

Effect of Diabetes Mellitus on Severity and Hospital Mortality in Patients with Acute Pancreatitis: a National Population-Based Study

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ABSTRACT

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 controls 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 adjusting for baseline characteristics, AP patients with diabetes had a higher risk of a severe attack than their non-diabetic counterparts (adjusted 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 (≥ 1 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.

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. While 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 of the United States (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 of 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 2000-2001 to 19.7% in 2008-2009 (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 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 (Supplemental Table S1), gastrointestinal bleeding (Supplemental Table S1) 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 (Figure 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 non-diabetic 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 non-diabetes to diabetes ratio of 2, we randomly selected 37,980 non-diabetic AP patients.

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 area) (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). And 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 (Supplemental Table S2) (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 (inter-quartile range) owing to a skewed distribution; discrete ones as count or percentage. In the univariate analysis, we used the Mann-Whitney *U* test (for continuous variables) or the Chi-square 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 Inc., Illinois, U.S.A.). A two-tailed p value of <0.05 was considered significant.

RESULTS

Baseline characteristics

Table 1 shows characteristics of the two study groups. Compared with non-diabetic ones, AP patients with diabetes were somewhat more likely to live in 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 non-diabetic 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 non-diabetic ones. The length of hospital stay was slightly longer in diabetic AP patients than in non-diabetic ones.

Outcomes

Table 2 shows the effect of diabetes on the risks of a criteria-specific severe attack in patients with acute pancreatitis. After adjusting 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 controls. 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 non-diabetic 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% confidence interval [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 controlling for all potential confounders (Model 5), diabetes was associated with a 23% lower risk of hospital mortality (0.77 [0.65-0.91]). No interaction was seen in stratified analysis by presence of diabetes-related complications (i.e., nephropathy, neuropathy, vasculopathy or retinopathy).

DISCUSSION

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, 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

multi-organ (≥ 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. Due to 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 (24,30,31). 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 (24,25,29,32) may be applicable to patients with AP since all these conditions can lead to a systemic inflammatory response syndrome and organ failure (33). The proposed biological mechanisms that favor diabetes during sepsis or critical illnesses include the anti-inflammatory effect of some anti-diabetic agents (such as insulin (34) and troglitazone (35)), a less disturbed hemostatic balance (29), an adaptation to hyperglycemia (32) and a protective effect of a higher BMI in diabetic patients (36). However, contrary to the finding in critically ill patients (36), a higher BMI has been shown to predict a severe attack, local complication and death in AP (37). The discrepant findings may be due to an increased release of pro-inflammatory adipokine from peri-pancreatic fat necrosis that is present mainly in obese patients with AP (37). The possible protective effect of insulin was not found in our study. Non-biological 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 glyceic control. Although information on glyceic control was not available in the database, some differences in processes of care might have been existed, as reflected by the change of odds ratio 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 (38), prior studies on critically ill patients suggested that the adverse effect of hyperglycemia may be modified by diabetes (39,40). In a retrospective cohort study on 4,946 critically ill patients, Egi and coworkers showed that non-diabetic 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 non-diabetic 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 (32). 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. Since diabetes is more likely to be under-diagnosed, 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 under-coded because of limited number of diagnostic codes. However, the selection of a more severe group of patients is non-differential and tends to bias the observed effect towards the null. Fourth, because first-attack AP was defined by the absence of AP-related hospitalization for at least 4 years prior to the inclusion, some patients with late relapses, albeit relatively uncommon, might have been enrolled in the study. Since 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. And 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 diabetes persons, which might cause residual confounding and is more likely to bias the estimate toward the null. Further, 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 under-coded 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 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. A more clinical attention should also be paid to the AP patients who also suffered from diabetes to further reduce the

incidence of sever attacks in AP patients.

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HNS designed the study, obtained funding, performed data mining and processing, did statistical analyses, drafted the initial manuscript, and revised important content. CLL contributed to analyses and interpretation of results, and revision for important content. CYL participated in interpretation of results and revision for important content. Professor Chung-Yi Li 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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The authors declare that there is no conflict of interest associated with this manuscript.

References

1. Shen H, Lu CL, Li CY. Epidemiology of First-Attack Acute Pancreatitis in Taiwan from 2000 through 2009: A Nationwide Population-Based Study. *Pancreas* (in press) 2011

2. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. *Pancreas* 2006;33:323-330
3. Shen HN, Lu CL. Incidence, resource use, and outcome of acute pancreatitis with/without intensive care: a nationwide population-based study in Taiwan. *Pancreas* 2011;40:10-15
4. Papachristou GI, Muddana V, Yadav D, O'Connell M, Sanders MK, Slivka A, Whitcomb DC. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am J Gastroenterol* 2010;105:435-441
5. Gravante G, Garcea G, Ong SL, Metcalfe MS, Berry DP, Lloyd DM, Dennison AR. Prediction of mortality in acute pancreatitis: a systematic review of the published evidence. *Pancreatology* 2009;9:601-614
6. Petrov MS, Shanbhag S, Chakraborty M, Phillips ARJ, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology* 2010;139:813-820
7. Vege TBGSS, Pearson STCRK, Topazian JECMD, Petersen MJLBT. The effect of age on hospital outcomes in severe acute pancreatitis. *Pancreatology* 2008;8:265-270
8. Martinez J, Johnson C, Sanchez-Paya J, De Madaria E, Robles-Diaz G, Perez-Mateo M. Obesity is a definitive risk factor of severity and mortality in acute pancreatitis: an updated

meta-analysis. *Pancreatology* 2006;6:206-209

9. Lloret Linares C, Pelletier AL, Czernichow S, Vergnaud AC, Bonnefont-Rousselot D,

Levy P, Ruszniewski P, Bruckert E. Acute pancreatitis in a cohort of 129 patients referred for severe hypertriglyceridemia. *Pancreas* 2008;37:13

10. Lankisch PG, Weber-Dany B, Maisonneuve P, Lowenfels AB. Frequency and severity of acute pancreatitis in chronic dialysis patients. *Nephrol Dial Transplant* 2008;23:1401

11. Pascual-Ramos V, Duarte-Rojo A, Villa AR, Hernandez-Cruz B, Alarcon-Segovia D, Alcocer-Varela J, Robles-Diaz G. Systemic lupus erythematosus as a cause and prognostic factor of acute pancreatitis. *J Rheumatol* 2004;31:707

12. Satoh K, Shimosegawa T, Masamune A, Hirota M, Kikuta K, Kihara Y, Kuriyama S, Tsuji I, Satoh A, Hamada S. Nationwide epidemiological survey of acute pancreatitis in Japan. *Pancreas* 2011;40:503-507

13. Frey C, Zhou H, Harvey D, White RH. Co-morbidity is a strong predictor of early death and multi-organ system failure among patients with acute pancreatitis. *J Gastrointest Surg* 2007;11:733-742

14. Noel RA, Braun DK, Patterson RE, Bloomgren GL. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. *Diabetes Care* 2009;32:834-838

15. Gonzalez-Perez A, Schlienger RG, Rodriguez LAG. Acute pancreatitis in association

with type 2 diabetes and antidiabetic drugs: a population-based cohort study. *Diabetes Care* 2010;33:2580-2585

16. Lai S-W, Muo C-H, Liao K-F, Sung F-C, Chen P-C. Risk of acute pancreatitis in type 2 diabetes and risk reduction on anti-diabetic drugs: a population-based cohort study in Taiwan. *Am J Gastroenterol* 2011

17. Shaw J, Sicree R, Zimmet P. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:4-14

18. Graham BB, Keniston A, Gajic O, Trillo Alvarez CA, Medvedev S, Douglas IS. Diabetes mellitus does not adversely affect outcomes from a critical illness. *Crit Care Med* 2010;38:16-24

19. National Health Insurance Research Database. Available from <http://w3.nhri.org.tw/nhird/en/index.htm>. Accessed 20 September 2011

20. Bradley EL, 3rd. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg* 1993;128:586-590

21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-383

22. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with

ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;45:613-619

23. Hanley JA, Negassa A. Statistical analysis of correlated data using generalized estimating equations: an orientation. *Am J Epidemiol* 2003;157:364
24. Esper AM, Moss M, Martin GS. The effect of diabetes mellitus on organ dysfunction with sepsis: an epidemiological study. *Crit Care* 2009;13:R18
25. Vincent J-L, Preiser J-C, Sprung CL, Moreno R, Sakr Y. Insulin-treated diabetes is not associated with increased mortality in critically ill patients. *Crit Care* 2010;14:R12
26. Bucerius J, Gummert JF, Walther T, Doll N, Falk V, Onnasch JF, Barten MJ, Mohr FW. Impact of diabetes mellitus on cardiac surgery outcome. *Thorac Cardiovasc Surg* 2003;51:11-16
27. Kao L, Todd S, Moore F. The impact of diabetes on outcome in traumatically injured patients: an analysis of the National Trauma Data Bank. *Am J Surg* 2006;192:710-714
28. Deedwania PC, Ahmed MI, Feller MA, Aban IB, Love TE, Pitt B, Ahmed A. Impact of diabetes mellitus on outcomes in patients with acute myocardial infarction and systolic heart failure. *Eur J Heart Fail* 2011;13:551-559
29. Stegenga ME, Vincent J-L, Vail GM, Xie J, Haney DJ, Williams MD, Bernard GR, van der Poll T. Diabetes does not alter mortality or hemostatic and inflammatory responses in patients with severe sepsis. *Crit Care Med* 2010;38:539-545
30. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, Bailey M. Blood

glucose concentration and outcome of critical illness: the impact of diabetes. Crit Care Med
2008;36:2249-2255

31. Graham BB, Keniston A, Gajic O, Trillo Alvarez CA, Medvedev S, Douglas IS.

Diabetes mellitus does not adversely affect outcomes from a critical illness. Crit Care Med
2010;38:16-24

32. Siegelaar SE, Devries JH, Hoekstra JB. Patients with diabetes in the intensive care unit;
not served by treatment, yet protected? Crit Care 2010;14:126

33. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, Schein RM, Sibbald
WJ. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies
in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest
Physicians/Society of Critical Care Medicine. Chest 1992;101:1644-1655

34. Dandona P, Aljada A, Mohanty P, Ghanim H, Hamouda W, Assian E, Ahmad S. Insulin
inhibits intranuclear nuclear factor κ B and stimulates I κ B in mononuclear cells in obese
subjects: evidence for an anti-inflammatory effect? J Clin Endocrinol Metab
2001;86:3257-3265

35. Aljada A, Garg R, Ghanim H, Mohanty P, Hamouda W, Assian E, Dandona P. Nuclear
factor- κ B suppressive and inhibitor- κ B stimulatory effects of troglitazone in obese patients
with type 2 diabetes: evidence of an antiinflammatory action? J Clin Endocrinol Metab
2001;86:3250-3256

36. Tremblay A, Bandi V. Impact of body mass index on outcomes following critical care. Chest 2003;123:1202-1207
37. Abu Hilal M, Armstrong T. The impact of obesity on the course and outcome of acute pancreatitis. Obes Surg 2008;18:326-328
38. Mentula P, Kylanpaa ML, Kempainen E, Jansson SE, Sarna S, Puolakkainen P, Haapiainen R, Repo H. Early prediction of organ failure by combined markers in patients with acute pancreatitis. Brit J Surg 2005;92:68-75
39. Whitcomb BW, Pradhan EK, Pittas AG, Roghmann M-C, Perencevich EN. Impact of admission hyperglycemia on hospital mortality in various intensive care unit populations. Crit Care Med 2005;33:2772-2777
40. Egi M, Bellomo R, Stachowski E, French CJ, Hart GK, Hegarty C, Bailey M. Blood glucose concentration and outcome of critical illness: The impact of diabetes. Crit Care Med 2008;36:2249-2255

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

Variables*	Diabetes (n=18,990)	Non-diabetes (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 Comorbid 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, d	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 intensive care unit setting.

ERCP: endoscopic retrograde cholangiopancreatography.

Table 2–*The effect of diabetes on the risk of severe attack in patients with acute pancreatitis* *

Severity criteria[†]	Diabetes (n=18,990), %	Non-diabetes (n=37,980), %	Adjusted odds ratio (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)

* 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 acute pancreatitis (alcohol, biliary, both and others) and Charlson Comorbidity Index (0, 1, 2, 3+).

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

Outcomes	Diabetes (n=18,990), %	Non-diabetes (n=37,980), %	Adjusted odds ratio (95% confidence interval)*				
			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)

* Multivariable logistic regression using Generalized Estimating Equations models adjusting for covariates (see below).

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 acute pancreatitis (alcohol, biliary, both and others) and Charlson Comorbidity Index (0, 1, 2, 3+), computed tomography, severity criteria (including intensive care unit 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.

Figure legends

Figure 1. *Study flow diagram*



