Background Diabetes mellitus can occur after acute pancreatitis (AP), but there are currently no tools for evaluating the risk of developing diabetes after an attack of AP. The aim of the study was to develop a nomogram for prediction of new-onset diabetes mellitus after the first attack of AP.

Patients and methods We enrolled 616 patients with first-attack AP. We collected and statistically analyzed demographic data (age, BMI, and duration of hospitalization) and laboratory data (glucose, low-density lipoprotein cholesterol, triglyceride, and cholesterol).

Results Univariate analysis suggested duration of hospitalization ($P = 0.0003$), BMI ($P = 0.0059$), cholesterol ($P = 0.0005$), triglyceride ($P = 0.0005$), hemoglobin ($P = 0.0229$), and glucose ($P < 0.001$) at admission were significantly associated with newly developed diabetes after the first-attack AP. Multivariate analysis showed that age (odds ratio (OR) = 1.01; 95% confidence interval (CI): 1.00–1.03; $P = 0.045$), BMI (OR = 1.06; 95% CI: 1.01–1.12; $P = 0.018$), glucose (OR = 1.07; 95% CI: 1.02–1.12; $P = 0.008$), triglyceride (OR = 1.03; 95% CI: 1.00–1.06; $P = 0.035$), and low-density lipoprotein-cholesterol (OR = 1.18; 95% CI: 1.00–1.38; $P = 0.044$) at admission were important predictors.

Conclusion The nomogram is a potentially clinically useful tool for predicting new-onset diabetes, which is currently clinically unprecedented. This finding is not confined to the patients with severe AP but is also for patients who have recovered from mild AP. The nomogram must to be validated externally.

Original article

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Keywords: acute pancreatitis, diabetes mellitus, nomogram

Introduction

Acute pancreatitis (AP) is a common clinical condition of varying severity [1]. Although AP has classically been considered a self-limiting, reversible disease, there is an expanding body of evidence that suggests the significance of new disturbances in glucose metabolism following AP [2]. A recent comprehensive meta-analysis showed that prediabetes and/or diabetes mellitus (DM) was observed in nearly 40% of the patients following AP [3]. This result challenged the widely accepted view that pancreatic injury is temporary, and that endocrine pancreatic function recovers fully after AP regardless of severity [4–6]. DM can occur after AP [3,7–9], but there remains no consensus regarding the extent of the risk following AP.

DM contributes significantly to all-cause worldwide mortality, attributable to one in 12 adult deaths [10]. DM owing to pancreatic disease, classified as type 3c according to the current classification system, accounts for 5–10% of the western diabetic population [11]. The complication rate with DM was high in patients following pancreatic surgery (28–100%) [12,13] and chronic pancreatitis (CP) (12–80%) [14,15]. However, 70–80% of patients with acquired impaired glucose metabolism following AP did not have CP or pancreatic surgery [8,16]. The risk of diabetes increases two-fold after AP. Therefore, we believe a long-term screening method is needed to evaluate diabetes risk after an attack of AP, regardless of severity [7].

A previous study suggested that pancreatic endocrine insufficiency after AP may be an underestimated problem [17], and risk factors for DM after AP remain elusive [18].

The primary aim of the study was to develop a nomogram for prediction of new-onset DM within 3 months of a first attack of AP without CP or pancreatic surgery. The secondary aim was to identify associated risk factors for DM following a first episode of AP. Our study was better than other research studies whose aim was merely to obtain risk factors for hyperglycemia or DM after AP [3,8,16,19].

Patients and methods

Patients population, data collection, and ethics

This study was a cross-sectional follow-up study including all patients consecutively admitted to the First Affiliated Hospital of Wenzhou Medical University with AP between January 2013 and December 2015. Inclusion criteria were as follows: diagnosis of AP based on international guidelines [20], at least 18 years of age, at least 3-month follow-up, and informed consent.
Exclusion criteria were as follows: more than 72 h after onset of symptoms, recurrent pancreatitis, previous diagnosis of diabetes, history of impaired fasting glucose or impaired glucose tolerance, CP, post-ERCP pancreatitis, malignant gastrointestinal tumor, liver disease, chronic kidney disease, pregnancy, intoxication, and death during admission.

Data collected included personal characteristics (age, sex, BMI, etiology, and alcohol intake), laboratory studies (blood biochemical indicators and complete blood counts), and abdominal imaging.

All patients provided full informed consent before clinical procedures to which they were subjected after study inclusion. This study protocol was approved by the Ethic Committee of the First Affiliated Hospital of Wenzhou Medical University.

Definitions

The diagnosis and the severity of AP were defined based on the 2012 revision of the Atlanta classification and definitions by international consensus [20], where patients must meet two of the following three criteria: (a) abdominal pain, (b) level of serum lipase or amylase at least three times greater than the upper limit of normal, and (c) findings on cross-sectional abdominal imaging consistent with AP. The severity of AP is further categorized into three levels: mild acute pancreatitis, moderately severe AP, and severe acute pancreatitis (SAP). SAP is defined as the presence of persistent organ failure (≥48 h). Organ failure is defined as a Marshall score of at least 2 for at least one of three involved organ systems: cardiovascular, respiratory, and renal [21].

DM is defined by persistent hyperglycemia. Pancreatic diabetes arising from pancreatic disease is now categorized as type 3c diabetes [22]. There are no universally accepted diagnostic criteria for this type. Conceptually, the diagnosis of type 3c diabetes requires the following characteristics: diagnostic criteria for diabetes, disease of the exocrine pancreas (including AP), and diabetes reasonably certain to be secondary to exocrine pancreatic disease [23]. According to the 1999 WHO classification, DM was defined as a fasting blood glucose of at least 7.0 mmol/l (126 mg/dl) or 2 h after oral glucose tolerance test of at least 11.1 mmol/l (200 mg/dl) [24]. These definitions accorded with those defined by a meta-analysis of 24 prospective clinical studies [3].

BMI (kg/m²) was determined using a digital medical scale with stadiometer. For height measurement (cm), study participants were asked to remove their shoes and head attire. For weight measurement (kg), patients were asked to remove shoes, jacket, belt, and watches and to empty their pockets [25].

Statistical analysis

A Shapiro–Wilk test was used to evaluate whether the continuous data showed a normal distribution. According to its results, continuous values were expressed by median and interquartile range and were compared using one-way analysis of variance or the Kruskal–Wallis nonparametric test. Categorical values were described by count and proportions and compared by the χ² test or Fisher’s exact test.

All variables were included as eligible factors in a forward-conditional stepwise logistic regression analysis. For this analysis, the conditional probabilities for stepwise entry and removal of a factor were 0.05 and 0.10, respectively [26]. Odds ratios (ORs) were calculated, with 95% confidence interval (CI) [27]. We generated a nomogram based on the multiple logistic regression analysis. We evaluated model calibration, representing the link between predicted and observed risk, by plotting the predicted-versus-observed deciles of predicted risk, and checked the result by Hosmer–Lemeshow goodness-of-fit test [28,29]. A Hosmer–Lemeshow test with greater than 0.05 indicates no significant differences between observed data and predicted data.

Differences were considered to be statistically significant if the two-tailed P value was less than 0.05.

Results

Patient characteristics

The median age of the 616 patients included in the study was 47 (37–63) years. Proportion of males was 62.7% (386). Demographic and clinical characteristics are displayed in Table 1. AP was most commonly biliary in nature. Degrees of AP were mild, 507 (76.70%); moderate/severe, 93 (14.07%); and severe, 61 (9.23%). Of the 31 (5.03%) patients who developed persistent organ failure, multiple-organ failure was noted in 25 (4.06%). The male and female drinking rates were 0.171 and 0.870, respectively. Eleven patients with who AP died following admission were excluded from our study. No patient died during follow-up.

Univariate and multivariate analyses

Using univariate and multivariate analyses, we tested 22 variables considered relevant to the presence of new-onset diabetes 3 months following the first episode of AP. Univariate analysis suggested that duration of hospitalization (P = 0.0005), BMI (P = 0.0059), cholesterol (P = 0.0005), triglyceride (P = 0.0005), hemoglobin (P = 0.0229) and glucose (P < 0.001) at admission were significantly associated with newly developed diabetes after the first-attack AP. The male and female drinking rates were inconsistent (P = 0.004), so the stratification analysis was performed. There was no significant difference between alcoholic AP and nonalcoholic AP in male and female newly diabetics (P = 0.7700). The factors on long-term alcohol intake of male and female patients were not statistically different (P = 0.2430 and 0.5650; Table 2).

Table 1. Demographic and clinical characteristics of 616 patients with acute pancreatitis

| Characteristics                                      | Data               |
|------------------------------------------------------|--------------------|
| Age [median (IQR)] (years)                           | 47 (37–63)         |
| Male [N (%)]                                        | 386 (62.66)        |
| Etiology (%)                                        |                    |
| Biliary                                              | 42.69              |
| Alcohol                                              | 13.96              |
| Hypertriglyceridemia                                | 4.22               |
| Food                                                 | 3.25               |
| Idiopathic                                           | 35.88              |
| Etiology of alcohol (male) [N (%)]                   | 66 (17.10)         |
| Etiology of alcohol (female) [N (%)]                 | 20 (8.70)          |
| BMI (IQR)                                            | 23.53 (21.07–26.12) |
| Duration of hospitalization (IQR)                    | 10 (7–14)          |
| Combined with hypertension [N (%)]                   | 141 (22.89)        |
| Single-organ failure [N (%)]                         | 31 (5.03)          |
| Multiple-organ failure [N (%)]                       | 25 (4.06)          |
| SAP [N (%)]                                         | 61 (9.90)          |

IQR, interquartile range; SAP, severe acute pancreatitis.
Logistic regression

Multivariate analysis by logistic regression identified the following five independent variables as predictors of persistent new-onset diabetes after the first-attack of AP: age (OR = 1.01; 95% CI: 1.00–1.03; P = 0.045), BMI (OR = 1.06; 95% CI: 1.01–1.12; P = 0.018), glucose (OR = 1.07; 95% CI: 1.02–1.12; P = 0.008), triglyceride (OR = 1.03; 95% CI: 1.00–1.06; P = 0.035), and low-density lipoprotein-cholesterol (LDL-C) (OR = 1.18; 95% CI: 1.00–1.38; P = 0.044).

Logistic regression and Hosmer–Lemeshow test

The accuracy of the logistic regression was evaluated by producing a calibration plot. Calibration plots indicate adequate predicted probabilities against observed proportions of incidence of new-onset diabetes after the first-attack pancreatitis (Fig. 1). The Hosmer–Lemeshow test of 0.3555 was greater than 0.05, indicating that the logistic regression fits the data better.

Nomogram

A predictive nomogram based on the logistic regression model was developed to predict probability of new-onset diabetes after the first-attack of pancreatitis (Fig. 2). Age, BMI, glucose, triglyceride, and LDL-C at admission were included in the nomogram, with probability of new-onset diabetes as the predicted outcome. It is a graphical version of the statistical model that reveals the relationship between the high-risk predictors and new-onset diabetes in proportional scale. In addition, the nomogram had a C-index of 0.686 (approximate to 0.7; Fig. 2). Nomogram C-index of 0.7 can verify the accuracy of the nomogram.

Discussion

To our knowledge, this is the first study to develop a nomogram for predicting new-onset DM within 3 months after a first-attack of AP. By logistic regression analysis and nomogram, BMI, age, glucose, triglycerides, and LDL-C at admission were significantly associated with increased risk of DM. The Hosmer–Lemeshow test (P = 0.3555) suggests the logistic regression was credible.
Nomograms visually display the results of multivariate modeling, unlike complex statistical models [30]. The verification method is convenient, and we can calculate the risk of diabetes in 1 min. Having age of 40 years, BMI of 23, triglyceride of 1 mmol/l, glucose of 11 mmol/l, and LDL-C of 3.15 mmol/l, a patient after AP has probability of DM of 2.5% by nomogram. With a total score of more than 15, the risk of DM significantly increases. In addition, the C-index verified the accuracy of nomogram.

We identified LDL-C as the largest predictor of new-onset diabetes after AP by the logistic analysis and nomogram. Kunutsor et al. [31] showed that the ratio of LDL-C/high-density lipoprotein-cholesterol was associated with higher prevalence of diabetes. There was hardly any literature study pointing out the direct intrinsic link between LDL-C and diabetes. However, we can establish an indirect correlation through obesity, alcohol intake, and abnormal glucose [32–34]. With the increase of BMI, the risk of developing DM increased proportionally on our nomogram, as previous literature studies [24,35,36]. Lipid metabolism (including LDL-C) had connection with alcohol consumption, and increased alcohol consumption (>200 g/week) was associated with increased LDL and triglycerides [34,37,38]. Moreover, most studies reported that AP caused by the excessive consumption of alcohol are as follows: daily average drinking in our study is low, and low drinking may have no significant correlation with DM. We also do not exclude the possibility of concealing the history of drinking.

Age proportionally increased the risk of developing DM after AP, according to our nomogram. Our result was similar to the studies of Huang et al. [9] and Pendharkar et al. [40]. According to our nomogram, with the increase of the glucose, risk of developing DM increased proportionally. Higher plasma glucose may represent a physiological response to a more severe form of pancreatitis in these patients [31], leading to a higher incidence of DM [8,41].

The choice of appropriate follow-up time is a matter of debate. A meta-analysis of 24 prospective studies on patients with first-episode AP without pancreatic surgery demonstrated that the risk of diabetes increases by at least two-fold at 5 years, compared with the risk at 12 months [3]. However, Shen et al. [7] showed that HR of DM after AP gradually decreased over time. Based on the feasibility of follow-up and sample size of our study increasing credibility, we chose 3 months as the follow-up interval for new-onset DM following AP.

To our knowledge, this is the first study to evaluate the possibility of DM after first AP using a predictive nomogram. The strength of this study included adequate sample size and excluded patients with recurrent AP, CP, and pancreatic surgery, which also led to endocrine insufficiency [7,14,15]. Furthermore, our study avoided relying
on diagnostic discharge codes for AP, the use of which results in at least 20% misclassification bias [40].

However, some limitations deserve comments. First, we did not test blood insulin, proinsulin, and C-peptide levels, which represent the true endocrine reserve of pancreas. Second, the factor on long-term drinking was qualitative data, so the analysis of this factor is not accurate enough.

Conclusion

We confirmed that AP is a major risk factor for diabetes (a rate of 20.0%). Age, BMI, glucose, triglyceride, and LDL-C at admission may predict development of DM following AP. This finding also holds for patients who have recovered from mild AP to SAP. Our nomogram has potential as a predictive tool for pancreatic diabetes, but it needs to be validated externally.

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Conflicts of interest

There are no conflicts of interest.

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