pancreatitis, and those with recurrent acute pancreatitis.

	Total AP (n = 501)	Single episode (n = 337)	RAP (1st attack) (n = 164)	p-value
Age, mean ± SD (year)	54.6 ± 19.2	57.1 ± 20.0	49.4 ± 16.3	<0.01
Sex (male) (%)	277 (55.3)	183 (54.3)	94 (57.3)	0.525
Body Mass Index (kg/m^2)	23.5 ± 4.2	23.6 ± 4.0	23.2 ± 4.6	0.343
Smoking/Alcohol (%)	219 (43.7)/308 (61.5)	110 (32.6)/178 (52.8)	109 (66.5 %/130 (79.3)	<0.01/<0.01
Lab finding, mean ± SD				
WBC (x10^3/μl)	11.9 ± 4.9	11.8 ± 5.0	12.0 ± 4.9	0.622
Hb (g/dL)	14.0 ± 2.2	13.7 ± 2.0	14.5 ± 2.5	<0.01
Hct (%)	40.6 ± 5.7	40.1 ± 5.3	41.7 ± 6.4	<0.01
Platelet (x10^3/μl)	230.1 ± 114.1	227.3 ± 118.0	236.1 ± 105.6	0.416
CRP (mg/dL)	5.9 ± 12.6	6.1 ± 14.4	5.5 ± 7.8	0.629
CRP2(at24 h) (mg/dL)	11.5 ± 40.3	12.3 ± 48.6	9.8 ± 8.4	0.438
Total bilirubin(mg/dL)	2.0 ± 7.9	2.3 ± 9.6	1.3 ± 1.3	0.645
AST/ALT (IU/L)	126.1 ± 195.8/100.5 ± 190.2	142.6 ± 219.1/118.4 ± 222.3	92.1 ± 129.9/63.6 ± 82.5	<0.01/<0.01
Amylase/Lipase (IU/L)	551.9 ± 704.9/2735.9 ± 3974.4	624.2 ± 765.2/2888.1 ± 4033.2	404.4 ± 534.3/2426.2 ± 3845.3	<0.01/0.225
TG (mg/dL)	274.9 ± 546.9	221.9 ± 432.1	384.7 ± 718.5	<0.01
Etiology (%)				<0.01
Biliary	208 (41.5)	172 (51.0)	36 (22.0)	
Alcohol	216 (43.1)	110 (32.6)	106 (64.6)	
HTG	22 (4.4)	14 (4.2)	8 (4.9)	
Autoimmune	6 (1.2)	3 (0.9)	3 (1.8)	
Anatomy	3 (0.6)	2 (0.6)	1 (0.6)	
Idiopathic	33 (6.6)	25 (7.4)	8 (4.9)	
Hypercalcemia	2 (0.4)	2 (0.6)	0 (0)	
Malignancy	11 (2.2)	9 (2.7)	2 (1.2)	
Severity scoring systems, mean± SD (median)				
Ranson (total)	2.17 ± 1.54(2.0, 0–8)	2.37 ± 1.57(2.0, 0–8)	1.75 ± 1.41(2.0, 0–6)	<0.01
APACHE II (at admission)	4.51 ± 3.85(4.0, 0–26)	5.00 ± 4.09(4.0, 0–26)	3.49 ± 3.03(3.0, 0–14)	<0.01
APACHE II (48 h)	3.70 ± 3.86(3.0, 0–41)	4.23 ± 4.19(3.0, 0–41)	2.60 ± 2.76(2.0, 0–13)	<0.01
BISAP	0.75 ± 0.84 (1.0, 0–4)	0.83 ± 0.89 (1.0, 0–4)	0.57 ± 0.68 (0, 0–3)	0.01
Atlanta classification				0.05
Mild	392 (78.2 %)	272 (80.7 %)	120 (73.2 %)	
Moderate severe/Severe	109 (21.8 %)	65 (19.3 %)	44 (26.8 %)	
CTSI	2.32 ± 1.79 (2.0, 0–10)	2.09 ± 1.72 (2.0, 0–10)	2.79 ± 1.83 (3.0,0–10)	<0.01
Hospital stay (day)	9.9 ± 10.9	9.8 ± 11.9	10.3 ± 8.8	0.664
Progression to CP	71(14.2 %)	14(4.2 %)	57(34.8 %)	<0.01

Abbreviations: AP, acute pancreatitis; RAP, recurrent acute pancreatitis; SD, standard deviation; WBC, white blood count; Hb, hemoglobin; Hct, hematocrit; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; TG, triglyceride; HTG, hypertriglyceride; CP, chronic pancreatitis; APACHE II, Acute Physiology and Chronic Health Evaluation II; BISAP, bedside index of severity in acute pancreatitis; CTSI, CT severity index.

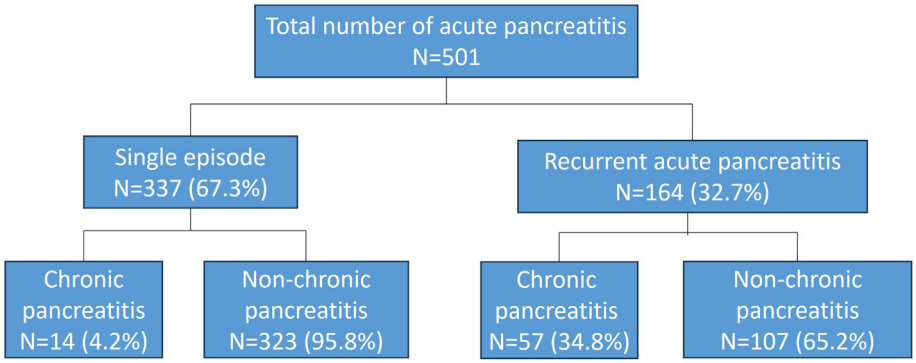

Fig. 1. Patient flowchart.

Table 2
Cox regression analysis of the risk factors associated with recurrent acute pancreatitis.

	n (%)	HR (95 % CI)	p-value
Age		0.998 (0.984–1.013)	0.782
Smoking	109 (66.5)	4.090 (2.752–6.078)	0.000
Alcohol	130 (79.3)	1.081 (0.684–1.708)	0.740
Ranson (total)		1.057 (0.939–1.189)	0.362
APACHE II (at admission)		0.993 (0.934–1.055)	0.814
APACHE II (48 h)		1.078 (1.009–1.152)	0.026
Atlanta classification (mild vs moderate severe and severe)		1.683 (1.106–2.562)	0.015
CTSI		0.878 (0.792–0.973)	0.013
Organ failure (at admission)	13 (7.9)	0.488 (0.192–1.240)	0.131
Organ failure (48 h)	5 (3.0)	3.518 (1.215–10.189)	0.020
Acute peripancreatic fluid collection	89 (54.3)	1.049 (0.711–1.547)	0.811
Acute necrotic collection	150 (91.5)	4.370 (0.575–33.203)	0.154

Abbreviations: HR, Hazard ratio; CI, confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II; CTSI, CT severity index.

significant associations with RAP; thus, a multivariate analysis was conducted focusing on those variables. These variables represent data from the baseline index hospitalization (Table 2). Smoking (hazard ratio [HR], 4.09; 95 % confidence interval [CI], 2.752–6.078, $p < 0.001$), was a significant independent risk factor for RAP, as was organ failure at 48 h of hospitalization (HR, 3.52; 95 % CI, 1.22–10.19, $p < 0.02$).

3.4. AP versus CP

Table 3 compares the clinical data at the time of the first AP episode between patients who did and did not progress to CP; 71 patients advanced to CP (CP group, 14.2 %), and 430 patients did not (non-CP group, 85.8 %). The mean duration to the CP diagnosis was 651.97 ± 546.41 days. Overall, age did not differ between the CP and non-CP groups. However, more patients were 60 years or older in the non-CP group than in the CP group (31.0 % vs. 40.5 %; $p = 0.044$). Sex did not differ between the groups. The rates of smoking and alcohol consumption were significantly higher in the CP group than in the non-CP group (69 % vs. 39.5 % and 84.5 % vs. 57.5 %, respectively; $p < 0.01$). The APACHE-II score 48 h after admission, Atlanta classification, and CTSI significantly differed between the groups. Specifically, the non-CP group had a significantly higher APACHE-II score 48 h after admission compared to that in the CP group (3.86 ± 3.99 vs. 2.76 ± 2.72; $p = 0.026$), and moderate to severe AP based on the Atlanta classification was more prevalent in the CP group than in the non-CP group (31.0 % vs. 20.2 %; $p = 0.033$). Furthermore, the CTSI score was significantly higher in the CP group than in the non-CP group. The incidence of RAP and the number of recurrences were significantly higher in the CP group than in the non-CP group (80.3 % vs. 24.9 %, 3.49 ± 3.72 vs. 1.67 ± 1.18, respectively; $p < 0.01$).

3.5. Risk factors for progression to CP

The multivariate analysis determined that age over 60 years (HR, 5.29; 95 % CI, 1.23–22.47, $p = 0.024$), smoking (HR, 2.50; 95 % CI, 1.04–6.01, $p = 0.04$), alcohol consumption (HR, 8.79; 95 % CI, 2.06–37.43, $p = 0.003$), CTSI (HR, 1.22; 95 % CI, 1.04–1.44, $p = 0.015$), and AP recurrence (HR, 70.69; 95 % CI, 2.61–1914.86, $p = 0.011$) were independent risk factors for CP (Table 4). These variables represent data from the baseline index hospitalization. Alcohol was the most common cause of RAP and a significant risk factor for progression to CP; therefore, we performed further alcohol-related analyses. For patients with alcohol-induced RAP, ≥3 recurrences (HR, 4.18; 95 % CI, 1.75–9.98, $p = 0.001$) was significant risk factors for progression to CP (Table 5). Fig. 2 presents the cumulative risk analysis for the development of CP stratified by recurrence and the CTSI score. Approximately 50 % of patients with RAP progressed to CP approximately 5.5 years after the onset of the initial AP episode. Additionally, approximately 50 % of patients with a CTSI score of ≥3 and 50 % of patients with a CTSI score of ≥4 or higher developed CP 3.5 and 2.9 years after the first AP episode, respectively.

4. Discussion

In our study, the most common causes of AP were alcohol consumption and gallstones, consistent with previous studies. Among the patients with gallstone-induced pancreatitis, 54.8 %

Table 3
Baseline demographics and characteristics at the first acute pancreatitis episode of patients who developed chronic pancreatitis.

	Development of chronic pancreatitis (n = 71)	Non-development of chronic pancreatitis (n = 430)	p-value
Age, mean ± SD (year)	52.4 ± 14.2	54.9 ± 19.9	0.188
Age > 60 years (%)	22 (31.0)	174 (40.5)	0.044
Sex (male) (%)	46 (64.8)	231 (53.7)	0.108
Body Mass Index (kg/m^2)	23.1 ± 4.5	23.5 ± 4.2	0.462
Smoking (%)	49 (69.0)	170 (39.5)	<0.001
Alcohol (%)	60 (84.5)	248 (57.5)	<0.001
Lab finding, mean ± SD			
Hct (%)	41.2 ± 6.4	40.6 ± 5.6	0.446
CRP (mg/dL)	5.0 ± 7.2	6.0 ± 13.2	0.457
CRP2(at 24 h) (mg/dL)	10.3 ± 8.8	11.7 ± 43.8	0.609
Total bilirubin(mg/dL)	1.1 ± 0.8	2.1 ± 8.5	0.016
AST/ALT (IU/L)	74.7 ± 100.1/46.0 ± 52.9	134.5 ± 206.1/109.4 ± 202.6	<0.001
Severity scoring systems, mean±SD (median, range)			
Ranson (total)	1.94 ± 1.53 (2.0, 0–5)	2.20 ± 1.54 (2.0, 0–8)	0.187
APACHE II (at admission)	3.97 ± 3.18 (3.0, 0–14)	4.59 ± 3.94 (4.0, 0–26)	0.206
APACHE II (48 h)	2.76 ± 2.72 (2.0, 0–11)	3.86 ± 3.99 (3.0, 0–41)	0.026
BISAP	0.69 ± 0.87 (1.0, 0–4)	0.76 ± 0.83 (1.0, 0–4)	0.540
Atlanta classification (%)			0.033
Mild	49 (69.0)	343 (79.8)	
Moderate severe/Severe	22 (31.0)	87 (20.2)	
CTSI	3.21 ± 2.07 (3.0, 0–10)	2.17 ± 1.69 (2.0, 0–10)	<0.001
Hospital stay (day)	11.6 ± 10.2	9.7 ± 11.1	0.168
Recurrence	57 (80.3 %)	107 (24.9 %)	<0.001
Number of recurrence, mean±SD	3.49 ± 3.72	1.67 ± 1.18	<0.001

Abbreviations: SD, standard deviation; Hct, hematocrit; CRP, C-reactive protein; AST, aspartate transaminase; ALT, alanine transaminase; APACHE II, Acute Physiology and Chronic Health Evaluation II; BISAP, bedside index of severity in acute pancreatitis; CTSI, CT severity index.

Table 4
Multivariate analysis of risk factors for progression to chronic pancreatitis.

	n (%)	HR (95 % CI)	p-value
Age > 60 years	21 (29.6)	5.293 (1.247–22.470)	0.024
Smoking	49 (69)	2.502 (1.041–6.014)	0.040
Alcohol	60 (84.5)	8.786 (2.062–37.426)	0.003
Ranson (total)		0.983 (0.753–1.283)	0.898
APACHE II (at admission)		0.891 (0.728–1.091)	0.264
APACHE II (48 h)		0.884 (0.720–1.085)	0.239
Atlanta classification (mild vs moderate severe and severe)	47 (66.2)	0.524 (0.232–1.183)	0.120
CTSI		1.221 (1.039–1.435)	0.015
Recurrence	57 (80.3)	70.689 (2.610–1914.858)	0.011
Number of recurrence≥3	23 (32,4)	2.734 (1.329–5.626)	0.060

Abbreviations: HR, Hazard ratio; CI, confidence interval; APACHE II, Acute Physiology and Chronic Health Evaluation II; CTSI, CT severity index.

Table 5
Univariate and multivariate analysis of risk factors for progression to chronic pancreatitis in patients with alcohol-induced recurrent acute pancreatitis

		Univariate analysis		Multivariate analysis	
	n (%)	OR (95 % CI)	p-value	OR (95 % CI)	p-value
Age ≥60	21 (19.8)	1.078 (0.688–1.688)	0.461		
Sex (male)	59 (55.7)	1.213 (0.854–1.718)	0.179		
Smoking	83 (78.3)	1.314 (0.499–4.190)	0.372		
Ranson ≥3	30 (28.3)	0.536 (0.452–2.482)	0.536		
Organ failure(at admission)	7 (6.6)	3.393 (0.628–18.343)	0.136		
Organ failure (48 h)	2 (1.9)	1.216 (0.077–20.707)	0.693		
Acute peripancreatic fluid collection	62 (58.5)	0.926 (0.426–2.014)	0.501		
Acute necrotic collection	12 (11.3)	2.821 (0.793–10.028)	0.090		
Atlanta classification (mild vs moderate severe and severe)	75(70.8)	0.954 (0.411–2.213)	0.541		
Number of recurrence≥3	34 (32.1)	2.061 (1.325–3.802)	0.001	4.182 (1.753–9.978)	0.001

Abbreviations: OR, Odds ratio; CI, confidence interval; CTSI, CT severity index.

underwent cholecystectomy during their initial hospitalization. Of the entire study population, 32.7 % progressed to RAP, and 14.2 % progressed to CP. Studies have reported that the incidence of RAP ranges from 11 to 36 % owing to variations in sample sizes, follow-up periods, and baseline patient characteristics [1]. Bingjun et al. conducted a study with a similar sample size to ours, reporting a 10.7 % incidence of RAP; the AP recurrence rate in our study was approximately three times higher than that [15]. This discrepancy may be attributed to the higher proportion of patients with alcoholic AP included in our study, which is a known cause of RAP.

Alcohol consumption is the most common cause of RAP and CP [8,25]. The average amount of alcohol consumed, the duration of alcohol consumption, and cumulative exposure are critical factors that significantly increase the risk of alcoholic pancreatitis [8,26].

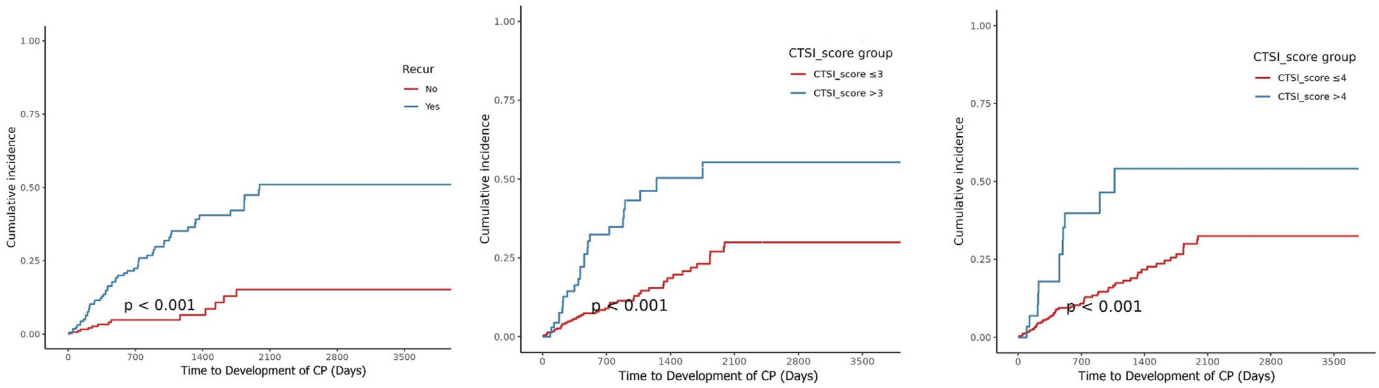

Fig. 2. Cumulative risk over time for developing CP stratified by period to first recurrence and the CTSI.
Abbreviations: CP, chronic pancreatitis; Recur, acute pancreatitis recurrence; CTSI, computed tomography severity index.

Alcohol increases susceptibility to pancreatitis by affecting pancreatic physiology at multiple levels, sensitizing the pancreas to other stimuli, such as smoking or genetic susceptibility [1,5,8]. However, alcohol, which has been identified as risk factors for RAP in previous studies, did not emerge as significant risk factors for RAP in our study. Instead, smoking, organ failure 48 h after hospitalization, the APACHE-II score 48 h after hospitalization, and the Atlanta classification were significant risk factors for RAP, differing from a previous study that reported no significant association between the severity of the first AP episode and pancreatitis recurrence [16]. Additionally, Cho et al. found that local complications at index admission was the strongest risk factor for RAP, whereas, in our study, the systemic inflammatory response due to AP was a strong risk factor for RAP [27].

Understanding the risk factors for RAP is crucial for its prevention based on the hypothesis that recurrent episodes of pancreatitis can progress to CP and eventually to pancreatic cancer [1,2]. In our study, 80.3 % of patients with CP experienced recurrent episodes of AP, with an average of 3.5 episodes occurring before progression to CP. Conversely, approximately 20 % of patients with CP were diagnosed with CP at their first hospitalization, suggesting that these patients may have had asymptomatic AP episodes or no prior history of AP. In this study, 4.2 % of patients in the single-episode group progressed to CP, indicating that the initial AP episode may have been the first manifestation of preexisting CP. CP can only be diagnosed based on advanced findings such as fibrosis, calcification, pancreatic ductal stricture or dilation, or endocrine and exocrine pancreatic dysfunction [10]. As this stage represents an irreversible condition and treatment is virtually impossible, it is essential to mitigate the risk factors before the progression to CP [8,10]. In this study, age, smoking, alcohol consumption, CTSI, AP recurrence, and the number of recurrences were risk factors for CP. Among these, recurrence was the most significant risk factor, followed by alcohol consumption. Although alcohol consumption was not a risk factor for the development of RAP, it was a significant risk factor for the progression to CP. Notably, one-quarter of patients with alcoholic pancreatitis progressed to CP. Although the recurrence of AP was identified as a significant risk factor for the development of CP, not all patients with RAP progressed to CP. Previous meta-analyses have shown that approximately 70 % of patients with RAP do not develop CP [1]. Similarly, in this study, 34.8 % of patients with RAP progressed to CP. Our multivariate analysis showed that the number of RAP episodes was an also significant risk factor for progression from RAP to CP. Patients who progressed from RAP to CP had an average of 3.4 relapses, and more of these patients were smokers and had an alcohol-related etiology compared to those who did not progress from RAP to CP.

Although smoking is an established CP risk factor, its impact on AP or RAP is less clear [15]. The high prevalence of alcohol problems and smoking among patients who progressed from RAP to CP may be attributed to the common coexistence of smoking in patients with alcohol dependence [9]. However, a meta-analysis found that after adjusting for alcohol use, the pooled risk estimates for current smokers developing CP was 2.5 (95 % CI, 1.3–4.6) compared with never-smokers [28]. This evidence suggests that smoking alone may influence the occurrence of pancreatitis. Another meta-analysis by Majumder et al. found that the risk of AP was highest in current smokers but persisted in those who had quit smoking [29]. Experimental studies investigating the mechanisms by which smoking induces pancreatitis suggest that smoking may alter the balance between trypsinogen and pancreatic-specific trypsin inhibitors or promote damage to pancreatic acinar cells. In addition, nicotine may activate several signaling pathways in acinar cells and induce oxidative stress. Smoking also damages vascular endothelial cells, potentially leading to recurrent episodes of pancreatitis [30–34]. Based on these findings alone, physicians should strongly encourage smokers at risk for AP or RAP to quit, and smoking cessation therapy should be an important part of pancreatitis management.

This study has several limitations. First, this is a retrospective data analysis, so it was not possible to quantitatively analyze the exact amount of alcohol consumption, duration of consumption, and smoking before and after the patient's first hospitalization. In addition, the smoking status may not be accurate because the data were obtained by relying on the patients' statement. Second, the association between HTG and pancreatitis was not rigorously analyzed. A significant number of patients did not have their lipid levels measured on the first day of hospitalization and were tested 24 h after admission, which may have resulted in lower triglyceride levels due to massive hydration as a first-line treatment for pancreatitis. Third, more than 50 % of patients with biliary AP underwent cholecystectomy during their initial hospitalization, making it difficult to properly analyze factors that influence the progression of biliary AP to RAP or CP. Fourth, whether patients had previously been treated for pancreatitis at another hospitals was ascertained by history taking from all patients and their families, which relies on self-reported data, so it is possible that some patients who initially presented with AP were included in the study cohort during their relapse. This is also a potential cause of the high

recurrence rate in this study. Finally, RAP episodes were not treated as time-varying risk factors. Therefore, the categorization for this independent variable is incorrect.

5. Conclusions

Our study demonstrated that the severity of AP, including factors such as organ failure, and smoking were the strongest risk factor for the occurrence of RAP. The most significant factor influencing progression to CP was pancreatitis recurrence, and patients who progressed to CP experienced an average of 3.5 recurrent episodes. Alcohol and tobacco use were risk factors for the development of CP; thus, providing long-term education on abstinence from alcohol and smoking cessation is crucial, particularly for patients with severe AP.

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