

Received: 2016.07.02
Accepted: 2016.07.21
Published: 2017.02.26

Risk Factors for Worsening of Acute Pancreatitis in Patients Admitted with Mild Acute Pancreatitis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Source of support: This study was supported by the Science and Technology Project of Wenzhou city (Grant No. 2015Y0069)

Background: The aim of the present study was to investigate risk factors for developing more severe pancreatitis, including moderately severe (MSAP) and severe acute pancreatitis (SAP), in patients admitted with mild acute pancreatitis (MAP).

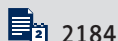
Material/Methods: Patients admitted with MAP to our hospital from March 2013 to May 2016 were included and prospectively evaluated. Possible risk factors for developing MSAP or SAP were age, blood glucose level on admission, etiology, sex, Ranson score, amylase level, Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores, C-reactive protein (CRP) level, serum calcium level, visceral fat area (VFA), body mass index (BMI), whether this was the first episode of AP, and method of administration of octreotide. The effects of variables for developing MSAP or SAP were evaluated using univariate and multivariate logistic regression models. Mortality, hospital duration, and rate of ICU transfer of patients were compared between patients who developed MSAP or SAP and patients who did not.

Results: A total of 602 patients admitted with MAP were recruited into this study (256 men and 346 women). Seventy-four patients (12.3%) developed MSAP or SAP. According to univariate logistic regression analyses, the results indicated that there were 5 significant differences between patients who developed MSAP or SAP and those who did not: VFA ($>100 \text{ cm}^2$) ($p=0.003$), BMI ($\geq 25 \text{ kg/m}^2$) ($p=0.001$), Ranson score ($p=0.004$), APACHE-II (≥ 5) ($p=0.001$), and blood glucose level on admission ($>11.1 \text{ mmol/L}$) ($p=0.040$). Further multivariate logistic regression analyses revealed that BMI ($\geq 25 \text{ kg/m}^2$) ($p=0.005$), APACHE-II (≥ 5) ($p=0.001$), and blood glucose level on admission ($>11.1 \text{ mmol/L}$) ($p=0.004$) were independent risk factors for developing MSAP or SAP in patients admitted with MAP. Moreover, patients who developed MSAP or SAP had a mortality rate of 5.4%.

Conclusions: Significant risk factors for developing MSAP or SAP in patients admitted with MAP included BMI ($\geq 25 \text{ kg/m}^2$), APACHE-II (≥ 5), and blood glucose level on admission ($>11.1 \text{ mmol/L}$). These factors should be used in the prediction of more severe pancreatitis in patients admitted with MAP.

MeSH Keywords: **Obesity • Pancreatitis • Risk Factors**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/900383>



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Background

Acute pancreatitis (AP) involves sterile inflammatory responses, with complex pathophysiology. Initial local autodigestive inflammatory processes in the pancreas can progress to a systemic inflammatory response and multi-organ failure [1]. AP is now classified into mild acute pancreatitis (MAP), moderately severe acute pancreatitis (MSAP), and severe acute pancreatitis (SAP), according to the new Atlanta Classification of 2012 revision [2]. These definitions of severity are based on the presence or absence of persistent organ failure and local and systemic complications [2]. MAP usually resolves within several days to a week, often without mortality. MSAP resolves more slowly, and it may require interventions and longer hospitalization, with increased morbidity and mortality (<8%) [2,3]. SAP is defined by persistent organ failure, and patients usually have 1 or more local and/or systemic complication. Patients with SAP are at a markedly increased risk (36–50%) of death [2–4].

Previous data showed that about 15% of AP patients first admitted with MAP developed MSAP or SAP [5]. For such patients, the importance of an accurate, early prediction of severity cannot be overemphasized, as rapid identification and resuscitation of patients with impending MSAP or SAP are essential for a favorable outcome and increased chance of survival [6].

However, the mechanisms by which MAP develops into MSAP or SAP remain unclear and may involve many risk factors. Many isolated prognostic parameters and scoring systems have been developed to enable accurate and early prediction of MSAP or SAP [7,8]. However, there is a lack of reports about risk factors for developing MSAP or SAP in patients admitted with MAP. We analyzed information from patients admitted with MAP to explore the risk factors for developing MSAP or SAP in patients admitted with MAP. Furthermore, we studied the outcomes of patients admitted with MAP who developed more severe pancreatitis.

Material and Methods

Patients

The study was conducted in our hospital from March 2013 to May 2016. The time interval from symptom onset to hospitalization was less than 48 hours. All enrolled patients in our study were MAP patients when admitted. The characteristics of patients, including sex, BMI, age, etiology, and other factors, were recorded in every patient at enrollment. Each enrolled patient was evaluated according to the Acute Physiology and Chronic Health Evaluation (APACHE-II scores) [9] and the Ranson scores [10]. An abdominal computed tomography (CT) scan was performed in every patient at enrollment. Progression

of MAP to MSAP or SAP was recorded. Clinical outcomes, including death, hospital duration, and transfer to ICU, were recorded. Our study was approved by the Ethics Committee of the Second Affiliated Hospital of Wenzhou Medical University, and informed consent was obtained from every participant.

Diagnosis and classification of AP

The diagnosis of AP involved a combination of symptoms, physical examination, and focused laboratory values, with 2 of the following 3 features: 1) upper abdominal pain of acute onset often radiating through to the back, 2) serum amylase or lipase activity greater than 3 times normal, and 3) findings on cross-sectional abdominal imaging consistent with acute pancreatitis. Every patient in our study underwent pancreatic imaging. AP was divided into 3 degrees based on severity: mild, moderately severe, and severe acute pancreatitis, according to the Atlanta Classification 2012 revision [2,11,12]. Patients diagnosed with MAP had an absence of organ failure and local/systemic complications. Patients diagnosed with MSAP had transient organ failure/organ failure that resolved within 48 hours and/or local or systemic complications. Patients diagnosed with SAP had persistent single or multiple organ failure (>48 hours duration).

Measurement of visceral fat area (VFA)

In this study, all patients underwent an abdominal computed tomography (CT) scan. VFA was determined by a single scan at the level of the umbilicus (L3–L4), which corresponds with total abdominal fat with 99% accuracy [13]. The CT images were processed by Adobe Photoshop 7.0 software (Kansas, USA). Adipose tissue was determined by thresholds within the range of –140 to –50 Hounsfield units. Visceral obesity (VO) was defined as a VFA of >100 cm² [2,14].

Data collection

Both univariate and multivariate logistic regression analyses were performed. The factors included in the present investigation were age, sex, etiology, C-reactive protein (CRP), VFA, BMI, APACHE-II scores, serum amylase, serum calcium, blood glucose level on admission, whether this was the first episode of AP, and method of administration of octreotide. All these parameters were assessed on admission, and all the laboratory results were studied at the central laboratory of the Second Affiliated Hospital of Wenzhou Medical University. Hospital duration of stay, rate of transfer to ICU, and mortality were recorded to establish the prognosis of patients who developed MSAP or SAP.

Statistical analysis

Results are expressed as the median (interquartile range) unless stated otherwise. Categorical variables are described in absolute numbers and in percentages. Continuous variables were compared using the Mann-Whitney *U* test, and categorical data were analyzed with the chi-square test. To identify the risk factors for developing MSAP or SAP, several series of univariate logistic regression analyses using the 13 aforementioned indices were performed. Variables which were $P < .10$ and considered potentially clinically significant were included in the multivariate analysis, and a multiple logistic regression analysis was performed; $P < .05$ was considered significant. Data were analyzed with SPSS 17.0 for Windows (SPSS Inc., Chicago, IL).

Results

During the observational period, 602 patients admitted with MAP were recruited for this study (256 men and 346 women). Table 1 shows the demographic and clinical characteristics of these patients on admission. In the present study, MSAP or SAP developed in 74 patients (12.3%), of whom 52 patients developed MSAP and 22 patients developed SAP. Twenty-two patients who developed SAP had persistent organ failure, 14 of whom had single pulmonary or renal failure, 4 of whom had pulmonary and renal failure, and the other 4 of whom had pulmonary and coagulopathy failure. Most MSAP or SAP cases developed within the first 7 days after admission. The average time for developing more severe pancreatitis, including MSAP and SAP, in those admitted with MAP was 3.1 ± 2.4 days after admission.

Table 2 shows the results of univariate logistic regression analyses for developing MSAP or SAP following admission with MAP, regarding the 13 indices. The results indicated that there were significant differences between patients who developed MSAP or SAP and patients who did not in the following aspects: VFA ($>100 \text{ cm}^2$), BMI ($\geq 25 \text{ kg/m}^2$), Ranson score, APACHE-II score (≥ 5), and blood glucose level on admission ($>11.1 \text{ mmol/L}$). The results in Table 2 correlated well with the statistical results shown in Table 1, which also suggested differences in these 5 parameters between patients who developed MSAP or SAP and patients who did not. Bringing these 5 significant variables by univariate analyses into the multiple logistic regression models, we proved 3 variables to be independent risk factors for developing MSAP or SAP: BMI ($\geq 25 \text{ kg/m}^2$), APACHE-II score (≥ 5), and blood glucose level on admission ($>11.1 \text{ mmol/L}$) (Table 3). Table 4 shows a variety of clinical variables with regard to the outcome of patients who developed more severe pancreatitis (MSAP or SAP). Results showed that patients who developed MSAP or SAP had longer hospital stay duration, higher mortality, and higher rate of ICU transfer when compared to patients

who did not develop more severe pancreatitis ($P < .05$). Four of 602 patients died during hospitalization: 2 from major bleeding, and the other 2 from pancreatic necrosis with infection and consequent septic complications. The mortality rate of patients who developed MSAP or SAP was 5.4% (2/37), which is lower than the rates of around 30% reported in patients presenting with MSAP or SAP [3,4], indicating that this group of patients carried a better prognosis when compared with patients presenting with MSAP or SAP.

Discussion

In the present investigation, the incidence of more severe pancreatitis, including MSAP and SAP, developing from MAP was 12.3%, which was lower than that reported in previous studies [5]. Additionally, we began the evaluation of risk factors for developing more severe pancreatitis in patients admitted with MAP, and found 3 variables to be independent risk factors: BMI ($\geq 25 \text{ kg/m}^2$), APACHE-II score (≥ 5), and blood glucose level on admission ($>11.1 \text{ mmol/L}$). Our data also suggested that patients who developed MSAP or SAP had much longer hospital stays and higher rates of ICU transfer and mortality compared with those who did not.

However, the mechanisms of developing more severe pancreatitis in patients admitted with MAP remain unclear, and may involve many factors. Many isolated prognostic parameters and scoring systems have been developed to enable accurate and early prediction of MSAP or SAP [7,8,15]. In our study, one risk factor for developing MSAP or SAP was obesity, identified as BMI $\geq 25 \text{ kg/m}^2$, and several previous studies identified obesity as a risk factor for SAP [16–19]. Obesity has been consistently associated with a complicated course, as shown by the increased risk that it confers for SAP [16–19]. One explanation for the relationship between obesity and occurrence of SAP is that obese patients have a chronic pro-inflammatory state that may predispose them to mount a greater inflammatory response once AP occurs. This is evidenced by the increase in various fat-associated cytokines released from visceral adipose tissue in the body [17]. Interestingly, although BMI $\geq 25 \text{ kg/m}^2$ was an independent risk factor for developing more severe pancreatitis in our study, VFA, a marker of visceral obesity, was not a risk factor in our study. Previous studies also found that VFA was not significantly different between cases with SAP and those with MAP [20], which was in accordance with our study, but the underlying mechanisms require further research.

Another risk factor for developing MSAP or SAP was higher APACHE-II scores (≥ 5). It has been reported that APACHE scores were correlated with the prognosis of SAP [21], and APACHE-II scores were positively correlated with the severity of SAP

Table 1. Characteristics of patients who developed more severe pancreatitis or not.

Factors	Total patients (n=602)	MSAP or SAP developed (n=74)	MAP only (n=528)	P
VFA (cm ²)				.002
≤100	308	20	288	
>100	294	54	240	
BMI (kg/m ²)				<.001
<25	342	22	320	
≥25	260	52	208	
Ranson	1.13±0.73	1.46±0.60	1.08±0.74	.003
APACHE-II				.000
1~4	292	2	290	
5~7	310	72	238	
Sex (M/F)	256/346	34/40	222/306	.702
Age (years)	52±17	54±17	51±16	.315
Etiology				.439
Biliary	348	34	314	
Alcohol	82	14	68	
Hypertriglyceridemia	66	10	56	
ERCP	62	8	54	
Idiopathic	44	8	36	
Amylase level (IU/l)	771.8±573.1	685.5±420.5	783.6±590.2	.331
Blood glucose (mmol/l)				.027
≤11.1	292	24	268	
>11.1	310	50	260	
Serum calcium level (mmol/L)	2.0±0.06	2.0±1.1	1.99±0.57	.425
First episode of AP				.818
Yes	528	64	464	
No	74	10	64	
Method of administration of octreotide				.748
Hypodermic injection	448	52	396	
Continuous intravenous injection	154	22	132	
CRP(mg/L)	60.26±34.30	53.16±28.20	62.87±39.00	.145

P value: "Progression to MSAP or SAP group" versus "MAP only group".

and the rates of complications and mortality [21,22]. In this study, we further proved that APACHE-II scores ≥5 were significant risk factors for developing more severe pancreatitis in patients admitted with MAP.

It has also been reported that an elevated admission blood glucose level offered more prognostic information than Glasgow and APACHE-II scores [23] in gallstone pancreatitis. Our study also identified blood glucose level on admission (>11.1 mmol/L)

Table 2. Univariate logistic regression analysis for developing more severe pancreatitis (MSAP or SAP).

Variables	OR	95% CI	P
VFA (>100 cm ²)	3.191	1.485–6.856	.003
BMI (≥25 kg/m ²)	3.523	1.670–4.473	.001
Ranson	2.160	1.275–3.660	.004
APACHE-II (≥5)	29.096	3.931–215.36	.001
Sex	0.553	0.276–1.107	.286
Age	1.011	0.99–1.031	.314
Etiology	1.169	0.918–1.489	.206
Amylase level	1.000	0.999–1.000	.331
Blood glucose on admission (>11.1 mmol/L)	–0.764	0.372–4.2181	.040
Serum calcium level	7.318	0.055–966.0	.424
First episode of AP	1.494	0.534–4.178	.444
Method of administration of octreotide	1.089	0.501–2.368	.830
CRP	0.992	0.982–1.003	.147

Table 3. Independent risk factors in a multivariate logistic regression analysis for developing more severe pancreatitis (MSAP or SAP).

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for EXP(B)	
							Lower	Upper
BMI (≥25 kg/cm ²)	–1.228	0.438	7.872	1	0.005	0.293	0.124	0.691
APACHE (≥5)	–3.287	1.035	10.085	1	0.001	0.037	0.005	0.284
Blood glucose level on admission (>11.1 mmol/L)	–1.167	0.411	8.073	1	0.004	0.311	0.139	0.696
VFA (>100 cm ²)	–0.278	0.463	0.59	1	0.549	0.758	0.306	1.878
Ranson	0.497	0.291	2.914	1	0.088	1.644	0.929	2.911

Table 4. Prognosis of patients who developed more severe pancreatitis or not.

	Total patients (n=602)	MSAP or SAP develop (n=74)	Still with MAP (n=528)	P
Hospital duration (days)	10±4	21±5	8±3	.022
Mortality (n, %)	4 (0.66%)	4 (5.4%)	0	.015
ICU transfer	20 (3.32%)	20 (27.0%)	0	<.001

P value: “Progression to MSAP or SAP group” versus “MAP only group”.

as a risk factor for developing MSAP or SAP in patients admitted with MAP. Thus, special attention should be paid to MAP patients with a higher blood glucose level on admission,

especially when more than 11.1 mmol/L, in regard to the risk of occurrence of more severe pancreatitis.

Serum calcium level was expected to be another significant risk factor for developing SAP. However, in the multivariate analysis serum calcium level failed to show an association with the occurrence of more severe pancreatitis. Calcium level has been used as a predictor of the severity of acute pancreatitis for quite a long time, and it was included in the Ranson criteria established in 1977 [8]. It is known that disturbances of intracellular calcium homeostasis, characterized by high cytosolic calcium concentration in the pancreatic acinar cells, are involved in the pathophysiology of the onset of acute pancreatitis [24]. Therefore, although serum calcium level on admission might be correlated with severity of AP on admission, it was not found to be a risk factor for progression to more severe pancreatitis in our study.

It has been reported that age was positively correlated with the prognosis of SAP [25]; however, in this study we found that age was not a significant risk factor for developing more severe pancreatitis in patients admitted with MAP.

Finally, we explored the prognosis of patients who developed MSAP or SAP. The mortality rate in this group of patients was 5.4%, which is lower than the reported rate of about 30% for MSAP and SAP in general [25], indicating that this group of patients still had a better prognosis when compared with patients presenting with MSAP or SAP.

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There are several limitations in our study. First, it is a single-center study with a limited sample size, and the nonparametric test applied may bring some uncertainty to the conclusions. Another possible drawback of this study pertains to the lack of detailed monitoring of inflammatory factors, such as interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α), which are thought to be helpful in the prediction of occurrence of SAP [26].

In conclusion, we demonstrated that BMI (≥ 25 kg/m²), APACHE-II score (≥ 5), and blood glucose level on admission (>11.1 mmol/L) were all significant risk factors for the development of more severe pancreatitis in patients admitted with MAP. Therefore, efforts should be made to ameliorate the effects of these factors on the progression of AP from MAP to MSAP or SAP. These factors should also be used in predicting the occurrence of more severe pancreatitis.

Conclusions

In this study, 602 patients with mild acute pancreatitis were included for evaluating risk factors for worsening of mild acute pancreatitis. Results showed that significant risk factors for developing MSAP or SAP in patients admitted with MAP included BMI (≥ 25 kg/m²), APACHE-II (≥ 5), and blood glucose level on admission (>11.1 mmol/L). Our results may provide potential data for predicting the occurrence of more severe pancreatitis in patients admitted with MAP.

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