Early identification of high-risk patients with recurrent acute pancreatitis progression to chronic pancreatitis

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Submitted: 29 November 2021; **Accepted:** 30 January 2022
Online publication: 6 February 2022

Arch Med Sci 2022; 18 (2): 535–539
DOI: https://doi.org/10.5114/aoms/146262

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Abstract

Introduction: The aim of the study was to develop a simple tool for early identification of high-risk patients with recurrent acute pancreatitis (RAP) progression to chronic pancreatitis (CP) in primary hospitals or outpatient clinics.
Methods: This retrospective cohort study included 265 patients with RAP.
Results: A nomogram for RAP progression to CP was developed and the C-index of the model was 0.817 (95% CI: 0.72–0.91). Patients were divided into two risk groups according to the nomogram prediction scores and a higher proportion of patients in the high-risk group progressed to CP.
Conclusions: The nomogram provided a means of predicting which patients were at high risk of progression to CP.

Key words: recurrent acute pancreatitis, chronic pancreatitis, risk factor, nomogram.

Chronic pancreatitis (CP) is a common disease that presents with fibrosis and dysfunction of the endocrine and exocrine glands of the pancreas [1]. The etiology of CP is complicated. Recurrent acute pancreatitis (RAP) is defined as ≥ 2 episodes of AP and is an important risk factor for CP, as confirmed by a large number of clinical studies [2]. However, not all patients with RAP develop to CP [3]. A meta-analysis showed that nearly 70% of RAP patients did not progress to CP [4]. Identifying risk factors for progression of RAP to CP is important because it could facilitate earlier intervention and may potentially delay or avoid the onset of CP, although there were some drugs that might delay CP progression [5]. To evaluate the risk factors of patients with RAP progression to CP, we designed a retrospective study involving a cohort of 265 patients with RAP.

Methods. We retrospectively retrieved the medical information of patients with RAP between January 2012 and December 2019, in the Department of Gastroenterology of Peking University Third Hospital. The study protocol was approved by the Human Ethics Review Committees of Peking University Third Hospital (No: M2019402). As a retrospective study, the ethics committee waived the need for written informed consent. Inclusion criteria were as follows: 1) Patients experienced at least

2 acute AP episodes before CP diagnosis. 2) The AP diagnosis was based on the revision of the Atlanta classification [6]. 3) All patients were evaluated for clinical diagnosis of chronic pancreatitis according to the M-ANNHEIM diagnostic criteria [7] and only patients with no signs of CP were included. Exclusion criteria were: < 18 years of age, autoimmune pancreatitis, mass within the pancreatic head, pancreatic cancer and patients who lacked imaging data of the pancreas which could prove the diagnosis of CP or not during follow-up. The etiology of AP was defined according to previous guideline [8]. All patients were evaluated for clinical diagnosis of chronic pancreatitis and underwent computed tomography (CT) scan, magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangio-pancreatography (ERCP) at each AP episode during follow-up and were diagnosed with defined CP according to the M-ANNHEIM diagnostic criteria [7]. SPSS 25.0 and R software (version 3.2.4) were used for data analysis. The nomogram scaled each regression coefficient to a scale of 0–100 points, which demonstrated their relative importance. Based on the total score from the nomogram, the optimal cutoff value was identified by X-tile software and patients were divided into two risk groups (low- and high-risk). Statistical significance was set at $p < 0.05$.

Results. A total of 265 patients diagnosed with RAP were included in our study. The patients' baseline characteristics are listed in Table I. During the follow-up, a total of 29 patients were diagnosed with CP. The median duration from the first onset of AP to the diagnosis of CP was 33 months (interquartile range: 10–57.5 months). Univariate analysis indicated that the risk factors for progression from RAP to CP included the severity and etiology at the first onset, number of RAP episodes, chronic pain, presence of pseudocysts, and body mass index (BMI) < 25 kg/m^2. In multivariate analysis, we divided the etiology of patients at the first onset into idiopathic and non-idiopathic. Multivariate analysis revealed that the risk factors

Table I. General characteristics of all 265 patients

Items	Total (n = 265) n (%)	RAP (n = 236) n (%)	RAP-CP (n = 29) n (%)	P-value
Female (%)	96 (36.2)	90 (38.1)	6 (20.7)	0.065
BMI [kg/m^2]:				0.005
< 25	155 (58.5)	131 (55.5)	24 (82.8)	
≥ 25	110 (41.5)	105 (44.5)	5 (17.2)	
Age at CP diagnosis [years]	42 (33–53)	41 (33–46)	43 (32–55)	0.148
Follow-up time [months]	38 (11.3–73.8)	74.5 (39–122)	33 (10–57.5)	0.185
Drinking history [years]	20 (10–30)	20 (10–30)	20 (10–30)	0.222
Smoking history [years]	20 (10–30)	20 (10–30)	20 (10–30)	0.344
Severity at first onset (%):				< 0.001
Mild	225 (84.9)	211 (89.4)	14 (48.3)	
Moderate	20 (7.5)	12 (5.1)	8 (27.6)	
Severe	20 (7.5)	13 (5.5)	7 (24.1)	
Etiology of first onset (%):				< 0.001
Biliary	87 (32.8)	85 (36.0)	2 (6.9)	0.001
Alcoholic	38 (14.3)	35 (14.8)	3 (10.3)	0.374*
Idiopathic	119 (44.9)	95 (40.3)	24 (82.8)	< 0.001
Other known causes	21 (7.9)	21 (8.9)	0 (0)	0.079*
Clinical characteristics:				
Episodes of AP attack	3 (2–4)	5 (4–8)	3 (2–4)	0.019
Cholecystectomy (%)	42 (15.8)	41 (17.4)	1 (3.4)	0.059
Chronic pain (%)	7 (2.6)	4 (1.7)	3 (10.3)	0.031
Pseudocyst (%)	40 (15.1)	26 (11.0)	14 (48.3)	< 0.001

*AP – acute pancreatitis, BMI – body mass index, CP – chronic pancreatitis, RAP – recurrent acute pancreatitis. *Fisher's exact test.*

of progression from RAP to CP were the number of RAP episodes, presence of pseudocysts, idiopathic pancreatitis and BMI < 25 kg/m^2 (Table II). Four independent predictors were used to develop a risk estimation nomogram for RAP progression to CP (Figure 1 A). The nomogram demonstrated good accuracy in estimating the risk of CP, with a C-index of 0.817 (95% CI: 0.72–0.91). The cali-

Table II. Predictive factors for RAP progression to CP

Predictors	*N* (%)	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
BMI [kg/m^2]:		0.242 (0.092–0.637)	0.004	0.356 (0.128–0.99)	0.048
< 25	155 (58.5)				
≥ 25	110 (41.5)				
Episodes of AP attack:		1.123 (1.048–1.203)	0.001	3.816 (1.655–8.797)	0.002
≤ 4	215 (81.1)				
> 4	50 (18.9)				
Pseudocyst (%)	40 (15.1)	7.036 (3.386–14.62)	< 0.001	2.882 (1.004–8.276)	0.049
Etiology at first onset (%):		7.124 (2.626–19.327)	< 0.001	3.139 (1.102–8.939)	0.032
Idiopathic	119 (44.9)				
Non-idiopathic	146 (55.1)				

AP – acute pancreatitis, BMI – body mass index, CP – chronic pancreatitis, HR – hazard ratio, RAP – recurrent acute pancreatitis.

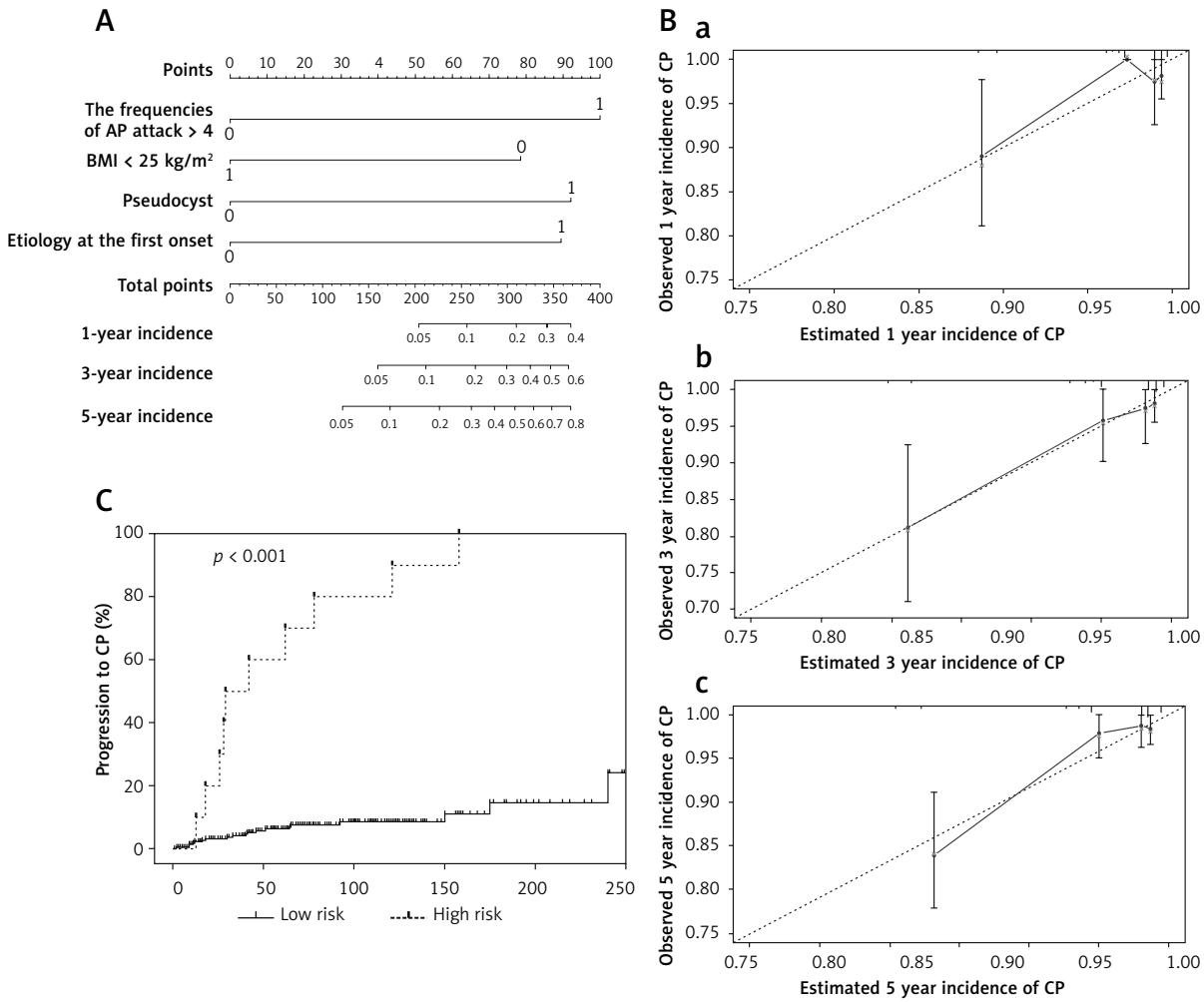

Figure 1. A – Nomogram for recurrent acute pancreatitis progression to chronic pancreatitis. **B** – Effectiveness of predictive performance of the nomogram in estimating the risk of CP. (**a**) 1-year incidence in the RAP cohort; (**b**) 3-year incidence in the RAP cohort; (**c**) 5-year incidence in the RAP cohort. The validity of the nomogram showed that the predictive value of progression to CP at 3 and 5 years is better than that at 1 year. This is consistent with our knowledge, as RAP often takes some time to progress to CP. **C** – Rate of progression to CP after a first attack of acute pancreatitis according to the hazard stratification (Kaplan-Meier curve and one minus survival)

bration curves showed good consistency between risk estimates through the nomogram and actual development of CP at 3 and 5 years after patients were admitted (Figure 1 B). The nomogram score of 192.2 points was the optimal cutoff value through the X-tile analysis. Patients were divided into a low-risk group (≤ 192.2 points) and a high-risk group (> 192.2 points) according to the nomogram prediction score. The Kaplan-Meier curve showed that the risk of progression to CP in the high-risk group was significantly higher than that in the low-risk group ($p < 0.001$) (Figure 1 C).

Discussion. There are some important findings of our study. First, we found that more than 4 episodes of RAP, idiopathic pancreatitis, BMI < 25 kg/m^2 and pseudocysts were independent risk factors for progression to CP. Second, we developed a simple tool to help clinicians early identify high-risk RAP patients who might progress to CP. Our results revealed that patients who experienced more than 4 episodes of AP had a higher risk of progression to CP (HR = 3.816, 95% CI: 1.655–8.797), which was consistent with Péter J. Hegyi's study [9].Their study also found that the pancreas of the mice could develop chronic pancreatitis-like changes if there were more than three episodes of RAP. And for patients with more than three RAP episodes, the total pancreatic volume decreased significantly, although there were no clinically common manifestations of CP [10]. Idiopathic pancreatitis is one of the risk factors for RAP progression to CP in our study and exhibited a higher rate of progression to CP. Idiopathic pancreatitis also often leads to an increased risk of progression to CP by a higher recurrent rate due to the lack of targeted treatment [11]. On the other hand, genetic factors might participate in and accelerate the procession of developing CP, such as SPINK1p.N34S in European patients and PRSS1 mutation in Chinese patients [11, 12]. These mutations could help us understand why the rate of progression to CP is so high in patients with idiopathic pancreatitis.

In our study, pancreatic pseudocysts were another independent risk factor for RAP progression to CP. All patients underwent evaluation of clinical diagnosis of CP when they were included in the cohort, so pseudocysts could not be the manifestation of CP. The incidence of pseudocysts increased significantly in patients with CP, which might be associated with pancreatic duct stones, protein embolism, and local fibrosis [13]. Although there have been no studies that described in detail the role of pseudocysts in RAP progression to CP, given the above mechanisms, we speculate that pseudocysts might lead to pancreatic duct damage and morphological changes. Patients with CP often lose weight due to pancreatic exocrine insufficiency, poor fat absorption and recurrent pain [14]. In the present study, BMI < 25 kg/m^2 was another risk factor for RAP progression to CP. Like the role of pseudocysts for progression to CP, lower BMI was not a manifestation of CP but a risk factor. We have assessed all RAP patients with underweight or pseudocysts carefully according to the M-ANNHEIM diagnostic criteria to exclude potential early CP of these patients. Since early CP is difficult to diagnose at present, there may still be some bias in the current study, which requires further evidence from a prospective study in the future.

In conclusion, according to the nomogram, we developed a simple tool to help clinicians use it in outpatient clinics to divide RAP patients into high-risk and low-risk groups. Patients in the high-risk group are more likely to progress to CP and need active intervention or close follow-up.

Acknowledgments

We thank Dr. Qingqing Tao and Dr. Mingna Xu for their help in collecting data.

Conflict of interest

The authors declare no conflict of interest.

References

1. Klöppel G, Maillet B. Pathology of acute and chronic pancreatitis. Pancreas 1993; 8: 659-70.
2. Bertilsson S, Swärd P, Kalaitzakis E. Factors that affect disease progression after first attack of acute pancreatitis. Clin Gastroenterol Hepatol 2015; 13: 1662-9.e1663.
3. Magnusdottir BA, Baldursdottir MB, Kalaitzakis E, Björnsson ES. Risk factors for chronic and recurrent pancreatitis after first attack of acute pancreatitis. Scand J Gastroenterol 2019; 54: 87-94.
4. Sankaran SJ, Xiao AY, Wu LM, et al. Frequency of progression from acute to chronic pancreatitis and risk factors: a meta-analysis. Gastroenterology 2015; 149: 1490-500.e1491.
5. Kazmierak W, Korolczuk A, Kurzepa J, et al. The influence of erythropoietin on apoptosis and fibrosis in the early phase of chronic pancreatitis in rats. Arch Med Sci 2021; 17: 1100-8.
6. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut 2013; 62: 102-11.
7. Schneider A, Löhr JM, Singer MV. The M-ANNHEIM classification of chronic pancreatitis: introduction of a unifying classification system based on a review of previous classifications of the disease. J Gastroenterol 2007; 42: 101-19.
8. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol 2013; 108: 1400-16.
9. Hegyi PJ, Soós A, Tóth E, et al. Evidence for diagnosis of early chronic pancreatitis after three episodes of acute pancreatitis: a cross-sectional multicentre international study with experimental animal model. Sci Rep 2021; 11: 1367-7.

10. DeSouza SV, Priya S, Cho J, Singh RG, Petrov MS. Pancreas shrinkage following recurrent acute pancreatitis: an MRI study. Eur Radiol 2019; 29: 3746-56.
11. Zou WB, Tang XY, Zhou DZ, et al. SPINK1, PRSS1, CTRC, and CFTR genotypes influence disease onset and clinical outcomes in chronic pancreatitis. Clin Transl Gastroenterol 2018; 9: 204.
12. Di Leo M, Bianco M, Zuppardo RA, et al. Meta-analysis of the impact of SPINK1 p.N34S gene variation in Caucasic patients with chronic pancreatitis. An update. Dig Liver Dis 2017; 49: 847-53.
13. Grace PA, Williamson RC. Modern management of pancreatic pseudocysts. Br J Surg 1993; 80: 573-81.
14. Hart PA, Conwell DL. Chronic pancreatitis: managing a difficult disease. Am J Gastroenterol 2020; 115: 49-55.