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A Nomogram for Predicting the Transition From Recurrent Acute Pancreatitis to Chronic Pancreatitis

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Objectives: Acute pancreatitis, recurrent acute pancreatitis, and chronic pancreatitis are recognized as a continuum of pancreatic diseases. Recurrence increases the risk of progression to chronic pancreatitis. The aim of this study was to search for clinical features that may promote the progression of chronic pancreatitis in patients with recurrent acute pancreatitis

Materials and Methods: We retrospectively reviewed patients with recurrent acute pancreatitis from Medical Information Mart for Intensive Care-IV database. They were divided into a training cohort and a validation cohort. A nomogram was constructed based on clinical features during the second hospitalization. The discrimination and calibration of the nomogram were evaluated using the concordance index, area under the time-dependent receiver operating characteristic curve, and calibration plots.

Results: A total of 432 recurrent acute pancreatitis patients were evaluated, of which 93 (21.53%) were diagnosed with chronic pancreatitis later. Age, biliary pancreatitis, admission interval, alcohol dependence, lipase, and platelet were selected. The concordance index was 0.717 (95% confidence interval: 0.691–0.743) for the training cohort and 0.718 (95% confidence interval: 0.662–0.774) for the validation cohort. The area under the time-dependent receiver operating characteristic curve was >0.7 over 1000 days.

Conclusions: A nomogram was developed and validated to evaluate the transition from recurrent acute pancreatitis to chronic pancreatitis.

Key Words: recurrent acute pancreatitis, chronic pancreatitis, biliary pancreatitis, risk factors

Abbreviations: AP = acute pancreatitis, CP = chronic pancreatitis, RAP = recurrent acute pancreatitis, MIMIC = Medical Information Mart for Intensive Care, BIDMC = Beth Israel Deaconess Medical Center, ICD = International Classification of Diseases, HLP = hyperlipidemia, ICU = intensive care unit, HCT = hematocrit, TBIL = total bilirubin, Alb = albumin, BUN = blood urea nitrogen, AST = aspartate aminotransferase, ALP = alkaline phosphatase, Hb = hemoglobin, WBC = white blood cell, HR = hazard ratios, CI = confidence interval, C-index = concordance index, ROC = receiver operating characteristic , time-dependent AUC= area under the time-dependent receiver operating characteristic curve, VIF = variance inflation factor, IQR = interquartile range, SAPE = Sentinel Acute Pancreatitis Event

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Pancreatitis is the leading cause of gastrointestinal disease-related hospital admissions and is associated with considerable morbidity, mortality, and socioeconomic burden,[1] with a steadily rising incidence over time in most high-income countries.[2] Chronic pancreatitis (CP) is a progressive inflammatory disease with pain as most important clinical problem. CP may cause various local complications and endocrine and exocrine pancreatic insufficiency. It is a long-standing inflammation characterized by irreversible damage to the pancreas that places a substantial economic and psychological burden. Previous studies suggest that acute pancreatitis (AP), particularly recurrent acute pancreatitis (RAP), is linked to the development of CP and, ultimately, pancreatic cancer.[3] Approximately 10% of patients experience the progression to CP following their initial episode of AP, while 30% of patients with recurrent episodes of AP advance to CP.[4] Extensive research indicates that CP serves as a significant risk factor for the development of pancreatic cancer.[5,6] According to a recent comprehensive cohort study conducted in Denmark and published in 2023, the incidence rates of transitioning to CP were found to be 12.1 (95% CI, 8.1–18.1) per 1000 person-years from AP, 46.8 (95% CI, 31.6–69.3) per 1000 person-years from RAP, and 0.07 (95% CI, 0.04–0.13) per 1000 person-years from a healthy state, highlighting the increased risk of CP development following AP and RAP.[7] These studies establish an epidemiological foundation for perceiving pancreatitis as a spectrum of diseases, wherein CP emerges in individuals with prior episodes of acute pancreatic inflammation. Moreover, the epidemiological observations are substantiated by fundamental and translational research, which emphasizes that the transition to CP is facilitated by the infiltration of immune cells within the pancreas, subsequently leading to the activation of stellate cells and the promotion of fibrosis.[8,9]

Therefore, the development of stable, quantitative CP prediction models is essential to provide preventive measures for RAP patients and may help prevent the development of cancer. Researchers are trying to figure out which risk factors are for CP in RAP patients.[10–12] However, there is a paucity of data regarding the risk factors of CP in RAP patients. Our study is aimed to identify risk factors from RAP to CP. Studying these aspects may offer a better understanding of disease progression and help clinicians identify high-risk RAP patients who might progress to CP early.

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MATERIALS AND METHODS

Cohort Selection and Variable Recode

Medical Information Mart for Intensive Care (MIMIC) database is an extensive, single-center, and freely accessible clinical database hosted by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology. It contains well-documented information on laboratory tests, medical behavior, and vital signs of 315,460 patients enrolled in Beth Israel Deaconess Medical Center (BIDMC), Boston, from 2008 to 2019.[13] This retrospective cohort study is based on the MIMIC-IV (v2.0) updated June 12, 2022.

Because there has been no consensus on how to define the best RAP[3,14,15] and the diagnosis of RAP is not included in the International Classification of Diseases (ICD) code, we described RAP as those 2 or more hospitalizations for AP without a diagnosis of CP in between. We collected patients' clinical information at their second episode of AP on disease course, hospital admission, and the results of library tests from the MIMIC database and then developed a nomogram.

The inclusion criteria were as follow: (a) AP was included in the first 3 diagnoses according to the ICD 9 or 10 code (Supplementary Information Table S1, http://links.lww.com/MPA/B272); (b) 2 or more episodes of AP recorded in the database. The exclusion criteria were as follows: (a) CP was diagnosed according to the ICD 9 or 10 code (Supplementary Information Table S1, http://links.lww.com/MPA/B272) on previous and current AP admission; (b) pancreatic neoplasms were diagnosed on previous and current AP admission; (c) younger than 18 years; (d) too much missing data; (e) death in the hospital. There were no restrictions regarding the severity of pancreatitis.

The patients were randomized into the training and validation cohorts with a ratio of 8:2 on follow-up time using the R package "caret." The training cohort was used to screen variables and construct the model. The validation cohort was used to validate the results obtained using the training cohort.

Variables Included and Outcome

We collected patient demographic and biological data at the time of the second hospitalization of AP. The following 23 variables from the MIMIC database were included: age, sex, race, alcohol dependence, tobacco dependence, hyperlipidemia (HLP), biliary pancreatitis (diagnosed as acute biliary pancreatitis, obstruction of the bile duct or calculus of bile duct/ gallbladder), diabetes, obesity, intensive care unit (ICU) admission, length of stay, the interval of time between the first and the second episode of AP (Interval), hematocrit (HCT), total bilirubin (TBIL), lipase, platelet, albumin (Alb), bicarbonate, blood urea nitrogen (BUN), aspartate aminotransferase (AST), alkaline phosphatase (ALP), hemoglobin (Hb), and white blood cell (WBC). Among these variables, alcohol dependence, tobacco dependence, HLP, biliary pancreatitis, diabetes, and obesity were identified based on the ICD-9 or ICD-10 code (Supplementary Information Table S1, http://links.lww.com/MPA/B272). People who had quit smoking and stopped drinking at admission were not classified as alcohol or tobacco dependence. Laboratory test results were the results of the first test after admission.

The study's outcome was the diagnosis of CP after the second episode of AP, which was defined as a CP event in this study. Based on different admissions, any admission with a CP diagnosis that differs from a previous AP diagnosis is regarded as an episode of CP following RAP. The time of admission is considered to be the time of CP diagnosis. According to the outcome, the training cohort was divided into 2 groups, as CP event group and the non-CP event group.

Statistical Analysis

Groups of quantitative variables were compared by using χ^2 or Fisher exact tests. Univariate Cox regression was performed for all 23 variables. The resulting hazard ratios (HRs) and 95% confidence interval (CI) were presented. Variables with P value <0.05 in univariable analyses were selected into Cox proportional risk regression analysis. A predictive nomogram was built according to the model of multivariable analyses. The 3-/5-/10-year CP risk was estimated in the nomogram. The concordance index (C-index) receiver operating characteristic curve (ROC) and area under the time-dependent receiver operating characteristic curve (time-dependent AUC) calculated by bootstrapping were used to evaluate discriminative ability. C-index and AUC values vary from 0.5 to 1.0, where 0.5 represents random chance, and 1.0 indicates a perfect fit. Typically, C-index and AUC values greater than 0.7 suggest a reasonable estimation. Risk stratifications obtained from the nomogram were evaluated using the Kaplan-Meier method and the Cox model.

We transform continuous variables into categorical variables to make the nomogram easier to use. The cutoff values of the variables, including age, length of stay, Interval, and risk stratification of total points obtained from the nomogram, were determined by X-tile software (Supplementary Information Fig. S1, http://links.lww.com/MPA/B279).[16] We used the method of multiple imputations to avoid bias induced by missing data (Supplementary Information Table S2, http://links.lww.com/MPA/B273). The inclusion of covariates in the nomogram followed Harrell's guideline (the number of events should exceed the number of covariates by at least 10 folds).[17] Meanwhile, the variance inflation factor (VIF) was assessed among the covariates in the nomogram. Variables with VIF > 10 were not included in the final model analysis, which was interpreted as indicating multicollinearity.

P value <0.05 was considered to indicate a statistically significant difference. All analyses were performed with R software (version 4.1.3) (http://www.r-project.org/).

RESULTS

Characteristics of Patients

A total of 432 patients with a second episode of AP were enrolled from the MIMIC IV database. The median age of all patients was 56 (interquartile range [IQR]: 24) years old. There were 22 0(50.93%) males in all. Ninety-three (21.53%) patients in all turned to CP. Among all patients who developed CP, the median follow-up time was 152 days (IQR: 336). The median follow-up time for patients who did not develop CP was 2435 days (IQR: 2259). They were randomly divided into training and validation cohorts by a ratio of 8:2 (Supplementary Information Fig. S2, http://links.lww.com/MPA/B280). Three hundred forty-eight patients with 75 (21.55%) patients diagnosed with CP later were included in the training cohort. Eighty-four patients with 18 (21.43%) patients diagnosed with CP later were included in the validation cohort. The media follow-up was 1837 (IQR: 2973) days in the whole population, 1837 (IQR: 2956) days in the training cohort, and 1835 (IQR: 2983) days in the validation cohort.

The comparison of demographic and clinical characteristics between the training cohort and validation cohort is summarized in Table 1. The detailed baseline characteristics of the CP event group and non-CP event group in the training cohort are displayed in Supplementary Information Table S3, http://links.lww.com/MPA/B274.

TABLE 1. Comparison Between the Training Cohort and Validation Cohort

Characteristic	Training Cohort [Cases (%)]	Validation Cohort [Cases (%)]	*P*
Total	**348**	**84**	
Age	57 (IQR: 24)	56 (IQR: 27)	0.750
Sex			0.675
Female	173 (49.71)	39 (46.43)	
Male	175 (50.29)	45 (53.57)	
Race			0.104
White	214 (61.49)	62 (73.81)	
Black	62 (17.82)	11 (13.10)	
Other	72 (20.69)	11 (13.10)	
Alcohol dependence			0.392
No	286 (82.18)	65 (77.38)	
Yes	62 (17.82)	19 (22.62)	
Tobacco dependence			0.556
No	246 (70.69)	56 (66.67)	
Yes	102 (29.31)	28 (33.33)	
HLP			0.334
No	231 (66.38)	61 (72.62)	
Yes	117 (33.62)	23 (27.38)	
Biliary pancreatitis			0.712
No	243 (69.83)	61 (72.62)	
Yes	105 (30.17)	23 (27.38)	
Diabetes			1.000
No	251 (72.13)	61 (72.62)	
Yes	97 (27.87)	23 (27.38)	
Obesity			0.892
No	319 (91.67)	78 (92.86)	
Yes	29 (8.33)	6 (7.14)	
ICU admission			0.098
No	301 (86.49)	66 (78.57)	
Yes	47 (13.51)	18 (21.43)	
Length of stay (day)	4 (IQR: 4)	4 (IQR: 7)	0.131
Interval (day)	59 (IQR: 259)	63 (IQR: 184)	0.832
HCT (%)			0.214
40–52	59 (16.95)	9 (10.71)	
<40	289 (83.05)	75 (89.29)	
TBIL (mg/dL)			1.000
0–1.5	299 (85.92)	72 (85.71)	
>1.5	49 (14.08)	12 (14.29)	
Lipase (IU/L)			0.445
0–540	270 (77.59)	69 (82.14)	
>540	78 (22.41)	15 (17.86)	
Platelet (K/uL)			0.063
150–440	265 (76.15)	56 (66.67)	
<150	51 (14.66)	13 (15.48)	
>440	32 (9.20)	15 (17.86)	
Alb (g/dL)			0.581
3.5–5.2	221 (63.51)	50 (59.52)	
<3.5	127 (36.49)	34 (40.48)	
Bicarbonate (mEq/L)			0.084
22–27	209 (60.06)	59 (70.24)	
<22	62 (17.82)	7 (8.33)	
>27	77 (22.13)	18 (21.43)	
BUN (mg/dL)			0.959
< =20	281 (80.75)	67 (79.76)	
>20	67 (19.25)	17 (20.24)	
AST (IU/L)			0.039
0–40	199 (57.18)	59 (70.24)	
>40	149 (42.82)	25 (29.76)	
ALP (IU/L)			0.593
< =130	253 (72.70)	58 (69.05)	
>130	95 (27.30)	26 (30.95)	
Hb (g/dL)			0.422
≥12 M/11 F	177 (50.86)	38 (45.24)	
<12 M/11 F	171 (49.14)	46 (54.76)	
WBC * (K/uL)			0.706
4–11	223 (64.08)	50 (59.52)	
<4	16 (4.60)	5 (5.95)	
>11	109 (31.32)	29 (34.52)	

Age, length of stay, and Interval are presented by mean and IQR.

Nomogram Construction

For continuous variables, the optimal cutoff value of age, length of stay, and Interval analyzed by X-tile software were 60 years old, 7 days, and 12 days respectively (Supplementary Information Fig. S1, http://links.lww.com/MPA/B279). The VIF values of variables were all <2 (Supplementary Information Table S4, http://links.lww.com/MPA/B275), indicating that no collinearity existed between screened variables.

A total of 348 patients in the training cohort were analyzed with univariate Cox regression. According to the results, 6 variables (age, alcohol dependence, biliary pancreatitis, Interval, lipase, and platelet) were significantly associated with CP event. In the multivariate Cox regression analysis, age (age ≥ 60 years old, $P = 0.008$, HR = 0.46, 95% CI: 0.26–0.82), alcohol dependence ($P = 0.3$, HR = 1.29, 95% CI: 0.76–2.20), biliary pancreatitis ($P = 0.004$, HR = 0.33, 95% CI: 0.15–0.69), Interval (Interval ≥ 12 days, $P = 0.027$, HR = 2.81, 95% CI: 1.12–7.03), platelet (platelet >440 K/uL, $P = 0.2$, HR = 1.53, 95% CI: 0.81–2.89, platelet <150 K/uL, $P = 0.2$, HR = 0.57, 95% CI: 0.25–1.27), and lipase (lipase >540 IU/L, $P = 0.072$, HR = 0.54, 95% CI: 0.27–1.06) were collected to build nomogram to predict the risk of CP event (Table 2).

The nomogram included 6 variables in the multivariate Cox regression analysis model. Figure 1 shows an example of using the nomogram to predict CP event probability for RAP patients. The total score was determined based on individual scores calculated using the nomogram. The patient was ≥60 years old without alcohol dependence, underwent biliary pancreatitis, and had a platelet count of 150–440 K/uL and lipase level of 0–540 IU/L, and the interval between the second admission to the hospital and his initial AP episode was <12 days. Red lines and dots are drawn upward to determine the points received by each variable; the sum (275) of these points is located on the total points axis, and a line is drawn downward to the CP event axes to determine the probability of 3-year (7.31%), 5-year (7.73%), and 10-year (7.94%) overall CP risk. Detailed scores are provided in the Supplementary Information (Supplementary Information Table S5, http://links.lww.com/MPA/B276). The higher the total score, the

TABLE 2. Univariate and Multivariate Analyses of the Proportional Hazards Model

	Univariable		Multivariable	
Characteristics	**Hazard Ratios (95% CI)**	***P***	**Hazard Ratios (95% CI)**	***P***
Age				
<60				
≥60	0.35 (0.20–0.61)	<0.001	0.46 (0.26–0.82)	0.008
Sex (%)				
F				
M	1.57 (0.99–2.50)	0.054		
Race				
White				
Black	1.30 (0.74–2.26)	0.360		
Other	0.64 (0.33–1.23)	0.183		
Alcohol dependence				
No				
Yes	2.05 (1.25–3.38)	0.005	1.29 (0.76–2.20)	0.300
Tobacco dependence				
No				
Yes	0.98 (0.60–1.61)	0.942		
HLP (%)				
No				
Yes	0.60 (0.35–1.02)	0.060		
Biliary pancreatitis				
No				
Yes	0.26 (0.12–0.53)	<0.001	0.33 (0.15–0.69)	0.004
Diabetes				
No				
Yes	1.42 (0.88–2.30)	0.150		
Obesity				
No				
Yes	1.03 (0.45–2.37)	0.950		
ICU admission				
No				
Yes	1.43 (0.75–2.71)	0.274		
Length of stay (day)				
≤7				
>7	1.51 (0.90–2.54)	0.122		
Interval (day)				
≤11				
>11	2.62 (1.06–6.50)	0.037	2.81 (1.12–7.03)	0.027
HCT * (%)				
40–52				
<40	1.27 (0.67–2.41)	0.459		
TBIL * (mg/dL)				
0–1.5				
>1.5	0.61 (0.28–1.34)	0.219		
Lipase (IU/L)				
0–540				
>540	0.49 (0.25–0.96)	0.037	0.54 (0.27–1.06)	0.072
Platelet (K/uL)				
150–440				
<150	0.64 (0.29–1.40)	0.264	0.57 (0.25–1.27)	0.200
>440	1.89 (1.01–3.53)	0.045	1.53 (0.81–2.89)	0.200

(Continued on next page)

TABLE 2. *(Continued)*

Characteristics	Univariable Hazard Ratios (95% CI)	*P*	Multivariable Hazard Ratios (95% CI)	*P*
Alb * (g/dL)				
3.5–5.2				
<3.5	1.24 (0.78–1.97)	0.365		
Bicarbonate (mEq/L)				
22–27				
<22	1.00 (0.53–1.89)	0.991		
>27	1.19 (0.69–2.03)	0.533		
BUN * (mg/dL)				
≤20				
>20	0.78 (0.41–1.49)	0.457		
AST * (IU/L)				
0–40				
>40	0.79 (0.49–1.25)	0.312		
ALP * (IU/L)				
< =130				
>130	0.62 (0.35–1.11)	0.105		
Hb * (g/dL)				
≥12 M/11 F				
<12 M/11 F	1.08 (0.69–1.69)	0.746		
WBC * (K/uL)				
4–11				
<4	2.00 (0.79–5.07)	0.142		
>11	1.38 (0.85–2.24)	0.187		

greater the risk of the CP event. The media score of all patients was 324 (IQR: 78).

Nomogram Validation

The C-index value was 0.717 (95% CI: 0.691–0.743) for the training cohort and 0.718 (95% CI: 0.662–0.774) for the validation cohort. The calibration curves of the nomogram show high consistencies between the predicted and observed CP event probability in both the training and validation cohorts (Fig. 2). ROC analysis illustrates that the prediction model of 3-year, 5-year, and 10-year non-CP are effective (Fig. 3) (95 CIs of AUC provided in Supplementary Information Table S6, http://links.lww.com/MPA/B277). The time-dependent AUC was >0.7 for the prediction of non-CP within 10 years in both the training and validation cohorts, indicating the satisfactory discriminative ability of the nomogram (Fig. 3).

The cutoff values of the total scores obtained from the nomogram were 298 and 343 for all patients (Supplementary Information Fig. S1, http://links.lww.com/MPA/B279). We compared these 3 levels of risk using the Kaplan-Meier method, indicating great discrimination among the 3 risk groups (Fig. 4).

DISCUSSION

CP is a progressive inflammatory disease of the pancreas that affects patients' quality of life and greatly increases society's public medical burden. The global incidence and mortality of CP were 9.62/100,000 and 0.09/100,000, respectively.[18] The disease continuum of AP-RAP-CP pancreatitis is well known. RAP is an independent risk factor for CP.[19] The global transition rate from the first episode of AP to a recurrent episode is 10%–20%, and the rate from RAP to CP is ~35%.[4,20] In a study with 8 years of follow-up, more than 64% of patients with CP had preceding RAP.[11] Among the causes of CP, the risk of RAP is even higher than that of smoking and drinking.[21] Several hypotheses regarding the relationship between AP, RAP, and CP exist. The "Sentinel Acute Pancreatitis Event (SAPE)" hypothesis was highly accepted.[22] The SAPE hypothesis is that an episode of AP alters the pancreas to make it hypersensitive to RAP and drives CP after the sentinel AP event. Another hypothesis of CP pathogenesis posits that RAP causes progressive inflammatory damage, micronecrosis, and fibrosis (necrosis-fibrosis sequence).[23] However, there is no consensus on the underlying mechanism of disease progression in pancreatitis from AP to CP.

Several findings were observed in our retrospective study based on the MIMIC database. The incidence rates of CP were 21.53% in a total of 432 RAP patients, and the median follow-up time was 152 (IQR: 336) days among patients who developed CP, which is similar to the previous study. In our study, 6 variables were enrolled to establish a nomogram, which were age, biliary pancreatitis, alcohol dependence, interval (the interval of time between the first and the second episode of AP), platelet count, and lipase level. Age, biliary pancreatitis, and interval were independent risk factors among these variables. The nomogram was built in the training cohort and validated in the validation cohort. The ROC and time-dependent AUC results showed the satisfactory discriminative ability of the nomogram.

Previous study showed that young age, smoking, and alcohol use are reported as risk factors in patients with RAP who progress to CP,[11] which is different from our present study. Many studies have found alcohol use and smoking to be the most significant risk factors for developing CP in patients with AP or RAP.[4,19,21]

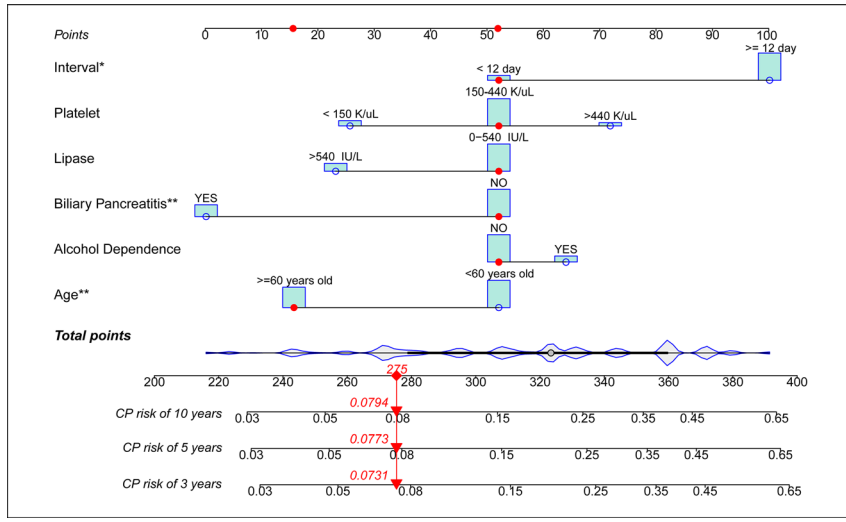

FIGURE 1. A constructed nomogram for chronic pancreatitis prediction. The density plot of total points shows their distribution. For category variables, their distributions are reflected by the size of the box. The importance of each variable was ranked according to the standard deviation along nomogram scales. *: $P < 0.05$, **: $P < 0.01$.

For the first episode of AP, progression was associated independently with alcoholic etiology, smoking, and a history of pancreatic necrosis. Smoking is the predominant risk factor for recurrent disease, whereas the combination of alcohol abuse and smoking produces the highest cumulative risk for CP.[19,24] A study on RAP and CP occurred in one-fifth of patients and found that both RAP and CP were related to alcoholic AP, while RAP was associated with smoking and the male sex.[12] In our study, age and alcohol dependence were consistent with previous studies. However, we did not include tobacco dependence in the model because it was not statistically significant in the univariate analysis. In our study, we did not separate past smokers from nonsmokers. Additionally, because we extracted tobacco dependence information from diagnoses, there is a possibility of underestimating the number of smokers due to potential biases introduced by human judgment. The tobacco dependence at admission is only used as a reference indicator for constructing the predictive model, and further research is needed.

The significant protective effect of biliary etiology in CP events may be because it can be relieved by surgery or manipulation.[14,19] Gallstone is the leading risk factor for AP.[25,26] Early cholecystectomy may play an essential protective role in this progression. It effectively reduces AP mortality and prevents recurrent episodes of biliary AP.[27–29] The recurrence rate was significantly lower after cholecystectomy than after conservative management.[30] Cholecystectomy resulted in fewer subsequent hospitalizations for AP and CP as compared with noncholecystectomy.[31] Consistent with the previous study, our result indicated that patients with nonbiliary RAP are prone to develop CP, suggesting a disease continuum from AP to RAP to CP. Moreover, the guideline suggests that early cholecystectomy for patients with acute biliary pancreatitis will be more beneficial.[32] Synthesis of the above conclusions, the patients with biliary obstruction should be relieved as soon as possible to avoid the occurrence of RAP and CP.

Based on the univariate results, platelet count was included in our model. In our study, the increase in platelet count increased the

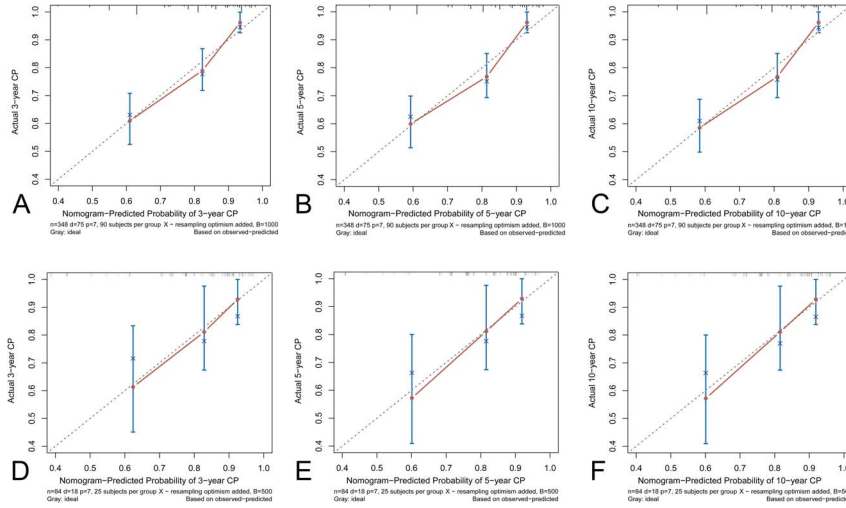

FIGURE 2. The calibration plots show the agreement between the predicted and actual chronic pancreatitis event and 95% CIs. A–C, Calibration plots of the training cohort. D–F, Calibration plots of the validation cohort.

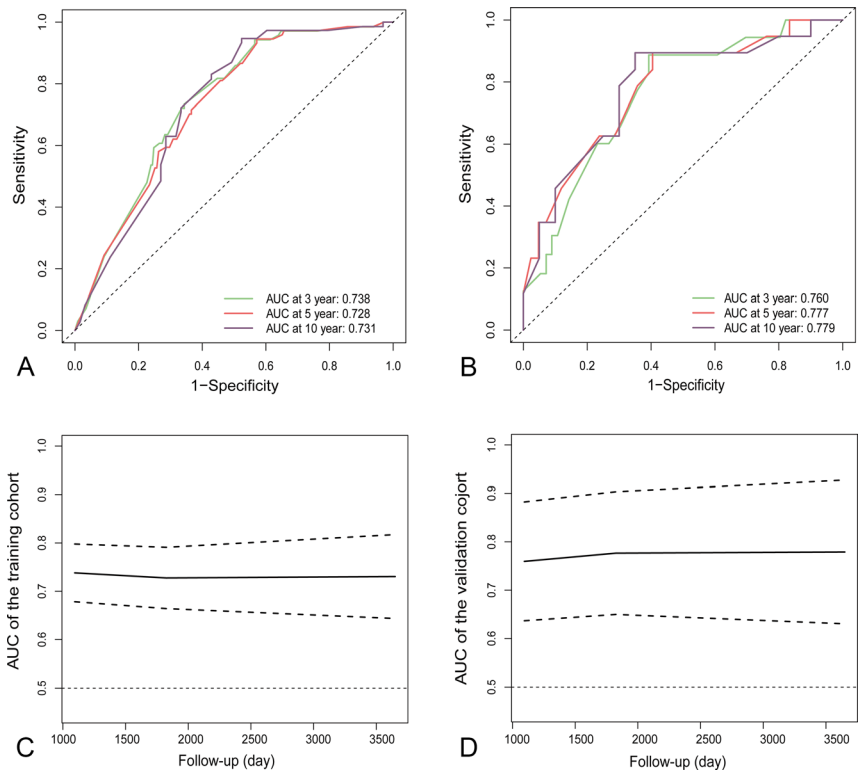

FIGURE 3. Receiver operating characteristic curves and time-dependent area under the time-dependent receiver operating characteristic curves of the training and validation cohorts. A–B, The training and validation cohorts' 3-year, 5-year, and 10-year receiver operating characteristic curves. C–D, Time-dependent area under the time-dependent receiver operating characteristic curves of using the nomogram to predict chronic pancreatitis probability within 10 years in the training and validation cohorts.

possibility of CP. Previous studies have used platelet count to construct a prognostic scoring model for CP.[33] Studies have shown a relationship between pancreatitis and extrahepatic portal venous system thrombosis in 35% of patients with acute/chronic alcoholic pancreatitis.[34] Splanchnic venous thrombosis is a kind of vascular complication of CP.[35,36] While platelets are widely recognized for their role in thrombosis, there is a growing acceptance of platelets as immune cells that also play a significant role in inflammation.[37] Although the involvement of platelets in chronic inflammation has been extensively documented,[33,38] no studies have been found specifically addressing their role in CP. Although platelet counts are not explicitly mentioned, earlier researches have highlighted

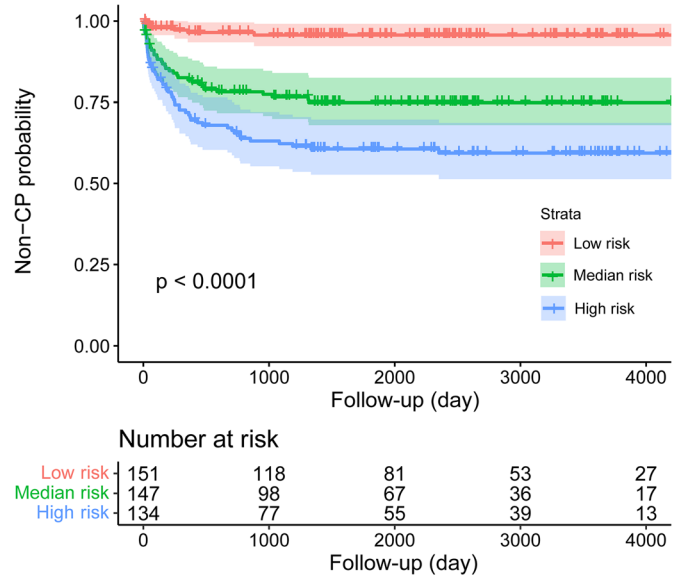

FIGURE 4. Kaplan-Meier analysis between different chronic pancreatitis risk stratification according to the total scores predicting patients with recurrent acute pancreatitis. Non-CP, nonchronic pancreatitis event.

the significant role of platelet-activating factors (PAF) in both acute AP and CP. Researchers investigated the role of PAF in AP by analyzing the levels of endogenous PAF in pancreatic tissue and evaluating the protective effects of TCV-309, a specific blocker of PAF, in rats with cerulein-induced pancreatitis.[39] During the chronic phase of obstructive pancreatitis induced by duct ligation, the levels of pancreatic PAF significantly increase.[40] Furthermore, recent research findings have revealed the unexpected role of platelets in the regulation of insulin secretion and glucose metabolism.[41] Further studies are needed to confirm the mechanism of platelet count in the progression of CP.

The function of pancreatic lipase is the hydrolysis of dietary triacylglycerols into diacylglycerols and then free fatty acids.[42] Lipase elevation more than 3 times the upper limit of normal is included in the diagnosis of AP.[43] Serum lipase appears more specific and remains elevated longer than amylase after disease presentation.[44] However, it is not only the pancreas that can secrete lipase. Elevated lipase levels may also be associated with other diseases, such as cholecystitis or biliary obstruction.[43,44] Combined with the relationship between biliary cause and the risk of CP, there may be a connection between biliary cause, lipase level, and the CP event. In our study, the higher the lipase level, the greater the probability of CP. Interestingly, studies report that low serum pancreatic lipase level is related to CP diagnosis.[45,46] Although this study found that lipase levels were associated with CP in patients with RAP, the mechanism is unclear.

There were certain limitations in our study that might impact the generalizability of the findings. These limitations include the absence of data on autoimmune pancreatitis, the small number of patients with idiopathic AP, and the exclusion of genetic factors from the analysis. It is important to consider these limitations when interpreting the results and extending the findings to broader populations. Because no diagnosis related to autoimmune pancreatitis was retrieved in the MIMIC database, we did not enroll in the autoimmune etiology. Because of the small number of patients diagnosed with idiopathic AP, studies on idiopathic AP were not included. Besides, we did not include genetic factors in the analysis of the unavailability of genetic data. Not many patients completed genetic testing at the time of initial AP or RAP. For information on available etiology or risk factors, we also searched for both hospital admissions, although only the second admission was presented in the text results section. The causes of initial and recurrent pancreatitis are described in Supplementary Information Table S7, http://links.lww.com/MPA/B278. We did not separate past smokers from nonsmokers in our study. The further research is needed to determine the role of smoking in the progression from RAP to CP. In our study, the etiology of the disease was extracted based on diagnoses identified by the ICD codes in the database. The number of people who smoke and drink alcohol may be underestimated. Scores related to the severity of pancreatitis were not included because the results of some laboratory tests were insufficient.

In conclusion, we developed a novel nomogram to help clinicians identify CP risk in RAP patients at the second episode of AP and divide patients into high-risk, median-risk, and low-risk groups. The diagnosis of RAP should be paid attention to in clinical practice. Our study may help to identify the risk of CP early and provide insights into the mechanistic studies of CP.

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