Change of Both Endocrine and Exocrine Insufficiencies After Acute Pancreatitis in Non-Diabetic Patients

A Nationwide Population-Based Study

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Abstract: Acute pancreatitis (AP) is the most common pancreatic disease and consists of an acute inflammation of the pancreas. AP can contribute to endocrine and exocrine insufficiencies in survivors as a result of the key role of the pancreas in both glucose metabolism and nutritional digestion. The aim of this population-based study was to determine the endocrine or exocrine insufficiencies in patients after initial AP with biliary or alcohol-associated causes.

We conducted a nationwide cohort study using data from Taiwan’s National Health Insurance Research Database collected between 2001 and 2010. A total of 12,284 patients with AP were identified.

Alcohol-associated AP (odds ratio, 1.894; 95% CI, 1.520–2.268; P < 0.001) and ≥2 admissions for AP (odds ratio, 1.937; 95% CI, 1.483–2.391; P < 0.001) were significantly associated with newly diagnosed diabetes mellitus after AP. Further, only alcohol-associated AP (odds ratio, 1.215; 95% CI, 1.133–1.297; P < 0.001) was significantly associated with pancreatic exocrine insufficiency after AP. Additionally, alcohol-associated AP (odds ratio, 1.804; 95% CI, 1.345–2.263; P < 0.001) and ≥2 readmissions for AP (odds ratio, 3.190; 95% CI, 2.317–4.063; P < 0.001) were significantly associated with both exocrine and endocrine insufficiencies after AP.

Our data showed that alcohol-associated AP, rather than a biliary cause, contributed to a higher extent to exocrine or endocrine insufficiencies. Furthermore, recurrent AP also led to endocrine insufficiency.

Abbreviations: AP = acute pancreatitis, CIPD = Catastrophic Illnesses Patient Database, DM = diabetes mellitus, GI = gastrointestinal, ICD-9-CM = International Classification of Disease, Ninth Revision, Clinical Modification, ICU = intensive care unit, NHIRD = National Health Insurance Research Database, PEI = pancreatic exocrine insufficiency, PSCs = pancreatic stellate cells.

INTRODUCTION

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas and is considered the most common pancreatic disease.1 Gallstones and alcohol consumption are the most frequent etiologies of AP in adults.2,3 A previous longitudinal population-based study has addressed the incidence trends following the first attack of AP.4 The incidence of AP has been reported to be markedly increasing, probably due to the increase in the incidence of gallstone disease and obesity in the population.5,6 AP can contribute to a systemic inflammatory response syndrome with significant morbidity and mortality. Although the case-fatality rate of AP has decreased over the decades,4,7 AP can contribute to endocrine and exocrine insufficiencies1,8–10 in survivors as a result of the key role of the pancreas in both glucose metabolism and nutritional digestion.

Diabetes mellitus (DM) is one of the most common non-communicable diseases in the world and it poses a heavy burden to society in the form of associated disabilities and healthcare costs. DM secondary to pancreatic diseases is classified as pancreatogenic diabetes or type 3c DM.8,11 In contrast to type 1 and type 2 DM, detailed clinical data on type 3c DM is scarce. Further, the time course of DM and exocrine insufficiency remains unclear.

Moreover, AP may contribute to pancreatic exocrine insufficiency (PEI), a condition characterized by a deficiency of the exocrine pancreatic enzymes resulting in maldigestion or malabsorption. The diagnosis of PEI is largely based on clinical symptoms,12 although some patients may present maldigestion and symptoms similar to those observed in other gastrointestinal (GI) diseases. Chronic pancreatitis is the most common cause of PEI, as a result of the pancreatic exocrine cell injuries.13 Management of PEI is mostly based on both pancreatic enzyme replacement and lifestyle modifications.

The aim of this study was to investigate the incidence rates, time course, and relative risks of both endocrine and exocrine insufficiencies after the first episode of AP with biliary or alcohol-associated causes based on a Taiwan national population-based study.

METHODS

Database

The National Health Insurance System in Taiwan is compulsory and covers about 23 million citizens (more than 99% of the population, except prisoners). The Taiwan National Health Insurance Research Database (NHIRD) was released for
research purposes by the National Health Research Institute. Information in the inpatient database included date of birth, sex, encrypted patient identification numbers, dates of admission and discharge, levels of medical institutions, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes of diagnoses (up to 5) and procedures (up to 5), order codes, and associated medical costs. We used the encrypted identification of the residents to link 5 data files, which included inpatient, outpatient, and pharmacy claims data, the registry of the Catastrophic Illnesses Patient Database (CIPD), and demographic information. All data files were linked with scrambled identifications to ensure patient privacy. The study was approved by the Ethics Review Board of the National Taiwan University Hospital (201405043W).

Definitions and Patients

Patients after first-attack AP from the NHIRD between 2000 and 2011 were included in the study. AP was defined by ICD-9-CM code 577.0 in the first position of the 5-inpatient diagnoses. The admission date of AP was defined as the AP index date. Further, severity criteria of AP were defined according to the modified Atlanta classification scheme, if patients met any of the following criteria: the presence of intensive care unit (ICU) admission, organ dysfunction or failure, major gastrointestinal bleeding, or accompanied complications. To ensure at least 1 year of follow-up, patients who presented first-attack AP in 2011 (n = 582) were excluded from the study. Moreover, cases who had AP in 2000 (n = 1568) were excluded to confirm the first-attack event as correctly as possible. Patients with follow-up of less than 6 months (n = 477), those who received pancreatic surgery (n = 23), and those <20 years (n = 35) were further excluded. In addition, patients were excluded if they were diagnosed with DM (ICD-9-CM code 250.x) before first AP index date (n = 23). The diagnostic accuracy of cancer was confirmed by both specific admission code (ICU) admission, organ dysfunction or failure, major gastrointestinal bleeding, or accompanied complications. To ensure at least 1 year of follow-up, patients who presented first-attack AP in 2011 (n = 582) were excluded from the study. Moreover, cases who had AP in 2000 (n = 1568) were excluded to confirm the first-attack event as correctly as possible. Patients with follow-up of less than 6 months (n = 477), those who received pancreatic surgery (n = 23), and those <20 years (n = 35) were further excluded. In addition, patients were excluded if they were diagnosed with DM (ICD-9-CM code 250.x) before first AP index date (n = 23). The diagnostic accuracy of cancer was confirmed by both specific admission code (ICU) admission, organ dysfunction or failure, major gastrointestinal bleeding, or accompanied complications.

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Etiology was defined as biliary diseases (ICD-9-CM code 577) or alcohol-related diseases (ICD-9-CM codes 291.0, 291.4, 291.81, 303, 305.0, 571.2, or 790.3) according to the associated diagnostic codes of admission for AP. To assess comorbidity, we collected data on the diagnoses made before AP first-attack index date for each patient: dyslipidemia (ICD-9-CM codes 272.0, 272.1, and 272.2), ischemic heart disease (ICD-9-CM codes 410–414), liver cirrhosis (ICD-9-CM codes 571.5), hypertension (ICD-9-CM code 401–405), and peptic ulcer diseases (ICD-9-CM code 531–535). The Charlson comorbidity index is a weighted summary measure of clinically important diseases that has been adapted for use with ICD-9-CM coded administrative databases.

Outcomes

In this study, there were 2 primary outcomes: exocrine and endocrine insufficiencies. Exocrine insufficiency was defined as the use of exogenous exocrine pancreatic enzymes in patients after first attack of AP. Endocrine insufficiency was defined as new diagnosis of DM after a first attack of AP. DM was defined if patients had at least 1 admission diagnosis or 2 or more outpatient clinic visits within a year with a diabetic diagnostic code (ICD-9-CM code 250). This definition of diabetes was evaluated and validated in the Taiwan NHIRD with a high level of sensitivity and a positive predictive value (93.2% and 92.3%, respectively).

Statistics

Normality of study variables was assessed with Kolmogorov–Smirnov normality test. Continuous variables with normal distribution are expressed as mean ± standard deviation; discrete ones are presented as count or percentage. Continuous variables with nonnormal distribution are presented as median and interquartile range. In the univariate analysis, we used the Mann–Whitney U test (for continuous variables) or the χ² test (for discrete ones) to compare differences between groups. Multivariable Cox regression analysis was used to evaluate independent effect of factors on newly diagnosed DM or pancreatic exocrine insufficiency after first-attack AP. Factors with P < 0.05 on univariate analysis were included in the regression model. Data were analyzed with SPSS for Windows, version 17.0. (SPSS Inc, Chicago, IL). A 2-tailed P value of <0.001 was considered to be significant.

RESULTS

Incidence of Newly Diagnosed DM After First-Attack AP

Among the 12,284 patients with first-attack AP, 618 patients (5.0%) were newly diagnosed with DM. Results of the univariate comparison between patients with and without newly diagnosed DM, are shown in Table 1. Alcohol-associated AP (P < 0.001), more readmissions for acute pancreatitis (P < 0.001), male sex (P < 0.001), and younger age (P = 0.003) presented a higher proportion of newly diagnosed DM after AP. The Cox logistic regression model was used to evaluate the factors associated with newly diagnosed DM (Table 2). Our Cox logistic regression model identified alcohol-associated AP (odds ratio, 1.894; 95% CI, 1.520–2.268; P < 0.001) and ≥2 readmissions for AP (odds ratio, 1.937; 95% CI, 1.483–2.391; P < 0.001) to be significantly associated with newly diagnosed DM after AP.

Incidence of Pancreatic Exocrine Insufficiency After First-Attack AP

Of the 12,284 first-attack AP patients, 5617 patients (45.7%) presented pancreatic exocrine insufficiency. Results of the univariate comparison between patients with and without pancreatic exocrine insufficiency are shown in Table 3. Alcohol-associated AP (P < 0.001), male sex (P = 0.020), younger age (P = 0.018), middle socio-economic status (P < 0.001), peptic ulcer disease (P < 0.001), and dyslipidemia (P = 0.024) presented a significantly increased proportion of pancreatic exocrine insufficiency after AP. The Cox logistic regression model was used to evaluate the factors associated with pancreatic exocrine insufficiency (Table 4). Our Cox logistic regression model showed that only alcohol-associated AP (odds ratio, 1.215; 95% CI, 1.133–1.297; P < 0.001) was significantly associated with pancreatic exocrine insufficiency after AP.

Incidence of Both Exocrine and Endocrine Insufficiency After First-Attack AP

In our study, 370 (3.0%) patients presented with exocrine and endocrine insufficiencies after AP. Results of the univariate comparison between patients with and without exocrine and endocrine insufficiencies are shown in Table 5. Alcohol-associated AP (P < 0.001), more readmissions for acute pancreatitis...
The Cox logistic regression model was used to evaluate the factors associated with exocrine and endocrine insufficiencies (Table 6). The Cox logistic regression model identified alcohol-associated AP (odds ratio, 1.804; 95% CI, 1.345–2.263; \( P < 0.001 \)) and \( /C21 \) readmissions for AP (odds ratio, 3.190; 95% CI, 2.317–4.063; \( P < 0.001 \)) as significantly associated with both exocrine and endocrine insufficiencies after AP.

DISCUSSION

In this study, alcohol-associated AP led to increased levels of exocrine or endocrine insufficiencies when compared with a biliary cause. The mechanism of alcohol-induced AP is multifactorial, including direct toxic effects of both alcohol and its metabolites on the pancreas.23 Other studies demonstrate that alcohol exerts its toxic effects on acinar cells and small pancreatic ducts, which become progressively occluded by pancreatic secretions and the formation of protein plugs.24 As condition worsens, alcohol and its metabolites damage the acinar cells, which may promote premature intracellular digestive enzyme activation, predisposing the gland to autodigestive injury.23,25 In addition, pancreatic stellate cells (PSCs) are activated by alcohol, its metabolites, cytokines, and oxidative stress to convert into a myofibroblast-like phenotype, which will be responsible for the ongoing inflammation and fibrosis of the pancreas.23

In our study, AP recurrence is associated with endocrine insufficiency. This finding is similar to a previous study that shows that AP recurrence is one of the most important factors determining the occurrence and the late consequences.26 Most recurrences occur within a few years after the first AP.27 Several factors (sustained alcohol consumption, young age at first episode, persistent pseudocysts, or smoking) affect the risk of disease recurrence in patients with alcohol-associated AP,26 being sustained alcohol consumption the most important issue. Abstinence from alcohol after the first AP may protect against recurrent disease, although few patients were able to achieve it.28 A previous randomized controlled trial showed that the recurrence of acute alcohol-associated pancreatitis can be reduced by implementing multiple intervention program.29

### TABLE 1. Comparison of Clinicodemographic Characteristics Between DM Cases and Non-DM Cases After Initial Acute Pancreatitis, Uni-Variable Analysis

|                          | n (%)     | n (%)     | \( P \) Value |
|--------------------------|-----------|-----------|--------------|
| **Cause of acute pancreatitis** |           |           |              |
| Biliary                  | 235 (3.6) | 6321 (96.4)| <0.001       |
| Alcohol                  | 383 (6.7) | 5345 (93.3)|              |
| **Severity of pancreatitis** |           |           | 0.991        |
| Mild                     | 580 (5.0) | 10,939 (95.0)|           |
| Severe                   | 38 (5.0)  | 727 (95.0)  |              |
| **Readmission before DM** |           |           | <0.001       |
| 0                        | 356 (4.0) | 8465 (96.0) |              |
| 1                        | 113 (6.1) | 1728 (93.9) |              |
| \( \geq 2 \)             | 149 (9.2) | 1473 (90.8) |              |
| **Sex**                  |           |           | <0.001       |
| Men                      | 503 (5.8) | 8175 (94.2) |              |
| Women                    | 115 (3.2) | 3491 (96.8) |              |
| **Age group, yr**        |           |           | 0.003        |
| Age < 49                 | 395 (5.6) | 6694 (94.4) |              |
| Age 50–64                | 116 (4.6) | 2393 (95.4) |              |
| Age > 65                 | 107 (4.0) | 2579 (96.0) |              |
| **Age (mean \( \pm SD \))** | 47.9 \(\pm 15.8\) | 50.3 \(\pm 16.7\) | <0.001 |
| **CCI**                  |           |           | 0.085        |
| CCI \( \leq 2 \)         | 342 (4.7) | 6870 (95.3) |              |
| CCI > 2                  | 276 (5.4) | 4796 (94.6) |              |
| **Monthly income (NT$)** |           |           | 0.314        |
| \(< 15,000\)             | 109 (5.7) | 1793 (94.3) |              |
| 15,000–22,798            | 238 (4.9) | 4597 (95.1) |              |
| \(\geq 22,798\)          | 271 (4.9) | 5276 (95.1) |              |
| **Comorbidity**          |           |           |              |
| Peptic ulcer disease     | 348 (5.3) | 6218 (94.7) | 0.148        |
| Liver cirrhosis          | 31 (5.9)  | 491 (94.1)  | 0.309        |
| Dyslipidemia             | 75 (6.1)  | 1159 (93.9) | 0.083        |
| Ischemic heart disease   | 75 (4.6)  | 1560 (95.4) | 0.394        |
| Hypertension             | 196 (5.5) | 3385 (94.5) | 0.158        |

CCI = Charlson comorbidity index; SD = standard deviation.

\( P < 0.001 \), male sex \( P < 0.001 \), and younger age \( P < 0.001 \) showed a significantly higher proportion of both exocrine and endocrine insufficiencies after AP. The Cox logistic regression model was used to evaluate the factors associated with exocrine and endocrine insufficiencies (Table 6). The Cox logistic regression model identified alcohol-associated AP (odds ratio, 1.804; 95% CI, 1.345–2.263; \( P < 0.001 \)) and \( /C21 \) readmissions for AP (odds ratio, 3.190; 95% CI, 2.317–4.063; \( P < 0.001 \)) as significantly associated with both exocrine and endocrine insufficiencies after AP.

The events (DM, exocrine insufficiency, and both) after initial AP are shown in Figure 1.
DM secondary to pancreatic diseases is classified as pancreatogenic diabetes. The prevalence of pancreatogenic DM among all patients with DM has been estimated to be approximately 5–10%. The prevalence varied from 7% to 37%, depending on the classification of impaired glucose metabolism, etiology of pancreatic diseases, or duration of follow-up. Of interest, nearly half of the necrotizing pancreatitis patients undergoing necrosectomy, who had pancreatic

### Table 2. Comparison of Clinicodemographic Characteristics Between DM Cases and Non-DM Cases After Initial Acute Pancreatitis, Multivariable Analysis

|                        | Hazard Ratio | 95% CI    | P Value |
|------------------------|--------------|-----------|---------|
| Cause of acute pancreatitis: alcohol (reference: Biliary) | 1.894 | 1.520–2.268 | <0.001 |
| Readmission before DM (reference: 0) |            |           |         |
| 1                      | 1.329 | 1.073–1.585 | 0.009  |
| ≥2                     | 1.937 | 1.483–2.391 | <0.001 |
| Age (reference: < = 49 yrs) |            |           |         |
| 50–64                  | 1.213 | 0.971–1.455 | 0.089  |
| > = 65                 | 1.363 | 1.053–1.673 | 0.019  |
| Female (reference: male) | 0.710 | 0.564–0.856 | 0.004  |

CI = confidence interval.

### Table 3. Comparison of Clinicodemographic Characteristics Between PEI Cases and Non-PEI Cases After Initial Acute Pancreatitis, Uni-Variable Analysis

|                      | PEI (n = 5617) | K (n = 6667) | P Value |
|----------------------|----------------|--------------|---------|
| Cause of acute pancreatitis |                |              | <0.001 |
| Biliary              | 2824 43.1      | 3732 56.9    |         |
| Alcohol              | 2793 48.8      | 2935 51.2    |         |
| Severity of pancreatitis |              |              | 0.277   |
| Mild                 | 5282 45.9      | 6237 54.1    |         |
| Severe               | 335 43.8       | 430 56.2     |         |
| Readmission before Exocrine |            |              | 0.198   |
| 0                    | 4576 46.1      | 5344 53.9    |         |
| 1                    | 640 43.2       | 841 56.8     |         |
| ≥2                   | 401 45.4       | 482 54.6     |         |
| Sex                  |                |              | 0.020   |
| Men                  | 4027 46.4      | 4651 53.6    |         |
| Women                | 1590 44.1      | 2016 55.9    |         |
| Age group, yr        |                |              | 0.018   |
| Age< = 49            | 3316 46.8      | 3773 53.2    |         |
| Age 50–64            | 1125 44.8      | 1384 55.2    |         |
| Age > 65             | 1176 43.8      | 1510 56.2    |         |
| Age (mean ± SD)      | 49.6 ± 16.6    | 50.7 ± 16.7  | <0.001  |
| CCI                  |                |              | 0.247   |
| CCI ≤ 2              | 3266 45.3      | 3946 54.7    |         |
| CCI >2               | 2351 46.4      | 2721 53.6    |         |
| Monthly income (NT$) |                |              | <0.001  |
| <15,000              | 855 45.0       | 1047 55.0    |         |
| 15,000–22,798        | 2339 48.4      | 2496 51.6    |         |
| ≥22798               | 2423 43.7      | 3124 56.3    |         |
| Comorbidity          |                |              |         |
| Peptic ulcer disease | 3129 47.7      | 3437 52.3    | <0.001  |
| Liver cirrhosis      | 221 42.3       | 301 57.7     | 0.116   |
| Dyslipidemia         | 602 48.8       | 632 51.2     | 0.024   |
| Ischemic heart disease | 741 45.3     | 894 54.7     | 0.729   |
| Hypertension         | 1610 45.0      | 1971 55.0    | 0.282   |

CCI = Charlson comorbidity index; PEI = pancreatic exocrine insufficiency; SD = standard deviation.
### TABLE 4. Comparison of Clinicodemographic Characteristics Between PEI Cases and Non-PEI Cases After Initial Acute Pancreatitis, Uni-Variable Analysis, Multivariable Analysis

| Hazard Ratio | 95% CI       | P Value |
|--------------|--------------|---------|
| Cause of acute pancreatitis: alcohol (reference: Biliary) | 1.215 | 1.133–1.297 | <0.001 |
| Age (reference: < = 49 yrs) | | | |
| 50–64 | 1.043 | 0.970–1.116 | 0.254 |
| > = 65 | 1.047 | 0.967–1.127 | 0.259 |
| Female (reference: male) | 1.016 | 0.951–1.081 | 0.636 |
| Monthly income (reference: <15,000) | | | |
| 15,000–22,799 | 1.085 | 1.002–1.168 | 0.044 |
| >= 22,799 | 0.966 | 0.892–1.040 | 0.398 |
| Peptic ulcer disease | 1.051 | 0.987–1.121 | 0.012 |
| Dyslipidemia | 1.106 | 1.016–1.196 | 0.021 |

CI = confidence interval; PEI = pancreatic exocrine insufficiency.

### TABLE 5. Comparison of Clinicodemographic Characteristics Between Both DM and PEI Cases and Others After Initial Acute Pancreatitis, Uni-Variable Analysis

| | Both DM and Exocrine (n = 370) | Others (n = 11,914) | P Value |
| | n | % | n | % |
| Cause of acute pancreatitis | | <0.001 | | | |
| Biliary | 126 | 1.9 | 6430 | 98.1 | |
| Alcohol | 244 | 4.3 | 5484 | 95.7 | |
| Severity of pancreatitis | | | | | 0.733 |
| Mild | 349 | 3.0 | 11,170 | 97.0 | |
| Severe | 21 | 2.7 | 744 | 97.3 | |
| Sex | | <0.001 | | | |
| Men | 306 | 3.5 | 8372 | 96.2 | |
| Women | 64 | 1.8 | 3542 | 98.2 | |
| Readmission before DM and exocrine insufficiency | | | | <0.001 |
| 0 | 166 | 1.9 | 8617 | 98.1 | |
| 1 | 70 | 3.8 | 1768 | 96.2 | |
| ≥2 | 134 | 8.1 | 1529 | 91.9 | |
| Age group, yrs | | | | <0.001 |
| Age< = 49 | 254 | 3.6 | 6835 | 96.4 | |
| Age 50–64 | 64 | 2.6 | 2445 | 97.4 | |
| Age > 65 | 52 | 1.9 | 2634 | 98.1 | |
| Age (mean ± SD) | | | | <0.001 |
| CCI | 45.8 ± 14.7 | 50.3 ± 16.7 | |
| CCI < 2 | 210 | 2.9 | 7002 | 97.1 | 0.454 |
| CCI ≥2 | 160 | 3.2 | 4912 | 96.8 | |
| Monthly income (NTS) | | | | 0.312 |
| <15,000 | 65 | 3.4 | 1837 | 96.6 | |
| 15,000–22,798 | 151 | 3.1 | 4684 | 96.9 | |
| ≥ 22,798 | 154 | 2.8 | 5393 | 97.2 | |
| Comorbidity | | | | | |
| Peptic ulcer disease | 216 | 3.3 | 6350 | 96.7 | 0.057 |
| Liver cirrhosis | 16 | 3.1 | 506 | 96.9 | 0.911 |
| Dyslipidemia | 43 | 3.5 | 1191 | 96.5 | 0.293 |
| Ischemic heart disease | 41 | 2.5 | 1594 | 97.5 | 0.216 |
| Hypertension | 111 | 3.1 | 3470 | 96.9 | 0.730 |

CCI = Charlson comorbidity index; PEI = pancreatic exocrine insufficiency; SD = standard deviation.
exocrine insufficiency during follow-up, also developed impaired glucose metabolism. To our knowledge, nutrient maldigestion induced by exocrine insufficiency results in impaired incretin secretion and decreased insulin release from β-cells. Patients with both pancreatogenic DM and exocrine pancreatic insufficiency should take adequate supplements of exocrine pancreatic enzymes, which may not only prevent a deficiency of fat-soluble vitamins but also reverse the impaired glucose metabolism due to decreased release of incretin. In our study, 224 cases (3.9%; interval between exocrine insufficiency and DM; mean SD: 1068 ± 862 days) developed DM among the 5617 patients with exocrine insufficiency during follow-up after initial AP (6 cases presented with simultaneous endocrine and exocrine insufficiencies). On the other hand, 140 patients (22.7%; interval between DM and exocrine insufficiency; mean ± SD: 632 ± 602 days) presented with exocrine insufficiency among the 618 patients with DM during follow-up after initial AP. Glucose metabolism or exocrine function tests should be performed whenever endocrine or exocrine insufficiency is suspected.

Theoretically, severe AP causes a more severe pancreatic injury when compared with mild AP, which may just contribute to exocrine or endocrine insufficiency. From our findings, severity of AP does not correlate with occurrence of exocrine or endocrine insufficiencies. Previous reports also addressed that severity of AP is not associated with glucose intolerance or exocrine insufficiency risk.

Our study is notable for its large sample size and its nationally representative characteristics. However, our study also has several limitations that need to be considered. First, the NHIRD does not include detailed results from laboratory data on glucose metabolism. Second, coding error or misdiagnosis is inevitable in a database. To decrease coding error in our study, the diagnostic accuracy of DM coding was confirmed by both admission and outpatient ICD-9 codes and hyperglycemia-lowering medication in pharmacy databases. Third, every inpatient had no more than 5 diagnoses, which means that a diagnosis of DM or exocrine insufficiency could have been missed. However, this nationwide database provides long-term medical records for every patient. DM is a major medical disease, and some may take hypoglycemia medication. Moreover, the definition of exocrine insufficiency is the use of exocrine pancreatic enzyme supplementation on the basis of a pharmaceutical database. Therefore, the underestimated DM or exocrine insufficiency diagnosis may be minimal in our study. Last, the most sensitive method for the detection of PEI requires not only stimulation of pancreatic cerulean and secretin, but also collection of gastric and duodenal juice with duodenal tube insertion, which is a relatively invasive procedure in clinical practice. The diagnosis of PEI in clinical services is usually performed based on the patient’s symptoms, response to exocrine pancreatic enzymes supplementation, or laboratory tests for stool (fecal elastase 1 or pancreolauryl tests). Nonetheless, some mild PEI may be ignored according to these criteria.

In summary, this population-based cohort retrospective study showed that rather than a biliary cause, alcohol-associated AP contributed to a higher proportion to exocrine or endocrine insufficiencies. In addition, recurrent AP also led to endocrine insufficiency.

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TABLE 6. Comparison of Clinicodemographic Characteristics Between Both DM and PEI Cases and Others After Initial Acute Pancreatitis, Multi-Variable Analysis

| Hazard Ratio | 95% CI | P Value |
|--------------|-------|---------|
| Cause of acute pancreatitis: alcohol (reference: Biliary) | 1.804 | 1.345–2.263 | <0.001 |
| Readmission before DM and exocrine insufficiency (reference: 0) | 1.756 | 1.324–2.188 | <0.001 |
| ≥2 | 3.190 | 2.317–4.063 | <0.001 |
| Age (reference: < = 49 yrs) | 1.191 | 0.886–1.496 | 0.247 |
| 50–64 | 1.201 | 0.840–1.562 | 0.315 |
| > = 65 | 0.755 | 0.555–0.955 | 0.074 |

CI = confidence interval; PEI = pancreatic exocrine insufficiency.

FIGURE 1. The events (DM, exocrine insufficiency, and both) after initial AP.
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