Research Square

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Metabolic Syndrome Components and Acute pancreatitis: A Case-Control Study in China

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Abstract

Background: Acute pancreatitis (AP) is a common inflammatory disorder of pancreas. Recent evidence has shown that metabolic syndrome was positively correlated with the severity of AP. However, only few studies have revealed the relationship between metabolic syndrome and the occurrence of AP. We therefore elucidated the association between the metabolic syndrome components and the incidence rate of AP.

Methods: A hospital-based case-control study was conducted. 705 patients admitted to our hospital from January 2016 to December 2018 were included in the study. Subjects were divided into case and control group according to their diagnosis: (1) According to the revised Atlanta classification from 2012, patients diagnosed as AP were enrolled into case group. (2) Patients without history of AP or any disease related to metabolic syndrome were allocated into control group. Controls were matched to cases individually by sex and age (control/case ratio=1). Risk factors were determined by univariate and multivariate logistic regression analyses.

Results: The incidence rate of metabolic syndrome with AP patients was 30.9%, which was more frequent than controls (13.2%) (OR=2.975; 95%CI 1.947-4.548, p<0.001). In multivariate regression analysis, histories of smoking or alcohol drinking, biliary stone were important predictors of AP. Besides, occurrence of AP was significantly associated with total cholesterol (TC) (OR=1.831; 95%CI 1.137-2.948, p=0.013), triglyceride (TG) (OR=2.058; 95%CI 1.332-3.179, p=0.001), fasting plasma glucose (FPG) (OR =2.345; 95%CI 1.395-3.940, p=0.001), as well as low values of apolipoprotein A (Apo A) (OR =0.247; 95%CI 0.146-0.416, p<0.001).

Conclusion: Metabolic syndrome and its components portend high risks of occurrence of AP.

Introduction

Acute pancreatitis (AP) is a pancreatic inflammatory disorder and may cause life-threatening consequences due to severe inflammatory responses[1]. According to a survey, the annual incidence rate of AP has increased by 100% over past several decades [2]. This has posed a great threat to human health and become the one of the largest contributors to aggregate medical cost[3]. Thus, there is an urgent need for setting up new strategies to impede the increasing trend. The main pathogenic causes of AP are gallstones and alcohol. Other factors, such as smoking and genetic factors, are also considered to be risk factors[3]. However, pathogenic immune mechanism of AP remains elusive, and the potential factors related to the stimulus of inflammation are still under investigation.

- Due to the huge economic development and social progress made in China over past decades, lifestyle and daily diet of Chinese people have changed substantially. This in turn has led to the high prevalence of metabolic syndrome in China (27.9% in men and 26.8% in women) and has caused serious public health problems[4]. Metabolic syndrome is defined as four interconnected factors including hyperglycemia, hyperlipidemia (particularly raised triglyceride[TG] and low high density

lipoprotein[HDL]), obesity and hypertension. It is generally considered as a risk factor of cardiovascular diseases[5]. Although there is still no universally accepted mechanism of metabolic syndrome[6], the best evidence suggests that the four components of metabolic syndrome may be intercorrelated with each other by sharing common pathophysiological processes. These processes mainly consist of insulin resistance, visceral adiposity, atherogenic dyslipidemia and endothelial dysfunction[7]. Besides, given the fact that the four components are more likely to appear together more than might be expected by chance, metabolic syndrome should thus be considered as an overall concept. It can gradually lead patients to proinflammatory state that associates with a series of diseases, such as venous thrombosis and psoriasis[7–9]. Since it is well believed that there is an interrelation between metabolic syndrome and inflammation[10, 11], we suspect that metabolic syndrome may also have a significant impact on AP. Although some studies have demonstrated that metabolic syndrome was positively associated with the severity of AP[1, 12], there is still lack of data showing the relationship between metabolic syndrome and the occurrence of AP in Chinese population. The study therefore investigated the association of metabolic syndrome and the occurrence of AP in Chinese population.

Materials And Methods

Study population

A hospital-based case-control study was conducted. 705 patients (349 AP patients and 356 controls) admitted to our hospital from January 2016 to December 2018 were included in the study. According to revised Atlanta classification from 2012[13], AP was defined if at least two of the following three criteria were presented: acute attack of severe upper abdominal pain with or without radiating to the back; serum amylase or lipase elevation at least 3 times above upper limit of normal level; and typical acute pancreatitis imaging found on computed tomography (CT) scan. Only the patients with first attack of AP would be included while patients with relapse of AP or chronic pancreatitis were excluded. The controls were selected from patients admitted to our hospital in the same period and frequency-matched to cases by sex and exact age. Control subjects were selected from patients who had excluded AP history in terms of clinical manifestation, laboratory tests, and abdominal CT scan. The participants who had histories of any cardiovascular disease (except hypertension) or psoriasis would not be enrolled into the two groups. Lastly, subjects would be excluded if they were younger than 18 years, pregnant, undergone surgery within 1 month or had cancer history.

Methods

Data was collected by researchers who were not informed of the detailed information of the study until collection completed. Collected data was from computer-based case report and would be checked by another two researchers to ensure there were no inconsistencies or errors. The following data of patients would be collected: sex, age, smoking history, alcohol drinking history (> 14 drinks/week in women or > 21 drinks/week in men), biliary stone, history of hepatitis B or hepatitis C, body mass index (BMI), blood

pressure and laboratory tests including total cholesterol (TC), TG, HDL, low density lipoprotein (LDL), apolipoprotein A (Apo A), apolipoprotein B (Apo B), fasting plasma glucose (FPG). BMI was calculated as body weight (kg) divided by square of the height (m). Blood pressure was measured by a mercury sphygmomanometer when patients were in a supine position and after 20 min rest. The blood sample was collected from median cubital vein of each patient after eight-hour fasting. The fasting venous blood was collected in polystyrene tubes and would be rapidly transmitted to the laboratory to ensure the accuracy of our indexes. The study was conducted according to Declaration of Helsinki and approved by institutional research board of Jinshan hospital (IEC-2020-S21). The informed consent was waived.

Metabolic Syndrome Components

The diagnostic criteria for metabolic syndrome were defined according to [14] and modified by Asia–Pacific criteria[15]. The criteria include (1) hypertension (blood pressure ≥ 130/85 mmHg or ongoing anti-hypertensive treatment). (2) hyperlipidemia (TG ≥ 150 mg/dL or HDL ≤ 40 mg/dL in men and 50 mg/dL in women or ongoing anti-lipidemic treatment). (3) hyperglycemia (FPG ≥ 110 mg/dL, previously physician-diagnosed type 2 diabetes mellitus [T2DM] or ongoing antidiabetic treatment). (4) obesity (BMI ≥ 25 kg/m² or waist circumference ≥ 90 cm for men or 80 cm for women).

Statistical Analysis

Student's t-test was used to analyze the differences between two independent groups. Fisher's exact test or chi-square test were used to compare different categorical variables. Univariate logistic regression analysis was used to preliminarily assess whether these individual variables were predictive factors of AP occurrence. Odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated. In order to evaluate the putative potential risk factors associated with AP, multivariate logistic regression was used to further test the risk factors with p value < 0.1 in univariate logistic regression. The accuracy of each marker on predicting the occurrence of AP was assessed by using Receiver operating characteristic (ROC) curves. P value < 0 .05 was defined as statistically significant. IBM SPSS v22. and MedCalc statistical software package, version 10 (MedCalc, Mariakerke, Belgium) were used for statistical analysis.

Results

Characteristics of Study Subjects

Based on the inclusive and exclusive criteria, 705 subjects with 349 AP patients and 356 non-AP patients were enrolled in our study. Table 1 showed the characteristics of the subjects. In univariable analysis, we found that there were no statistically significant differences between cases and controls with respect to age (p = 0.989), gender (p = 0.923), hepatitis C (p = 0.349), LDL (p = 0.447) and Apo B (p = 0.617). However, we noted that AP patients were associated with history of cigarette smoking(p < 0.001), alcohol drinking (p < 0.001), biliary stone (p < 0.001), hepatitis B (p = 0.049), obesity (p = 0.002), higher values of TC (p < 0.001), TG (p < 0.001), HDL (p < 0.001), Apo A (p < 0.001), FPG (p < 0.001) and proportion of hypertension history (p = 0.012) compared to controls.

Table 1
Risk factors for acute pancreatitis: univariate logistic regression analysis

	Controls n (%)	Cases n (%)	*p*	Crude OR (95%CI)
Mean age, years (SD)	51.21 ± 15.898	51.19 ± 15.940	0.989	1.000 (0.991–1.009)
Gender				
Female	140 (39.3)	136 (39.0)	1 (reference)	
Male	216 (60.7)	213 (61.0)	0.923	1.015 (0.750–1.374)
Smoking history				
No	294 (82.6)	224 (64.2)	1 (reference)	
Yes	62 (17.4)	125 (35.8)	0.000	2.646 (1.864–3.757)
Alcohol drinking history				
No	303 (85.1)	248 (71.1)	1 (reference)	
Yes	53 (14.9)	101 (28.9)	0.000	2.328 (1.604–3.379)
Biliary stone				
No	348 (97.75)	248 (71.1)	1 (reference)	
Yes	8 (2.25)	101 (28.9)	0.000	17.716 (8.469–37.059)
Hepatitis B				
No	339 (95.2)	342 (98.0)	1 (reference)	
Yes	17 (4.8)	7 (2.00)	0.049	0.408 (0.167–0.997)
Hepatitis C				
No	353 (99.16)	348 (99.71)	1 (reference)	
Yes	3 (0.84)	1 (0.29)	0.349	0.338 (0.035–3.226)
BMI				
≥25 kg/m^2	236 (66.3)	192 (55.0)	1 (reference)	

	Controls n (%)	Cases n (%)	*p*	Crude OR (95%CI)
≥25 kg/m^2	120 (33.7)	157 (45.0)	0.002	1.608 (1.186–2.181)
TC				
220 mg/dL	295 (82.9)	243 (69.6)	1 (reference)	
≥220 mg/dL	61 (17.1)	106 (30.4)	0.000	2.110 (1.475–3.017)
TG				
150 mg/dL	259 (72.8)	187 (53.6)	1 (reference)	
≥150 mg/dL	97 (27.2)	162 (46.4)	0.000	2.313 (1.690–3.167)
HDL				
40 mg/dL (M) or 50 mg/dL (F)	173 (48.6)	216 (61.9)	1 (reference)	
≥40 mg/dL (M) or ≥50 mg/dL (F)	183 (51.4)	133 (38.1)	0.000	0.582 (0.431–0.786)
LDL				
140 mg/dL	271 (76.1)	257 (73.6)	1 (reference)	
≥140 mg/dL	85 (23.9)	92 (26.4)	0.447	1.141 (0.812–1.605)
Apo A				
1 g/L	35 (9.8)	119 (34.1)	1 (reference)	
≥1 g/L	321 (90.2)	230 (65.9)	0.000	0.211 (0.139–0.319)
Apo B				
1 g/L	256 (71.9)	245 (70.2)	1 (reference)	
≥1 g/L	100 (28.1)	104 (29.8)	0.617	1.087 (0.785–1.505)
FPG				
110 mg/dL	319 (89.6)	256 (73.4)	1 (reference)	
≥110 mg/dL	37 (10.4)	93 (26.7)	0.000	3.209 (2.112–4.876)

	Controls n (%)	Cases n (%)	*p*	Crude OR (95%CI)
Hypertension				
No	227 (63.8)	190 (54.4)	1 (reference)	
Yes	129 (36.2)	159 (45.6)	0.012	1.473 (1.089–1.991)

Effect of Metabolic Syndrome Components on AP

After sex and age adjustment, the multivariate logistic regression models revealed that AP patients were associated with smoking history, alcohol drinking history, biliary stone, elevated level of TC, TG, FPG, lower values of Apo A (OR = 3.106; 95% CI 1.865–5.172, $p < 0.001$; OR = 1.923; 95% CI 1.133–3.262, $p = 0.015$; OR = 32.921; 95%CI 14.648–73.992, $p < 0.001$; OR = 1.831; 95% CI 1.137–2.948, $p = 0.013$; OR = 2.058; 95% CI 1.332–3.179, $p = 0.001$; OR = 2.345; 95% CI 1.395–3.940, $p = 0.001$ and OR = 0.247; 95% CI 0.146–0.416, $p < 0.001$, respectively). However, obesity was not observed to be associated with the occurrence of AP after adjustment ($p = 0.186$) (shown in Table 2). After adjusted by age, gender, smoking history, alcohol drinking history and biliary stone, the prevalence of metabolic syndrome were more common in AP patients (30.9%) than those without AP (13.2%) (OR = 2.975; 95% CI 1.947–4.548, $p < 0.001$) (shown in Table 3). As shown in Fig. 1, for all AP patients, raised value of TG, low Apo A and FPG predicted AP with statistical significance ($p < 0.001$, $p < 0.001$, $p < 0.001$). Their AUC are 0.620, 0.679 and 0.767 respectively. Among three indicators, FPG had the best sensitivity (67.54%) and TG had the best specificity (90.17%) when the indicators were at their best cut-off value (shown in Table 4).

Table 2
Multivariate Analysis Examining the Components of the Metabolic Syndrome

Adjusted model	*p*	Adjusted OR (95% CI)
Age	0.026	1.017 (1.002–1.032)
Gender		
Male	0.006	0.517 (0.324–0.827)
Smoking	0.000	3.106 (1.865–5.172)
Alcohol drinking	0.015	1.923 (1.133–3.262)
Biliary stone	0.000	32.921 (14.648–73.992)
Hepatitis B	0.124	0.417 (0.137–1.271)
BMI (≥ 25 kg/m2)	0.186	1.312 (0.877–1.963)
TC	0.013	1.831 (1.137–2.948)
TG	0.001	2.058 (1.332–3.179)
HDL	0.511	0.869 (0.573–1.320)
Apo A	0.000	0.247 (0.146–0.416)
FPG	0.001	2.345 (1.395–3.940)
Hypertension	0.113	1.399 (0.924–2.118)
Abbreviations:		
TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo A, apolipoprotein A; FPG, fasting plasma glucose.		
SI conversion factors: To convert cholesterol to millimoles per liter, multiply by 0.0259; FPG to millimoles per liter, multiply by 0.0555; HDL, LDL, TG to millimoles per liter, multiply by 0.0113.		

Table 3
Association Between the Metabolic Syndrome and AP

	Prevalence of Metabolic syndrome(%)	Unadjusted OR (95%CI)	*p*	Adjusted* OR (95%CI)	*p*
AP	108 (30.9)	2.946 (2.011–4.315)	0.000	2.975 (1.947–4.548)	0.000
Control	47 (13.2)				
*Adjusted by age, sex, smoking history, alcohol drinking history and biliary stone. OR indicates odds ratio; CI: confidence interval. **Abbreviations**: AP, acute pancreatitis.					

Table 4
Identification of TG, Apo A and FPG in the patients with AP

Variable	AUC	p-value	Cut-off	Sensitivity(%)	Specificity(%)	+LR	-LR
TG	0.620	0.000	2.47	39.08	90.17	3.98	0.68
Apo A	0.679	0.000	1.15	63.16	66.85	1.91	0.55
FPG	0.767	0.000	6.39	67.54	78.93	3.21	0.41

Abbreviations: TG, triglyceride; Apo A, apolipoprotein A; FPG, fasting plasma glucose.

Association Between the Number of Metabolic Syndrome Components and AP

As shown in Fig. 2, the incidence rate of AP obviously increased when there were more than three metabolic syndrome components. Moreover, the incidence rate of AP significantly declined when there was no metabolic syndrome component.

Discussion

To our knowledge, this is the first case-control study demonstrating the relationship between metabolic syndrome and occurrence of AP in Asian population. Our results showed that metabolic syndrome was a risk factor of AP. Among metabolic components, we revealed that the increased values of TC, TG, FPG and decreased values of Apo A were independently associated with AP.

Hyperglycemia has been considered to be associated with AP for decades[16]. However, only few studies have shown higher incidence rate of AP patients with hyperglycemia[17–20]. Our results revealed that hyperglycemia would lead to a 2.345-fold increased risk of AP. Moreover, Shih-Wei Lai et, al observed a significant reduction of AP risk if patients with T2DM received anti-diabetic treatment. This further supported a causal relationship between hyperglycemia and AP[20]. Although the exact mechanism between hyperglycemia and AP remains unclear, several underlying biological theories have been proposed. High plasma glucose enhances mitochondria oxidative stress by promoting the production of reactive oxygen species(ROS) and lipid oxidation through cytosolic Ca^{2+} accumulation[21–23]. Meanwhile, owing to the dysfunction of Beta cell and resultant hyperinsulinemia, the inhibitory hormone named somatostatin may lose its sensitivity to Beta cell, which may be an important factor to induce AP[24]. Moreover, insulin resistance, as a crucial pathophysiological factor of hyperglycemia, its involvement in AP development was reported. Various proinflammatory factors or cytokines were activated due to insulin resistance, including Nuclear factor κB (NF κB), Tumour necrosis factor α (TNF-α), amylin and interleukin-6, and these proinflammatory factors may be responsible for the initiation and progression of AP[25–29].

It is well known that hypertriglyceridemia is associated with the morbidity and mortality of AP[30–32]. Our study showed TG had a 2.058-fold increased risk of AP compared to controls. Furthermore, we found

that there were 1.831-fold increases and 0.247-fold decreases in risk associated with TC and Apo A, which demonstrated that atherogenic lipid profiles also participated in the development of AP. Triantafilou M et, al reported that cholesterol may trigger the inflammatory responses that could lead to chronic inflammation and insulin resistance via TLR4, and ultimately causes lysosomal damage, ROS generation and proinflammatory cytokines secretion[33, 34]. This theory may explain why acinar injury would be induced by hypercholesterolemia through inflammation response. Furthermore, as lipoprotein, HDL often opposes cholesterol accumulation and reduces inflammation by ATP-binding cassette transporter A1(ABCA1) pathway[35]. This ability may be impaired if Apo A is oxidized by macrophage myeloperoxidase (MPO). Shao B et, al reported the impaired function of HDL and Apo A in patients with atherosclerosis[36], which may be similar in AP. However, our results only showed that the value of Apo A was negatively associated with the incidence rate of AP while we did not observe the association between HDL and AP. Based on our present study, it is hard to tease out the exact role of HDL in AP. In future studies, it will be important to find out the exact function that HDL and Apo A exert in AP development.

Nowadays obesity is considered as a global pandemic which poses great threat to human health. Some studies have shown that obesity was positively correlated with severity of AP[37, 38, 12]. However, due to the paucity of studies between obesity and incidence of AP, their relationship has been a matter of dispute. Blomgren et al. found that the crude risk ratio (RR) between obesity and occurrence of AP was 1.8 (95% CI:1.3 to 2.6) while the author did not display the results after adjustment[39]. Contrary to previous beliefs, our current study did not find an association between BMI and AP ($p = 0.186$), which is consistent with a recent large scale prospective cohort study (RR = 1.02, 95%CI: 0.68 to 1.53)[40]. In animal model, obesity was shown related to an inflammatory status by secreting proinflammatory cytokines such as TNF and interleukin-6[41]. Moreover, the level of adiponectin, an anti-inflammatory cytokine, will be reduced under an obesity environment. Therefore, according to our results, we suppose that obesity may aggravate the severity of AP but is not enough to initiate the development of AP without other risk factors in a non-AP person.

Limitations of our study are as followings: (1) Our study is a retrospective hospital-based case-control study, which may inevitably produce selection bias, especially on control subjects. (2) Although we found strong association between metabolic syndrome components and AP, we did not evaluate the effect of treatment of each component on individual, which may have an impact on the results. Major strengths are as followings: (1) This is the first study to illustrate the association between metabolic syndrome and development of AP in Asian population. (2) Given the completeness of behavior and epidemiologic data, we can ensure the accuracy of clinical diagnosis and high quality of data and minimize the recall bias.

Conclusion

The study revealed that patients with metabolic syndrome portends high incidence rate of AP. For its components, high level of TC, TG, FPG and low value of Apo A were independently associated with development of AP. Since metabolic syndrome can be treated by lifestyle alterations or pharmacological

treatment, we are looking forwards to a new, simple and effective methods to impede the increasing incidence rate of AP.

Abbreviations

AP: Acute pancreatitis

BMI: Body mass index

TC: Total cholesterol

TG: Triglyceride;

HDL: High density lipoprotein

LDL: Low density lipoprotein

Apo A: Apolipoprotein A

Apo B: Apolipoprotein B

FPG: Fasting plasma glucose

Declarations

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Statement of Ethics

Since it is a retrospective study and did not involve any experimental maneuver, we have no ethical conflicts to disclose.

Disclosure Statement

There are no conflicts of interest to declare in the study.

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Author Contributions

Mr. Peilong Sun proposed the study. Mr. Zhemin Shen and Ms. Xueqiao Wang contributed equally to the article in the aspects of drafting work as well as collecting, analyzing and interpreting the data; Mr. Zili Zhen and Mr. Yao Wang made essential contribution to the manuscript.

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Figures

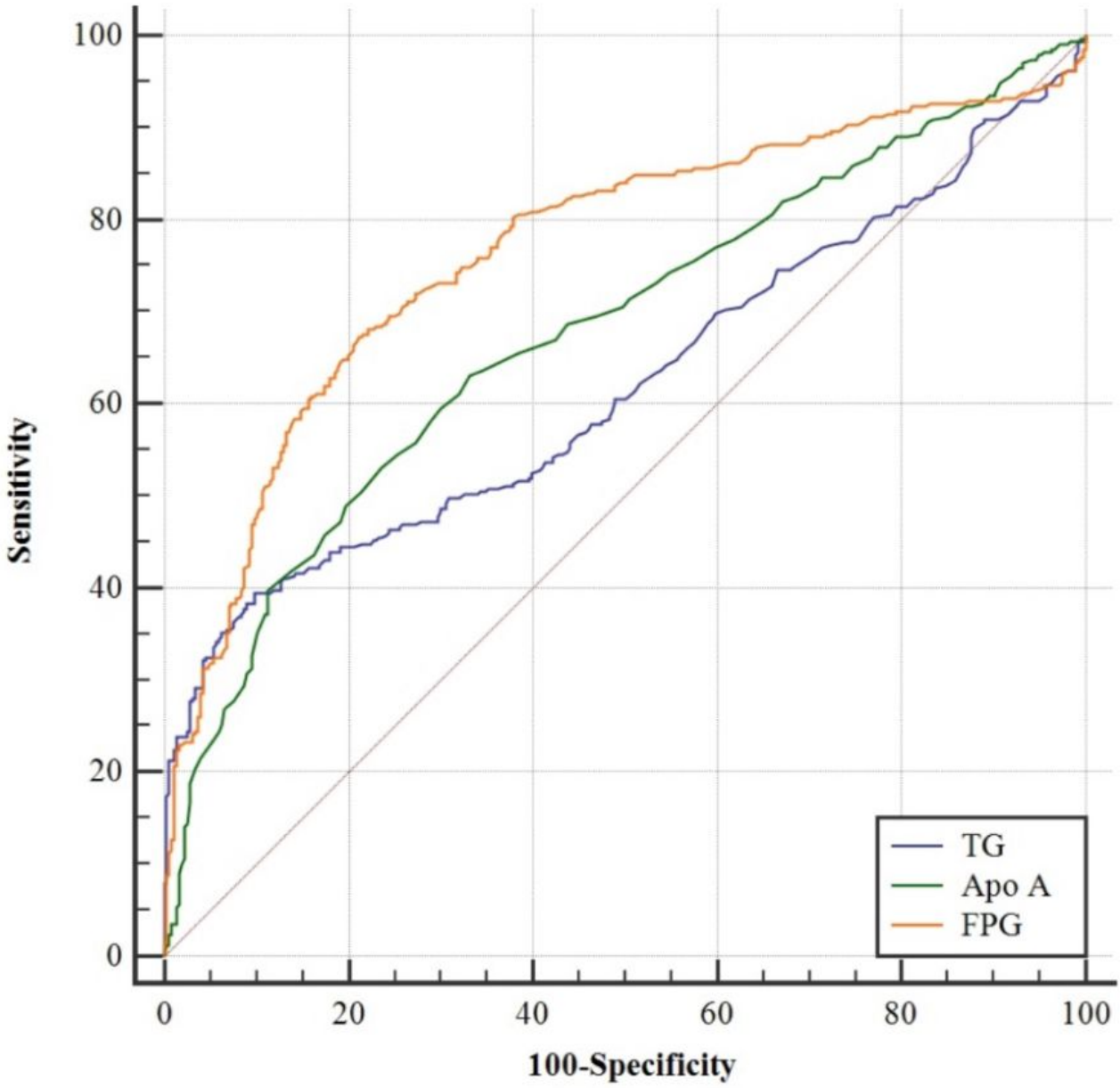

Figure 1

Receiver operating characteristic (ROC) curve analysis for predicting the occurrence of acute pancreatitis by TG, Apo A and FPG in the estimation cohorts. Abbreviations: TG, triglyceride; Apo A, apolipoprotein A; FPG, fasting plasma glucose.

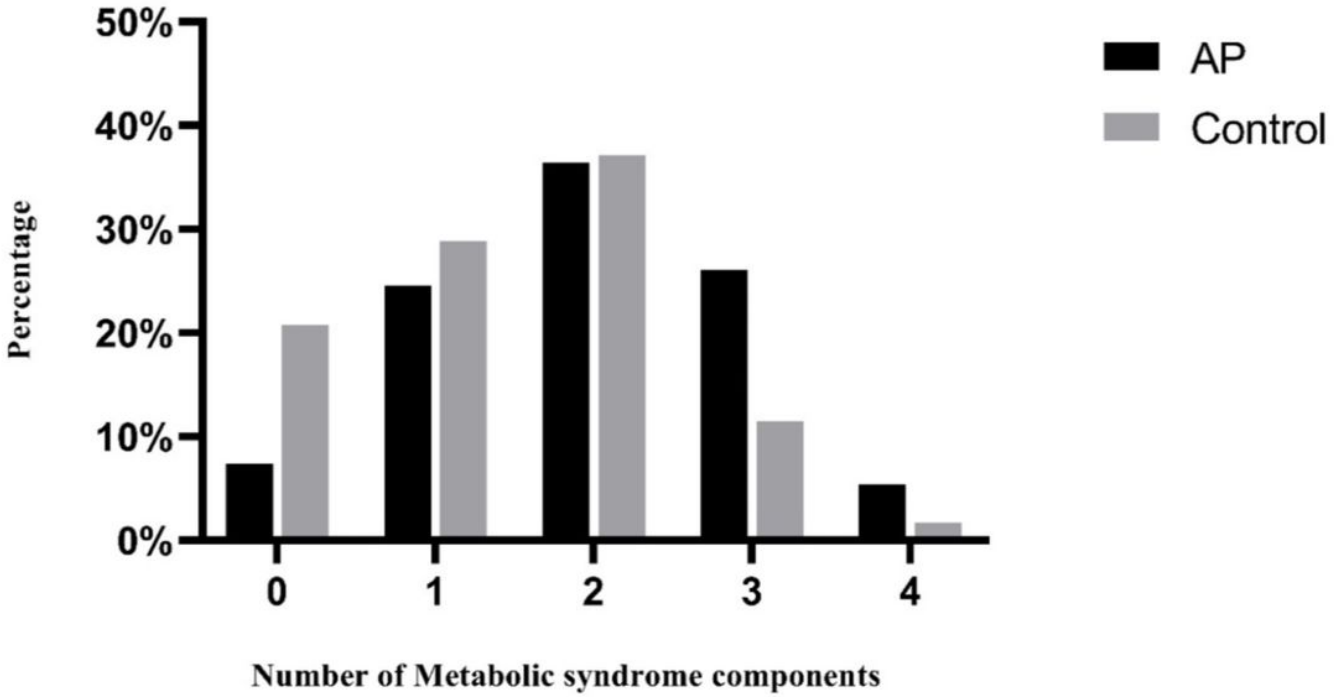

Figure 2

The number of Metabolic Syndrome components in relation to the severity of AP. Abbreviations: AP, acute pancreatitis.