Risk factor for diabetes mellitus in pediatric chronic pancreatitis patients

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Abstract

Pediatric patients suffer from chronic pancreatitis (CP), especially with those diabetes mellitus (DM). This study aimed to identify the incidence of and risk factors for DM in pediatric CP.

CP patients admitted to our center from January 2000 to December 2013 were assigned to the pediatric (<18 years old) and adult group according to their age at onset of CP. Cumulative rates of DM and risk factors for both groups were calculated and identified. The median follow-up duration for the whole cohort was 7.6 years. In these 2153 patients, 13.5% of them were pediatric. The mean age at the onset and the diagnosis of CP in pediatric were 11.622 and 19.727, respectively. DM was detected in 13.1% patients and 31.0% patients in the pediatric group and adult group, respectively. Age at the onset of CP, smoking history, body mass index (BMI), and etiology of CP were identified risk factors for DM in pediatric.

DM was detected in 13.1% pediatric patients. Age at the onset of CP, smoking history, BMI, and etiology of CP were identified risk factors for the development of DM in pediatric CP patients. The high-risk populations were suggested to be monitored frequently. They could also benefit from a lifestyle modification.

Abbreviations: AIP = autoimmune pancreatitis, BMI = body mass index, CI = confidence interval, CP = chronic pancreatitis, DM = diabetes mellitus, GP = groove pancreatitis, HR = hazard ratio.

Keywords: chronic pancreatitis, diabetes mellitus, pediatric, risk factor

1. Introduction

Chronic pancreatitis (CP) in adolescent patient is an ongoing inflammatory disorder characterized by the irreversible destruction of the pancreatic parenchyma.\textsuperscript{[1,2]} Inflammation and fibrosis lead to a decrease in beta cells and insulin resistance which contribute to diabetes mellitus (DM).\textsuperscript{[2,3]} DM is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. DM occurring secondary to CP in adolescents is a rare disease which is recognized as pancreatogenic diabetes (type 3c diabetes) in adolescents.\textsuperscript{[4,5]}

Type 3c DM in CP patients involves a deficit of insulin, which associated with development of cardiovascular disease, end-stage kidney disease, retinopathy leading to blindness and limb amputations.\textsuperscript{[5]} As for adolescents, the development and progression of clinical complications might be especially rapid, and long duration of diabetes present delay in growth and delayed onset of puberty.\textsuperscript{[5]} Some children with DM even have neuropsychiatric disease, including depression, schizophrenia, bipolar disorder, autism, mental retardation, attention-deficit hyperactivity disorder, obsessive-compulsive disorders, and...
behavior disorder. Thus, type 3c DM in adolescents affects long-term quality of life for adolescent patients with CP, which is a big challenge for us to control. In this sense, much more attention should be paid urgently for type 3c DM in adolescent patients nowadays.

Identification of CP patients in adolescents at high risk of developing type 3c DM contributes to early detection of DM. This may decreasing type 3c DM-associated complications, and increasing quality of life for adolescent CP patients in the long term. The identification of risk factors may be conducive to risk stratification of adolescent CP patients; therefore, help reduce detriment caused by type 3c DM. To our best knowledge, there is no pediatric study about risk factors for DM in CP patients. Thus, we aimed to determine the incidence of DM, and identified the risk factors for this complication in pediatric and adult CP patients respectively, based on a retrospective-prospective cohort of 2153 CP patients with a long duration of follow-up after the onset of CP.

2. Materials and methods

2.1. Patients and database

Since the 1990s, an electronic medical record system (GOOD-WILL Inc., Beijing, China) has been used in the Changhai Hospital (Shanghai, China) and has facilitated several studies on CP. To track changes consistently throughout the course of CP and facilitate the evaluation and the study of this disease, a dedicated database, the Changhai CP Database (version number 2.1, YINMA Information Technology Inc., Shanghai, China), was established in 2005 to collect the clinical data of CP patients who were admitted to the Changhai Hospital. Data from January 2000 to December 2004 were retrospectively collected according to the electronic medical record system and were complemented through telephone, letter, and e-mail inquiries. Data were prospectively collected since January 2005. The following information was documented in detail: demographic data (age, sex, birthplace, etc), the course of CP, medical history, history of other diseases, smoking and alcohol history, family history of pancreatic diseases and DM, laboratory and imaging findings, and treatment strategy.

The database system was set to remind the investigators to call patients for clinical check-ups. In addition to clinic visits due to complaints of discomfort related to CP, all patients were periodically (at least annually) called for clinical check-ups and investigations. Transabdominal ultrasound, magnetic resonance imaging, or computed tomography was selected as the evaluation modality during each follow-up visit. Evaluations of each revisit or of telephone inquiries for patients who did not return to the Changhai Hospital were added to the CP database. In December 2013, we contacted all the patients in our database for a final evaluation, except those who were lost to follow-up or had died. The duration of follow-up was defined as the duration from the onset of CP to the date of the last personal contact, death, or the end of follow-up (December 2013), whichever came first (Fig. 1).

The exclusion criteria were as follows: pancreatic cancer diagnosed within 2 years after the diagnosis of CP, groove pancreatitis (GP), and autoimmune pancreatitis (AIP). Patients were assigned into pediatric group (onset before 18 years
of age) and adult group (onset after 18 years of age). In the risk factor analysis for DM in both groups, patients who have family history of insulin-dependent DM and had DM at/before CP diagnosis were also excluded, respectively.

The study was approved by the Ethics Committee of Changhai Hospital. Written informed consent was obtained from all participating patients. All of the diagnostic and therapeutic modalities were carried out in accordance with the approved guidelines.

### 2.2. Definitions

The diagnosis of CP was established according to the Asia-Pacific consensus.[21] Onset of CP was considered when the first manifestation related to CP occurred. Such as recurrent pancreatic pain, chronic pancreatic pain, acute pancreatitis attack, DM, steatorrhea, or asymptomatic patients diagnosed of CP in the course of physical examinations. Alcoholic CP was considered when alcohol intake exceeded 80 g/d for males or 60 g/d for females for at least 2 years in the absence of other causes.[22] Hereditary CP refers to 2 first-degree relatives or ≥3 second-degree relatives, in ≥2 generations with recurrent acute pancreatitis and/or CP, for which there were no precipitating factors.[23] Although it remains a controversy whether abnormal anatomy of pancreatic duct (including pancreas divisum and anomalous pancreatico-biliary junction) is a cause of CP, we defined it as an etiology.[24] Patients were defined as having post-traumatic CP when there was a history of abdominal trauma with imaging evidence of pancreatic injury and subsequent ductal dilation. Hyperlipidemia is considered as an etiology when blood triglyceride is >1000 mg/dL.[25] Patients with CP were considered idiopathic when none of the above causes were found.

DM was diagnosed according to the criteria of the American Diabetes Association.[26] Plasma C-peptide was tested to identify type 1 DM. In cases of DM diagnosed within 2 years before the symptomatic onset of CP, DM was considered as the initial manifestation of painless CP, and the corresponding time of DM diagnosis was considered as that of the onset of CP.[27]

### 2.3. Treatment strategy

Endoscopic treatment was the principle method of therapy, including extracorporeal shockwave lithotripsy/endoscopic retrograde cholangiopancreatography for stone removal and main pancreatic duct drainage.[12,28–31] Surgical treatment, such as pancreaticoduodenectomy, distal pancreatectomy, was considered when endoscopic treatment was ineffective, especially in CP patients with pancreatic pseudocysts or pseudoaneurysms.[32] For CP patients who did not experience pain, interventions were performed only when complications such as biliary stricture, infection, or pancreatic pseudocyst enlargement occurred.[33] DM and/or steatorrhea were not indications for invasive treatment of CP.

### 2.4. Statistical analysis

The continuous variables are expressed as the mean ± standard deviation and were compared using an unpaired, 2-tailed t test. The categorical variables were compared using the χ² test or the Fisher exact test. The cumulative rates of DM in pediatric and adults after the onset of CP were calculated using the Kaplan–Meier method.[34]

Patients who had type 1 DM and DM at/before the diagnosis of CP were excluded. CP patients who onset before 18 years of age were assigned into the pediatric group and after 18 years of age were assigned into adult group. The significance of each variable was assessed by a multivariate Cox regression analysis using SPSS (version 21.0) to investigate the independent risk factors for DM development after a diagnosis of CP in both groups.

## 3. Results

### 3.1. General characteristics of the subjects

As shown in Figure 1, from January 2000 to December 2013, a total of 2,287 CP patients were entered into the Changhai CP Database. After the exclusion of 134 patients, including 10 patients diagnosed with GP, 108 patients diagnosed with AIP, and 16 patients diagnosed with pancreatic cancer within 2 years after the diagnosis of CP, a cohort of 2153 patients with CP was established. The median duration of follow-up was 7.6 years (range 0.0–52.7 years).

The general characteristics of the pediatric patients with CP are presented in Table 1. The mean age at the onset and the diagnosis of CP were 11.622 and 19.727, respectively. For pediatric CP patients, age at the diagnosis of CP, smoking history, steatorrhea, type of pain and treatment were significantly different between DM and without DM patients in pediatric of CP (all \( P < .05 \)). The alcohol consumption, etiology, and biliary stricture were also significantly different between the 2 groups (all \( P < .001 \)).

### 3.2. Cumulative rates of DM

DM was found in 28.6% (616/2153) of patients after the onset of CP. The proportions were 13.1% (38/291) in pediatric patients and 31.0% (578/1862) in adult patients. The cumulative proportions of DM in pediatric patients were 2.1% (95% confidence interval [CI], 1.3%–2.9%), 2.7% (95% CI, 1.6%–3.8%), and 5.2% (95% CI, 3.6%–6.8) at 3, 5, and 10 years after the diagnosis of CP, respectively. The cumulative proportions of DM in adult patients were 17.0% (95% CI, 16.1%–17.9%), 19.8% (95% CI, 18.8%–20.8%), and 25.1% (95% CI, 23.9%–26.3%) at 3, 5, and 10 years after the diagnosis of CP, respectively. Pediatric and adult patients showed significant difference in the rate of DM (\( P < .001 \); Fig. 2).

### 3.3. Predictors for DM development in pediatric patients

After the exclusion of 134 patients with type 1 DM and 324 patients diagnosed with DM before/at the diagnosis of CP, a total of 1695 patients with CP were finally enrolled in the present study. Patients were assigned into the pediatric group (n=237) and the adult group (n=1,458) according to their age at onset of CP. A univariate analysis for DM development among the 237 pediatric patients included in the study is shown in Table 2. Four variables showed a \( P \)-value of less than .15: age at the onset of CP, smoking history, body mass index (BMI) at the diagnosis of CP, and etiology.

For the multivariate analysis, the 4 predictors above were included in the Cox proportional hazards regression model. Finally, 4 predictors for DM development in pediatric patients were identified. The risk of developing DM was significantly higher in pediatric patients with younger age at the onset of CP (hazard ratio [HR], 0.962, 95% CI, 0.706–1.312), smoking...
| Items                              | Pediatrics (n = 291) | With DM (n = 38) | Without DM (n = 253) | P-value |
|-----------------------------------|----------------------|------------------|----------------------|---------|
|                                   | n (%)                | n (%)            | n (%)                |         |
| Male sex                          | 143 (49.1%)          | 20 (52.6%)       | 123 (48.6%)          | .644    |
| Age at the onset of CP, yr*       | 11.62±4.652          | 11.96±4.786      | 11.57±4.639          | .640    |
| Age at the diagnosis of CP, yr**  | 19.72±8.953          | 27.88±15.485     | 18.50±6.746          | .001    |
| Smoking history                   | 16 (5.5%)            | 6 (15.8%)        | 10 (4.0%)            | .003    |
| Alcohol consumption 0 g/d         | 272 (93.5%)          | 29 (76.3%)       | 243 (96.0%)          | <.001   |
| Alcohol consumption 0–20 g/d      | 8 (2.7%)             | 5 (13.2%)        | 3 (1.2%)             |         |
| Alcohol consumption 20–80 g/d     | 8 (2.7%)             | 2 (5.3%)         | 6 (2.4%)             |         |
| Alcohol consumption >80 g/d       | 3 (1.0%)             | 2 (5.3%)         | 1 (0.4%)             |         |
| Body mass index*                  | 19.38±3.362          | 20.43±3.573      | 19.22±3.312          | .058    |
| Etiology                          |                      |                  |                      | <0.001  |
| ICP                               | 248 (85.2%)          | 25 (65.8%)       | 223 (88.1%)          |         |
| Abnormal anatomy of pancreatic duct | 24 (8.2%)          | 6 (15.8%)        | 18 (7.1%)            |         |
| HCP                               | 12 (4.1%)            | 3 (7.9%)         | 9 (3.6%)             |         |
| Post-traumatic CP                 | 3 (1.0%)             | 0 (0.0%)         | 3 (1.2%)             |         |
| Hyperlipidemic CP                 | 2 (0.7%)             | 2 (5.3%)         | 0 (0.0%)             |         |
| Initial manifestations            |                      |                  |                      | .162    |
| Abdominal pain                    | 280 (96.2%)          | 35 (92.1%)       | 245 (96.8%)          |         |
| Endocrine/exocrine dysfunction    | 9 (3.1%)             | 3 (7.9%)         | 6 (2.4%)             |         |
| Others                            | 2 (0.7%)             | 0 (0.0%)         | 2 (0.8%)             |         |
| Pancreatic stones†                | 269 (92.4%)          | 37 (97.4%)       | 232 (92.7%)          | <.001   |
| Age at pancreatic stones diagnosis* | 20.44±8.547       | 29.45±11.587     | 19.00±6.982          | <.001   |
| Time between onset and pancreatic stone* | 8.82±6.174 | 17.28±13.242     | 7.48±7.552           | <.001   |
| DM                                |                      |                  |                      |         |
| Age at DM diagnosis†              | 28.57±11.965         | 28.57±11.965     | –                    |         |
| Time between onset and DM†        | 16.61±13.447         | 16.61±13.447     | –                    |         |
| Steatorrhea                       | 46 (15.8%)           | 12 (31.6%)       | 34 (13.4%)           | .004    |
| Age at steatorrhea diagnosis†     | 25.89±9.358          | 33.31±10.774     | 23.25±7.315          | .009    |
| Time between onset and steatorrhea† | 13.92±10.562     | 22.08±10.867     | 11.07±5.971          | .001    |
| Pancreatic pseudocyst             | 30 (10.3%)           | 2 (5.3%)         | 28 (11.1%)           | .273    |
| Age at pancreatic pseudocyst diagnosis† | 16.23±7.210 | 25.87±2.286      | 15.49±6.922          | .047    |
| Time between onset and pancreatic pseudocyst† | 5.60±5.828 | 12.59±3.412      | 5.10±5.660           | .079    |
| Bilary stricture                  | 19 (6.5%)            | 9 (23.7%)        | 10 (4.0%)            | <.001   |
| Age at biliary stricture diagnosis† | 31.54±13.686    | 42.63±11.197     | 21.57±5.459          | <.001   |
| Time between onset and biliary stricture† | 21.19±17.565 | 33.78±14.944     | 9.86±10.843          | .001    |
| Pancreatic cancer                 | 1 (0.3%)             | 0 (0.0%)         | 1 (0.4%)             | .698    |
| Death                             | 2 (0.7%)             | 0 (0.0%)         | 2 (0.8%)             |         |
| Morphology of MPD                 |                      |                  |                      | .437    |
| Pancreatic stone alone            | 95 (32.6%)           | 15 (39.5%)       | 80 (31.6%)           |         |
| MPD stenosis alone                | 57 (19.6%)           | 4 (10.5%)        | 53 (20.9%)           |         |
| MPD stenosis and stone            | 128 (44.0%)          | 17 (44.7%)       | 111 (43.9%)          |         |
| Complex pathologic changes        | 11 (3.8%)            | 2 (5.3%)         | 9 (3.6%)             |         |
| Type of pain                      |                      |                  |                      | .013    |
| Recurrent acute pancreatitis      | 102 (35.1%)          | 9 (23.7%)        | 93 (37.3%)           |         |
| Recurrent pain                    | 65 (22.3%)           | 14 (36.3%)       | 51 (20.2%)           |         |
| Recurrent acute pancreatitis and pain | 106 (36.4%)       | 13 (34.2%)       | 93 (36.8%)           |         |
| Chronic pain                      | 14 (4.8%)            | 0 (0.0%)         | 14 (5.5%)            |         |
| Without pain                      | 4 (1.4%)             | 2 (5.3%)         | 2 (0.8%)             |         |
| Severe acute pancreatitis         | 7 (2.4%)             | 0 (0.0%)         | 7 (2.8%)             | .299    |
| Pancreatic duct successful drainage† | 255 (87.6%)   | 38 (100.0%)      | 217 (85.8%)          | .013    |
| Overall treatment                 |                      |                  |                      | .002    |
| Endotherapy alone                 | 247 (84.9%)          | 27 (71.1%)       | 220 (87.3%)          |         |
| Surgery alone                     | 10 (3.4%)            | 3 (7.9%)         | 7 (2.8%)             |         |
| Both endotherapy and surgery      | 20 (6.9%)            | 2 (5.3%)         | 18 (7.1%)            |         |
| Conservative treatment            | 14 (4.6%)            | 6 (15.6%)        | 8 (3.2%)             |         |
| DM in first-/second-/third-degree relatives | 38 (13.1%)       | 6 (15.8%)        | 32 (12.8%)           | .592    |
| Pancreatic diseases in first-/second-/third-degree relatives (excluding hereditary CP) | 15 (5.2%) | 3 (7.9%) | 12 (4.7%) | .413 |

ACP = alcoholic chronic pancreatitis, CP = chronic pancreatitis, DM = diabetes mellitus, HCP = hereditary chronic pancreatitis, ICP = idiopathic chronic pancreatitis, MPD = main pancreatic duct.

† Pancreatic calcifications were also regarded as stones that are located in branch pancreatic duct or ductulus.
‡ Patients with successful main pancreatic duct (MPD) drainage are those whose CP was established after ERCP or pancreatic surgery or those who underwent successful MPD drainage during administration when CP diagnosis was established.

* Mean ± SD.

< Xie et al. Medicine (2019) 98:48
history (HR, 5.030, 95% CI, 0.229–110.610), higher BMI (HR, 1.195, 95% CI, 0.811–1.761). Etiology of CP was also identified risk factor for DM development in pediatric CP patients.

3.4. Predictors for DM development in adult patients

A univariate analysis for DM development among the 1458 adult patients included in the study is shown in Table 3. Six variables showed a P-value of less than 0.05: gender, age at the onset of CP, alcohol consumption, biliary stricture, morphology of main pancreatic duct, and type of pain.

For the multivariate analysis, the 6 predictors above were included in the Cox proportional hazards regression model. Finally, 5 predictors for DM development in adult patients were identified. The risk of developing DM was significantly higher in male patients (HR, 1.437, 95% CI, 0.994–2.076) and patients with a history of biliary stricture before the diagnosis of CP (HR, 2.025, 95% CI, 1.345–3.051). Adult patients with an older age at the onset of CP (HR, 1.019, 95% CI, 1.009–1.029) were associated with decreased risk of developing DM. Type of pain was also identified risk factor for DM development in adult patients.

4. Discussion

We focused on CP in pediatrics in the present study. As far as we know, this is the first study to analyze the risk factors for DM in pediatric CP patients. In this study, 13.1% (38/291) of pediatric patients with CP developed DM, and 31.0% (578/1862) of adult patients developed DM. A previous study showed that exocrine and endocrine insufficiency developed more slowly in early-onset CP than that in late-onset CP. This could be due to a better preservation of pancreatic function and better repair capacity after injury in pediatric CP patients. However, after a long term of follow-up for more than 40 years, the cumulative rate of DM in pediatrics was similar or even higher than in adults (Fig. 2). Therefore, pediatric CP patients had a reduced risk of DM compared to adults in the early period of CP course, but the risk increased with the prolongation of follow-up.

In the risk factor analysis, age at the onset of CP, smoking history, BMI, and etiology were identified significantly associated with DM development in pediatric CP patients. This is not exactly the same as risk factors in adult patients. In adult CP patients, genders, age at the onset of CP, biliary stricture before the diagnosis of CP, and type of pain were identified risk factors for DM development. In the previous study, risk factors for DM development in the general population are similar with the adult group in the present study. Experimental results revealed that smoking might lead to insulin resistance in peripheral tissues, and elevated level of catecholamines due to smoking might also cause insulin resistance in pediatric patients. Higher BMI was associated with increased insulin resistance and decreased insulin sensitivity, which may be the most important pathogenic factor for DM. It is approved moderate BMI reduction could prevent one-third of DM.

The risk factor analysis of DM may be helpful for the early diagnosis of DM in pediatric CP patients. A degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before diabetes is detected. Pediatric CP patients with DM suffer from long-term damage, dysfunction, and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Also, the long duration of diabetes in pediatrics present delay in stature and weight, as well as delayed onset of puberty. This may cause incredible suffering for the children and families who live with them. This study provided a relatively accurate risk factor analysis. The pediatric patients with high risk were suggested to be closely monitored.

These high-risk populations in pediatric CP patients may benefit from a more frequent DM monitoring and lifestyle modification. According to the present study, the screening interval for DM should be further individualized with consideration of the risk of DM. The most recent consensus statement released at PancreasFest 2012 recommended an annual screening for DM in patients with CP. That pediatric patients with higher risk of DM should be screened more frequently. Also, the identification of modifiable risk factors provides evidence for guiding clinical practice and patient education. As smoking history and BMI were identified risk factors for DM in pediatric CP patients, they may benefit from lifestyle modifications such as smoking cessation and weight reduction.

Our study has some limitations. First, our study failed to distinguish DM secondary to CP (type 3c DM) from type 2 DM. We had made efforts to exclude patients with type 1 DM. In fact, in most cases of DM occurring in patients with CP, the diagnosis is type 3c. Second, the retrospectively acquired data collected between 2000 and 2004 may introduce a recall bias. Nevertheless, the statistical analysis showed that there were no significant differences between the clinical characteristics of the patients admitted before and after January 2005. In this sense, the recall bias minimally influenced the results of the study. Third, the risk factor analysis did not include all potential factors related to the development of pancreatic cancer. Fourth, 603 CP patients were followed up for less than 2 years after the diagnosis of CP; among these patients, several pancreatic cancer patients may have been misdiagnosed as CP.
In conclusion, DM was detected in 13.1% pediatric patients, which is extremely harmful for children. Age at the onset of CP, smoking history, BMI, and etiology of CP were identified risk factors for the development of DM in pediatric CP patients. Therefore, pediatric patients in these high-risk populations were suggested to be followed and inspected closely. They may also benefit from a lifestyle modification.

**Author contributions**

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Table 3
Predictive factors for DM development in adult CP patients after the diagnosis of CP (1458 cases).

| Predictors                              | n (%) | Univariate Analysis | Multivariate Analysis |
|-----------------------------------------|-------|---------------------|-----------------------|
|                                         |       | P                   | HR (95% CI)           | P                   | HR (95% CI)           |
| Male sex                                | 1045  | 0.02                | 1.679 (1.218–2.134)   | 0.054               | 1.437 (0.994–2.076)   |
| Age at the onset of CP, yr              | 42.47±14.001 | <.001                | 1.020 (1.010–1.029)   | <.001               | 1.019 (1.009–1.029)   |
| Age at the diagnosis of CP, yr          | 46.19±13.136 | .766               | 0.988 (0.881–1.099)   |                    |                      |
| Smoking history                         | 518   | .694                | 0.947 (0.722–1.242)   |                    |                      |
| Alcohol consumption                     |       | 0.18                | Control               | 0.021               | Control               |
| 0 g/d                                   | 937   | (64.3%)             | Control               |                     |                      |
| 0–20 g/d                                | 44    | (3.0%)              | 1.979 (1.006–3.895)   | .024               | 2.225 (1.110–4.458)   |
| 20–80 g/d                               | 171   | (11.7%)             | 0.853 (0.551–1.321)   | .487               | 0.848 (0.533–1.349)   |
| >80 g/d                                 | 306   | (21.0%)             | 1.420 (1.058–1.906)   | .061               | 1.371 (0.986–1.906)   |
| Body mass index                         | 21.19±5.466 | .065               | 1.042 (0.997–1.089)   |                    |                      |
| Etiology                                |       | 0.68                | Control               |                     |                      |
| ICP                                     | 1107  | (75.9%)             | 1.429 (1.070–1.907)   |                    |                      |
| ACP                                     | 294   | (20.2%)             | 0.760 (0.503–1.159)   | .034               | 1.020 (0.987–1.054)   |
| Abnormal anatomy of pancreatic duct     | 28    | (1.9%)              | 0.366 (0.120–1.124)   | .061               | 1.020 (0.987–1.054)   |
| HCP                                     | 12    | (0.8%)              | 0.743 (0.508–1.084)   | .081               | 1.020 (0.987–1.054)   |
| Post-traumatic CP                       | 7     | (0.5%)              | 0.000 (0.000–1.096)   | .002               | 1.020 (0.987–1.054)   |
| Hypertrophic CP                         | 10    | (0.7%)              | 2.666 (0.802–8.484)   | .004               | 2.666 (0.802–8.484)   |
| Initial manifestations                  |       | .369                | Control               |                     |                      |
| Abdominal pain                          | 1277  | (87.6%)             | 1.565 (0.829–2.953)   |                    |                      |
| Endocrine/exocrine dysfunction          | 61    | (4.2%)              | 1.684 (0.700–3.051)   |                    |                      |
| Others                                  | 120   | (8.2%)              | Control               |                     |                      |
| Pancreatic stones                       | 1023  | (70.3%)             | 1.328 (0.986–1.788)   |                    |                      |
| Biliary stricture                       | 112   | (7.7%)              | 2.456 (1.671–3.609)   | .001               | 2.025 (1.345–3.051)   |
| Steatorrhoea                            | 173   | (11.9%)             | 1.068 (0.739–1.549)   | .686               | 1.068 (0.739–1.549)   |
| Pancreatic pseudocyst                   | 114   | (7.8%)              | 1.239 (0.774–1.983)   | .476               | 1.239 (0.774–1.983)   |
| Morphology of MPD                       |       | .005                | 0.89                  |                    |                      |
| Pancreatic stone alone                  | 360   | (24.7%)             | 0.698 (0.467–1.037)   | .623               | 0.698 (0.467–1.037)   |
| MPD stenosis alone                      | 471   | (32.3%)             | 0.641 (0.441–0.939)   | .766               | 0.641 (0.441–0.939)   |
| MPD stenosis and stone                  | 448   | (30.7%)             | 0.478 (0.318–0.718)   | .152               | 0.478 (0.318–0.718)   |
| Complex pathologic changes              | 179   | (12.3%)             | Control               |                     |                      |
| Type of pain                            |       | .014                | 0.13                  |                    |                      |
| Recurrent acute pancreatitis            | 431   | (29.6%)             | 0.694 (0.457–1.052)   | .403               | 0.694 (0.457–1.052)   |
| Recurrent pain                          | 403   | (27.6%)             | 0.755 (0.469–1.148)   | .537               | 0.755 (0.469–1.148)   |
| Recurrent acute pancreatitis and pain   | 367   | (25.2%)             | 0.521 (0.334–0.812)   | .071               | 0.521 (0.334–0.812)   |
| Chronic pain                            | 62    | (4.3%)              | 0.230 (0.070–0.753)   | .051               | 0.230 (0.070–0.753)   |
| Without pain                            | 195   | (13.4%)             | Control               |                     |                      |
| Severe acute pancreatitis               | 48    | (3.3%)              | 1.353 (0.738–2.480)   | .202               | 1.353 (0.738–2.480)   |
| Pancreatic duct successful drainage     | 210   | (14.4%)             | 1.160 (0.812–1.656)   | .476               | 1.160 (0.812–1.656)   |
| Treatment strategy                      |       | .320                | Control               |                     |                      |
| Endotherapy alone                      | 112   | (7.7%)              | 0.709 (0.404–1.243)   |                    |                      |
| Surgery alone                           | 87    | (6.0%)              | 1.421 (0.853–2.368)   |                    |                      |
| Both endotherapy and surgery            | 13    | (0.9%)              | 0.000 (0.000–3.670E128) | .001 | 0.000 (0.000–3.670E128) |
| Conservative treatment                  | 1246  | (85.5%)             | Control               |                     |                      |
| Pancreatic diseases in first-/second-/third-degree relatives (excluding hereditary CP) | 12   | (0.8%)              | 0.049 (0.00–46.355)   |                    |                      |

ACP = alcoholic chronic pancreatitis, CP = chronic pancreatitis, DM = diabetes mellitus, HCP = hereditary chronic pancreatitis, HR = hazard ratio, ICP = idiopathic chronic pancreatitis, MPD = main pancreatic duct.

*Mean±SD.
†Before or at the diagnosis of CP.
‡Pancreatic calcifications were also regarded as stones that are located in branch pancreatic duct or ductule.
§Patients with successful main pancreatic duct (MPD) drainage are those whose CP was established after ERCP or pancreatic surgery or those who underwent successful MPD drainage during administration when CP diagnosis was established.

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