Effect of Diabetes on Severity and Hospital Mortality in Patients With Acute Pancreatitis

A national population-based study

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OBJECTIVE—Diabetes may increase the risk of acute pancreatitis (AP). We aimed to further investigate whether diabetes may also adversely affect outcomes of patients with AP.

RESEARCH DESIGN AND METHODS—In this retrospective cohort study, we compared 18,990 first-attack AP with diabetes to 37,980 matched control subjects from Taiwan's National Health Insurance Research Database between 2000 and 2009. Primary outcomes were development of severe AP, defined by a modified Atlanta classification scheme, and hospital mortality. Analyses were performed using univariable and multivariable logistic regression model with generalized estimating equations accounting for hospital clustering effect.

RESULTS—After baseline characteristics were adjusted, AP patients with diabetes had a higher risk of a severe attack than their nondiabetic counterparts (adjusted odds ratio [OR] 1.21, 95% CI 1.16–1.26). When severity criteria were analyzed individually, diabetic AP patients had a 58% higher risk of intensive care unit admission and a 30% higher risk of local complications, but a 16% lower risk of gastrointestinal bleeding, than AP patients without diabetes. The risk of organ failure at least one system) was similar between the two groups. Conversely, AP patients with diabetes were associated with a lower risk of hospital mortality (adjusted OR 0.77, 95% CI 0.65–0.91).

CONCLUSIONS—Although diabetes may adversely affect the disease process of AP, it seems to protect patients from AP-related mortality.

Diabetes Care **35:1061–1066, 2012**

Acute pancreatitis (AP) is an acute inflammatory disease of the pancreas. The local inflammation is usually self-limited within a few days, but it can be destructive and cause a severe local complication and/or systemic reaction leading to organ failures and death. Although the case-fatality rate has been decreasing over the decades (1,2), severe cases still carry a high mortality (20–50%) and consume nearly half of the resources and costs incurred by all patients with AP (3). Accordingly, many efforts have been made to identify correlates of severity and predictors for mortality in patients with AP (4–6).

In addition to older people (7), patients with certain comorbidities, such as obesity (8), hypertriglyceridemia (9), chronic renal failure (10), and systemic lupus erythematosus (11), are shown to be associated with greater risk of not only the incidence but also the severity and mortality of AP. Among various comorbidities, diabetes mellitus is relatively common in patients with AP; the prevalence was 11% in Japan (12), 17.7% in California (U.S.), (13) and 19.3% in Taiwan (3). These figures are expected to continuously increase in the future because diabetic patients not only are at risk for developing AP (14–16) but also are growing in prevalence worldwide (17). Nonetheless, the effect of diabetes on outcomes of patients with AP has not been adequately studied, and the results of available reports are inconsistent (13,18). For example, Frey and colleagues examined the effect of comorbidities on patients with AP and found that diabetes was not associated with early mortality (13), whereas Graham and coworkers assessed the effect of diabetes on critically ill patients and showed a reduced risk of hospital mortality in a subgroup patients with AP (18). In both studies, however, the effect of diabetes was not specifically examined and detailed analyses were not performed (13,18).

In a recent national population-based study on Taiwanese patients with first-attack AP, we found that the prevalence of diabetes increased from 15.6% in 2000 to 2001 to 19.7% in 2008 to 2009 (1). In this study, we used the same cohort (1) to further investigate the effect of diabetes on outcomes of these patients. Because diabetic patients are likely to have a higher comorbid burden and hence a poorer reserve for acute illnesses, we hypothesized that diabetes is associated with a higher risk of severe attacks and hospital mortality in adult patients with first-attack AP.

RESEARCH DESIGN AND METHODS

Database

The National Health Insurance System in Taiwan is compulsory and covers all citizens except prisoners. The Taiwan National Health Insurance Research Database (NHIRD) was released for research purposes by the National Health Research Institute (19) and is one of the largest and most comprehensive databases in the world. Information included in the inpatient database incorporated sex, date of

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Received 8 October 2011 and accepted 1 February 2012.
DOI: 10.2337/dc11-1925
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-1925/-/DC1.

birth, encrypted patient identification numbers, residential or work area, dates of admission and discharge, medical institutions providing the services, the International Classification of Diseases (Ninth Revision) Clinical Modification (ICD-9-CM) codes of diagnoses (up to five) and procedures (up to five), outcome at hospital discharge (recovered, died, or transferred out), order codes, and hospital charges. The approval from the human subjects institutional review board and informed consent from the patients were exempt for the use of the encrypted administrative database.

Definitions and patients

The patients were described in a recent study on the epidemiology of first-attack AP in Taiwan from 2000 through 2009 (1). AP was defined by ICD-9-CM code 577.0 in any position of the five diagnoses. We validated the diagnostic code previously, showing a positive predictive value of 90.0% (95% CI 79.2–96.2%) (1). Severity criteria of AP were defined primarily according to the Atlanta classification scheme (20), but were modified into the presence of intensive care unit (ICU) admission (as a surrogate of acute physiology and chronic health evaluation [APACHE] II score ≥8), organ failure or dysfunction (Supplementary Table 1), gastrointestinal bleeding (Supplementary Table 1), or local complications (defined by physician-order codes for drainage of pancreatic abscesses or cysts) (1,3).

Between 2000 and 2009 (inclusive), we identified 106,458 patients (≥15 years) with first-attack AP from the NHIRD; among them, 18,990 (17.8%) had diabetes (Fig. 1) (1). Diabetes was defined by ICD-9-CM code 250.x, including those with (codes 250.4, 250.5, 250.6, 250.7) and without (250.0, 250.1, 250.2, 250.3, 250.8, 250.9) diabetes-related complications, in any position of the five diagnosis codes. Because diabetic AP patients were older (median age 58 vs. 51 years) and had less male predominance (59.3 vs. 66.2%) than nondiabetic ones, we managed to achieve the comparability of the study groups by performing a frequency matching technique on sex, 5-year age strata, and year of admission without replacement. With a nondiabetes-to-diabetes ratio of 2, we randomly selected 37,980 nondiabetic AP patients.

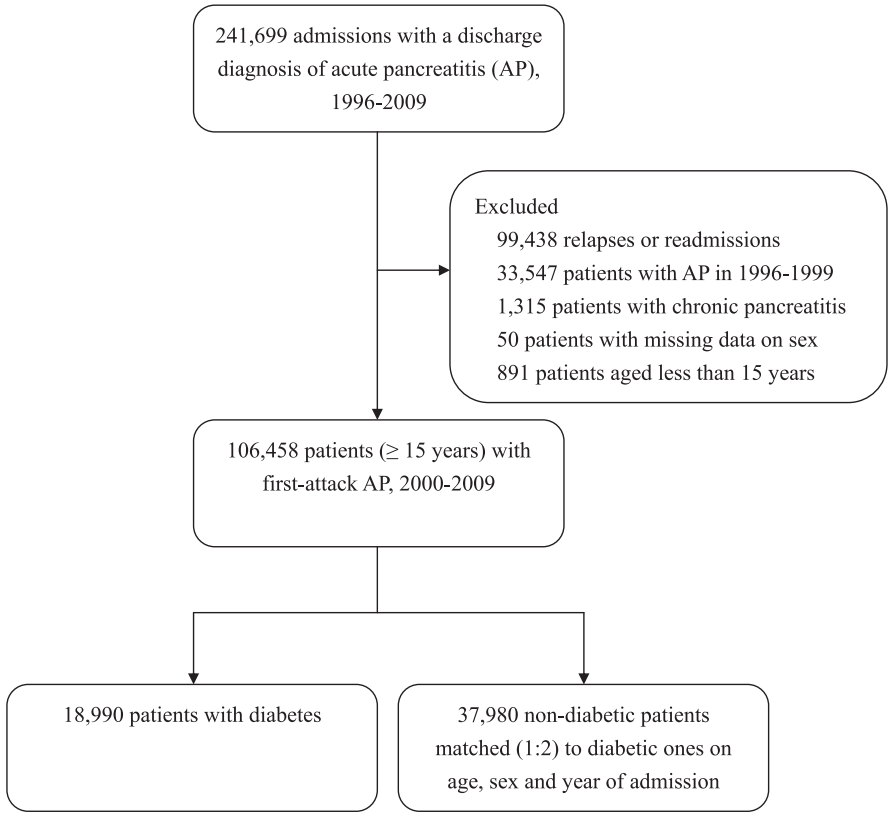

Figure 1—*Study flow diagram.*

Covariates

To better understand the effect of diabetes on outcomes of AP patients especially as relates to mortality, five levels of covariates were included in sequential models (see below). First, patient demographics included age, sex, year of admission, and urbanization level (including urban, suburban, and rural areas) (1). Second, hospital features included only hospital level (including medical center [>500 beds], regional [250–500 beds], and district hospitals [20–249 beds]). Third, pancreatitis characteristics were prevalence of selected comorbid conditions, Charlson comorbidity index (21,22), causes of AP (biliary or alcohol-related) (3), computed tomography, and severity criteria (including ICU admission, organ failure, gastrointestinal bleeding, and local complications). Fourth, inpatient stay features were related to processes of care, length of hospital stay, and various treatments, including endoscopic retrograde cholangiopancreatography (ERCP), cholecystectomy, and life-supporting measures (including total parenteral nutrition, hemodialysis and use of vasopressors and mechanical ventilation) (3). Finally, the covariate in the fifth level was insulin therapy. The Charlson comorbidity index is a weighted summary measure of clinically important concomitant diseases that has been adapted for use with ICD-9-CM coded administrative databases (Supplementary Table 2) (21,22). Because diabetes mellitus is a variable of primary interest in this study, diabetes with or without complications was not counted in the Charlson index.

Outcomes

Primary outcome was hospital mortality (1). Secondary outcome was the development of severe AP. The severe criteria, including ICU admission, organ failure, gastrointestinal bleeding, and local complication, were examined jointly and separately.

Statistics

Continuous variables are presented as median (interquartile range) owing to a skewed distribution; discrete ones are presented as count or percentage. In the univariate analysis, we used the Mann-Whitney *U* test (for continuous variables) or the χ^2 test (for discrete ones) to compare differences between patients with and without diabetes. To account for hospital clustering, the effect of diabetes was analyzed using logistic regression model with generalized estimating equations methods (23), specifying an exchangeable structure of a working correlation matrix, to construct regression models. The binary outcomes were regressed with a logit link function. Both univariable and multivariable analyses were performed to

yield the crude and adjusted risks. In the multivariable analysis for risk of severe AP, we adjusted only for patient demographics, hospital level, causes of AP (alcohol, biliary, both, and others) and Charlson Comorbidity Index (0, 1, 2, 3+). In the multivariable analysis for the risk of hospital mortality, we performed five sequential regression models adjusting for the five levels of covariates, consecutively and additively. To assess the effect of diabetes-related complications on hospital mortality, the above analyses were repeated by stratifying patients with diabetes according to the status of these complications. The multicollinearity among covariates was examined and found if a tolerance level was less than 0.1. Data were analyzed with SPSS for Windows, version 17.0. (SPSS, Chicago, IL). A two-tailed *P* value of <0.05 was considered significant.

RESULTS

Baseline characteristics

Table 1 shows characteristics of the two study groups. When compared with nondiabetic ones, AP patients with diabetes were somewhat more likely to live in an urban area and to be admitted to regional hospitals. They also had fewer biliary and alcohol-related causes and had smaller Charlson Comorbidity Index scores. However, the prevalence of certain comorbid conditions, including cerebrovascular, cardiovascular, and renal diseases, was higher in diabetic AP patients than in nondiabetic ones. Hepatic disease and peptic ulcer were the most common comorbid conditions and were less prevalent in AP patients with diabetes.

Additionally, diabetic AP patients received fewer invasive procedures of ERCP and cholecystectomy but more computed tomography, insulin therapy, and life-supporting treatments, especially hemodialysis and mechanical ventilation, than nondiabetic ones. The length of hospital stay was slightly longer in diabetic AP patients than in nondiabetic ones.

Table 1—*Characteristics of the patients with AP according to the presence of diabetes*

Variables	Diabetes (*n* = 18,990)	Nondiabetes (*n* = 37,980)	*P* values
Age (year)	58 (45–71)	58 (45–71)	—
Male	59.3	59.3	—
Urbanization			<0.001
Urban	55.0	52.7	
Suburban	32.9	34.3	
Rural	12.1	13.0	
Hospital level			<0.001
Medical center	28.1	29.5	
Regional hospital	47.4	45.3	
District hospital	24.5	25.2	
Cause			
Biliary	22.7	30.4	<0.001
Alcohol	2.9	3.9	<0.001
Charlson Comorbidity Index†	0 (0–1)	1 (0–1)	<0.001
0	51.6	45.3	
1	33.0	34.9	
2	10.3	12.1	
≥3	5.1	7.7	
Comorbid conditions			
Cerebrovascular	3.0	2.2	<0.001
Cardiovascular	2.7	2.3	0.004
Respiratory	2.2	3.1	<0.001
Renal	6.3	4.3	<0.001
End-stage renal disease	5.4	3.5	<0.001
Hepatic	21.7	28.0	<0.001
Cirrhosis	7.2	9.4	<0.001
Peptic ulcer	16.9	21.0	<0.001
Cancer	3.3	6.1	<0.001
Computed tomography	39.6	36.4	<0.001
Insulin therapy	66.1	8.6§	<0.001
ERCP	6.5	9.0	<0.001
Cholecystectomy‡	5.2	7.3	<0.001
Life-supporting treatment			
Total parenteral nutrition	3.8	3.6	0.379
Vasopressors	6.5	6.3	0.344
Hemodialysis	4.8	3.5	<0.001
Mechanical ventilation	7.5	7.0	0.040
Hospital length of stay (days)	7 (4–12)	6 (4–10)	<0.001

Values are expressed as median (interquartile range) or percentages. †Diabetes was excluded from the index. ‡The surgery was performed during admission for first-attack acute pancreatitis. §Patients without diabetes might receive insulin therapy for tight glycemic control, especially in the ICU setting.

Outcomes

Table 2 shows the effect of diabetes on the risks of a criteria-specific severe attack in patients with AP. After adjustment was made for patient demographics, hospital level, causes of AP, and Charlson Comorbidity Index, diabetes was associated with a 21% increased risk of any severe attack. However, when these severity criteria were analyzed separately, the AP patients with diabetes suffered from a 58% higher risk of ICU admission and a 30% higher risk of local complications, but experienced a 16% lower risk of gastrointestinal bleeding, than control subjects. The risk of organ failure (≥1 system) was similar between the two groups. However, the relative risk of failure in individual organ systems varied: diabetes was associated with a reduced risk of cardiovascular (odds ratio [OR] = 0.82), hepatic (OR = 0.71), and hematologic (OR = 0.47) failures but associated with an increased risk of renal (OR = 1.20) and metabolic (OR = 1.49) failures. The risks of neurologic and respiratory failures were similar in both groups.

Hospital mortality was lower in diabetic AP patients than in nondiabetic ones (3.5% vs. 4.1%, $P < 0.001$). As shown in Table 3, diabetes was associated with a lower risk of death in the five sequential models. The effect of diabetes was similar in Model 1 and Model 2 (OR and 95% CI 0.83 [0.70–0.99] and 0.84 [0.72–0.98], respectively), slightly increased in Model 3 (0.70 [0.62–0.79]), and then attenuated in Model 4 (0.82 [0.72–0.95]). After all potential confounders (Model 5) were controlled, diabetes was associated with a 23% lower risk of hospital mortality (0.77

Table 2—*The effect of diabetes on the risk of severe attack in patients with AP

Severity criteria†	Diabetes (n = 18,990)	Nondiabetes (n = 37,980)	Adjusted OR (95% CI)
Any	25.2	24.2	1.21 (1.16–1.26)
ICU admission	16.2	10.7	1.58 (1.51–1.67)
Organ failure			
Any	12.9	13.2	0.99 (0.93–1.04)
Neurologic	0.5	0.5	1.11 (0.87–1.42)
Respiratory	6.2	5.7	1.03 (0.95–1.11)
Cardiovascular	2.4	2.7	0.82 (0.73–0.92)
Renal	3.5	2.6	1.20 (1.12–1.37)
Hepatic	2.7	4.5	0.71 (0.64–0.79)
Hematologic	0.4	0.8	0.47 (0.36–0.61)
Metabolic	0.7	0.4	1.49 (1.18–1.89)
Gastrointestinal bleeding	5.4	6.7	0.84 (0.78–0.91)
Local complications	1.8	1.4	1.30 (1.13–1.50)

Data are percentages unless otherwise indicated. *Multivariable logistic regression using Generalized Estimating Equations models adjusting for covariates (see below). †Adjusted covariates included age, sex, year of admission, urbanization, hospital level, causes of AP (alcohol, biliary, both, and others), and Charlson Comorbidity Index (0, 1, 2, 3+).

[0.65–0.91]). No interaction was seen in stratified analysis by presence of diabetes-related complications (i.e., nephropathy, neuropathy, vasculopathy, or retinopathy).

CONCLUSIONS—In this study, we found that diabetes was associated with an increased risk of severe attacks in patients with AP, but the risk of individual severity criteria for AP associated with diabetes varied in magnitude and direction. AP patients with diabetes had more ICU admissions and local complications, but had less frequent gastrointestinal bleeding. Despite that the overall risk of organ failure was not affected by diabetes, and the risks of renal and metabolic failures were increased. Although more severe attacks were seen in AP patients with diabetes, the risk of death was significantly lower in these patients, suggesting a protective effect on mortality by diabetes in first-attack AP patients.

Our finding of an increased risk of severe AP and a lower risk of death in diabetic AP patients is somewhat different from that found by Frey and coworkers (13), who analyzed 84,713 patients with AP from the California Patient Discharge Data in 1992–2002 to investigate the predictive value of comorbidity. They found that diabetes increased the risk of multiorgan (≥2 systems) failure (OR 1.6, 95% CI 1.4–1.8), but was not associated with early (≤14 days) mortality (13). When individual severity criteria were analyzed, we did not find the association between overall organ failure and diabetes. Instead, we found that diabetes was associated with increased risks of only ICU admission and local complications. Because of limited availability of medical order data and incomplete information on diabetes duration, we were unable to further assess the potential roles of incretin-based therapies and disease duration in causing the association of diabetes with severity in AP patients.

Our study also showed that the effect of diabetes on the risk of organ failure is different across systems. Diabetes was found to associate with the increased risk of renal failures and the reduced risk of hematologic failure in AP patients with diabetes. Similar results were also found in studies on sepsis and critical illnesses (24,25). A poorer metabolic reserve and a higher prevalence of chronic renal disease in diabetes may explain the higher risk of renal and metabolic failures in diabetic AP patients. On the other hand, the reduced risk of hepatic failure and gastrointestinal bleeding may probably reflect lower prevalence of hepatic disease and peptic ulcer in diabetic patients. Although a survival effect might explain the lower prevalence of some comorbid conditions in diabetic patients (because those with multiple comorbidities would die earlier), these findings suggest that comorbidities in patients with AP have important implications in the disease process and call a need for further investigations.

Recent studies have shown that diabetes is usually associated with a greater severity and morbidity but not necessarily associated with a higher short-term mortality in patients undergoing cardiac surgery (26) or having trauma (27), acute myocardial infarction (28), or critical illnesses (18,29). In fact, a survival advantage of diabetes has been reported in patients with sepsis or critical illnesses including AP (18,24,30). Although findings from the current analysis were not perfectly consistent with our research hypothesis, such seemingly beneficial survival effect of diabetes is not unique.

It is not clear why diabetes may have such intriguingly protective effect on mortality in AP patients. Some explanations addressed in sepsis and critical care studies (24,25,29,31) may be applicable to patients with AP since all these conditions can lead to a systemic inflammatory response syndrome and organ failure (32). The proposed biological mechanisms that favor diabetes during sepsis or critical illnesses include the anti-inflammatory effect of some antidiabetic agents (such as insulin (33) and troglitazone) (34), a less disturbed hemostatic balance (29), an adaptation to hyperglycemia (31), and a protective effect

Table 3—*The effect of diabetes on the risk of hospital mortality in patients with AP*

Outcomes	Diabetes (n = 18,990)	Nondiabetes (n = 37,980)	Adjusted OR (95% CI)*				
			Model 1	Model 2	Model 3	Model 4	Model 5
Hospital mortality	3.5	4.1	0.83 (0.70–0.99)	0.84 (0.72–0.98)	0.70 (0.62–0.79)	0.82 (0.72–0.95)	0.77 (0.65–0.91)

Data are percentages unless otherwise indicated. Model 1 was adjusted for age, sex, year of admission, and urbanization. Model 2 was adjusted for hospital level and covariates in Model 1. Model 3 was adjusted for causes of AP (alcohol, biliary, both, and others) and Charlson Comorbidity Index (0, 1, 2, 3+), computed tomography, severity criteria (including ICU admission, gastrointestinal bleeding, local complication, and organ failure), and covariates in Model 2. Model 4 was adjusted for endoscopic retrograde cholangiopancreatography, cholecystectomy, life-supporting treatments (total parenteral nutrition, hemodialysis, vasopressors, and mechanical ventilation), length of hospital stay, and covariates in Model 3. Model 5 was adjusted for insulin therapy and covariates in Model 4. *Multivariable logistic regression using Generalized Estimating Equations models adjusting for covariates (see above).

of a higher BMI in diabetic patients (35). However, contrary to the finding in critically ill patients (35), a higher BMI has been shown to predict a severe attack, local complication, and death in AP (36). The discrepant findings may be a result of an increased release of proinflammatory adipokine from peri-pancreatic fat necrosis that is present mainly in obese patients with AP (36). The possible protective effect of insulin was not found in our study. Nonbiological explanations for the protective effect of diabetes may include differences in processes of care such as the intensity of acute services, the closeness of monitored care, and the degree of glycemic control. Although information on glycemic control was not available in the database, some differences in processes of care might have existed, as reflected by the change of OR after adjusting for inpatient stay features (adjusted OR changed from 0.70 in Model 3 to 0.82 in Model 4). Further research is needed to address the underlying mechanisms relevant in AP patients.

Although hyperglycemia on admission is associated with an increased risk of organ failure and death in patients with AP (37), prior studies on critically ill patients suggested that the adverse effect of hyperglycemia may be modified by diabetes (30,38). In a retrospective cohort study on 4,946 critically ill patients, Egi and coworkers showed that nondiabetic patients were 1.74 times more likely than diabetic ones ($n = 728$) to die in the ICU in the same range of a time-weighted glucose concentration (between 8.0 and 10.0 mmol/L) (30). In addition, they found that hyperglycemia was associated with outcome only in nondiabetic patients but not in diabetic ones (30). These findings suggest that acute and chronic hyperglycemia are distinct pathophysiological entities and hence may have different clinical consequences (31). It would be interesting in future studies to find whether this phenomenon is also present in patients with AP.

Some limitations deserve comments. First, misclassification is likely because the diagnosis of diabetes relies on the coding and the values of blood glucose and glycated hemoglobin are not available in the database. Because diabetes is more likely to be underdiagnosed, the misclassification would tend to underestimate the observed differences between patients with and without diabetes. Besides, because differentiation between type 1 and type 2 diabetes cannot be made in this study, specific interpretations of the study results are therefore limited. Second, although it is uncommon that diabetes could have occurred during the period of hospitalization for AP, some patients might have newly diagnosed diabetes before admission for first-attack AP. If a longer duration of diabetes is favorably associated with the survival of AP patients, we believe that inclusion of these newly diagnosed patients with diabetes would tend to underestimate the seemingly protective effect of diabetes. Third, the definition of severe AP in this study tended to include patients who had a more severe attack and received intensive and/or invasive treatments. For example, some patients might not be included if they had an APACHE II score ≥8 but were cared for only outside an ICU or if they had local complications but did not receive invasive procedures. Besides, some patients with organ failures may also be missed or undercoded because of limited number of diagnostic codes. However, the selection of a more severe group of patients is nondifferential and tends to bias the observed effect toward the null. Fourth, because first-attack AP was defined by the absence of AP-related hospitalization for at least 4 years before the inclusion, some patients with late relapses, albeit relatively uncommon, might have been enrolled in the study. Because we are not aware the respective percentage of patients with late relapses in the two groups, it is hard to assess the potential influence of the inclusion of these patients on the risk estimates. Finally, residual confounding is likely to be present. For example, a limited number of spaces for diagnostic codes would reduce the available number of comorbid conditions, if existed, especially in people with diabetes, which might cause residual confounding and is more likely to bias the estimate toward the null. Furthermore, the low yield in retrieving the causes would limit the adjustment, especially for biliary and alcohol-related AP. The diagnosis code for obesity (ICD-9-CM code 278.0) was present in only 0.2% of the patients, which was apparently undercoded and hence not included in the analysis. Besides, important clinical features such as BMI and APACHE II score are not available. Although the effect of the residual confounding is uncertain, we believe that it is not likely to oppositely change the conclusion. Nevertheless, our study is strengthened by the large number of patients retrieved from a national population–based database, which can provide an unbiased selection and enhance its generalizability.

In conclusion, diabetes is relatively common in patients with AP and has significantly posed an adverse effect on the disease process and a favorable influence on patient mortality risk. Future studies are needed to further illustrate the underlying mechanisms with which diabetes may reduce the risk of mortality and to find whether an interaction between hyperglycemia and diabetes is also present in patients with AP. More clinical attention should also be paid to the AP patients who also suffered from diabetes to further reduce the incidence of severe attacks in AP patients.

Acknowledgments—The study was supported by grants from the Chi Mei Medical Center (CMFHR10025) and the National Scientific Council (NSC-100-2314-B-006-052) and is based in part on data from the NHIRD provided by the Bureau of National Health Insurance and the Department of Health and managed by National Health Research Institutes.

The interpretation and conclusions contained herein do not represent those of Bureau of National Health Insurance, Department of Health, or National Health Research Institutes.

No potential conflicts of interest relevant to this article were reported.

H.-N.S. designed the study, obtained funding, performed data mining and processing, did statistical analyses, drafted the initial manuscript, and revised important content. C.-L.L. contributed to analyses and interpretation of results and revision for important content. C.-Y.L. participated in interpretation of results and revision for important content. C.-Y.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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