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Retrospective Study

Risk factors and their interactive effects on severe acute pancreatitis complicated with acute gastrointestinal injury

INTRODUCTION

Severe acute pancreatitis (SAP) refers to a disease in which pancreatic enzymes are activated due to a variety of reasons, resulting in a local inflammatory response. This disease is a common critical condition of the digestive system[1,2]. Statistically, the death rate due to SAP is up to 10%-30%[3], and has been on the rise in recent years, which seriously endangers the life and health of patients. Acute gastrointestinal injury (AGI) is a common complication of SAP. AGI patients have gastrointestinal dysfunction and mucosal injury, which can cause gastrointestinal motility slowing, intestinal obstruction, intestinal flora shift, impaired immune function, ulcer, gastrointestinal bleeding, *etc*., which aggravates the degree of pancreatitis, causes multiple organ dysfunction, and endangers the life of patients[4]. AGI is an important prognostic factor for SAP patients. Relevant studies have found that when AGI occurs in SAP patients, the mortality and incidence of complications are significantly increased[5]. However, there are numerous risk factors for AGI[6,7]. Therefore, examining the risk factors for AGI is of great significance for controlling the development of AGI, improving the prognosis of SAP, and taking effective intervention measures to improve the treatment of patients. However, most studies have investigated the risk factors for AGI, while reports on the interaction between risk factors are few. Therefore, the present study

aimed to analyze the risk factors for AGI and determine their interactive effects on SAP to provide a rationale for clinical treatment.

MATERIALS AND METHODS

General information

A retrospective analysis of 168 patients with SAP treated in our hospital, and enrolled between December 2019 and June 2022 was conducted. Inclusion criteria were as follows: (1) According to the "Guidelines for the diagnosis and treatment of acute pancreatitis in China (2021)"[8], all patients were diagnosed by abdominal color Doppler ultrasound, CT or MRI; and (2) The age of patients ranged from 18 to 65 years. Exclusion criteria were: (1) patients with gastrointestinal bleeding and complete intestinal obstruction; (2) severe heart, kidney or other important organ dysfunction; and (3) long-term use of corticosteroids or immunosuppressants. According to the AGI diagnostic criteria "European Society for the Critical Care Medicine (2012) Consensus on Acute Gastrointestinal Injury"[9], patients were divided into the AGI group (n = 64) and non-AGI group (n = 104).

Clinical data collection

Clinical data were collected from the patients. These data included gender, age, comorbidities (hypertension, diabetes, coronary heart disease), smoking history, acute physiological and chronic health scoring system II (APACHE II) score, and multiple organ dysfunction syndrome (MODS). Admission laboratory indicators included white blood cell (WBC) count in peripheral blood, hemoglobin, total bilirubin, creatinine (CRE), and serum amylase.

Statistical analysis

The SPSS 23.0 software was applied for analysis and processing. Quantitative data that conformed to a normal distribution are shown as mean ± SD, and t-tests were used for comparisons between the groups. Count data are expressed as n (%), and the χ^2 test was

used for comparisons between the groups. Logistic regression was applied to analyze the associated risk factors. The interaction of two factors was investigated using regression models. The attributable proportion of interaction (API), relative excess risk of interaction (RERI) and the synergy index (S) were calculated. $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of clinical and laboratory data between the two groups

Univariate analysis showed that the percentage of patients with MODS, APACHE II score and CRE level were higher in the AGI group than in the non-AGI group, with a significant difference between the two groups ($P < 0.05$), as shown in Table 1.

Logistic multi-factor analysis of SAP and concurrent AGI

Variables that were statistically significant in univariate analysis were included as independent variables, and the influencing factor variable assignment is shown in Table 2. The results of the multifactorial regression analysis indicated that an APACHE II score > 15 and CRE > 100 μmol/L were risk factors for complications of AGI in patients with SAP ($P < 0.05$), as shown in Table 3.

Interaction analysis of risk factors for AGI

The RERI of the interaction between the increase in APACHE II score and the increase in CRE level was 220.059, the API was 0.678%, and the S was 3.123. This indicated that there was a positive interaction between the two factors, as shown in Table 4.

Receiver operating characteristic curve analysis on the predictive value of APACHE Ⅱ and creatinine

Receiver operating characteristic (ROC) curve analysis showed that the predictive value of joint detection of APACHE II and CRE was better than that of single detection ($P < 0.001$). The ROC curves of the three were significantly different ($P < 0.05$) (Figure 1).

DISCUSSION

SAP is a special type of acute pancreatitis, which is caused by biliary tract disease, overeating, and heavy drinking, which leads to the activation of pancreatic enzymes and an acute chemical inflammatory reaction of pancreatic tissue[10]. In the early stage of SAP, a large number of inflammatory mediators, cytokines and bacterial toxins are produced, which lead to hemodynamic abnormalities and damage to organs such as heart, liver, kidney and the gastrointestinal tract, and in severe cases, organ failure[11]. AGI is one of the most common complications in SAP patients. As the gastrointestinal tract is the reservoir for systemic flora, it has functions such as regulating immune and inflammatory functions. When AGI occurs, it causes intestinal flora shift, gastrointestinal ulcer, gastrointestinal nutrition disorders, *etc*., which aggravate the inflammatory response, induce multiple organ failure in patients, prolong the length of hospital stay, and increase patient mortality[12]. Wang *et al*[13] found that AGI was an independent risk factor for SAP. Therefore, active treatment of AGI to promote the recovery of gastrointestinal function is the key to alleviating SAP, reducing mortality, and improving prognosis.

The results of this study indicated that patients with SAP complicated by AGI had a significantly higher MODS ratio, leukocyte level, CRE level, and APACHE II score compared to the non-AGI group, with significant differences. Logistic regression analysis indicated that APACHE II scores > 15 and increased CRE levels were the main risk factors for complications of AGI in SAP. Targeted measures should be taken against the above factors to strengthen prevention. The gastrointestinal tract plays an important role in the human body. Various injuries, surgeries, severe infections, massive bleeding and so on can promote the release of inflammatory factors. These inflammatory factors can activate the signal transduction of nuclear factors in gastrointestinal mucosal epithelium, causing microcirculation disorders in the gastrointestinal tract resulting in impaired gastrointestinal function[14]. The findings in the present study indicate that AGI patients have higher levels of WBCs than non-AGI patients. It is suggested that the

increase in these indices may be the risk factors of SAP complicated by AGI. CRE is a product of human muscle metabolism, and increased CRE will have a considerable impact on the body. When the CRE level increases, this indicates that the body's metabolism is abnormal, and a large amount of toxins and waste are accumulated, which results in disordered human functions and leads to various metabolic imbalances[15]. In addition, increased CRE level will accumulate in the heart, respiratory system, gastrointestinal system, *etc*., and will indirectly reflect glomerular and gastrointestinal system dysfunction, which will lead to gastrointestinal injury and systemic injury[16]. Jin *et al*[17] found that elevated serum CRE level was a risk factor for gastrointestinal failure, and the results of this study were consistent with these findings.

The APACHE II scoring system consists of a total score of three components: acute physiology, age, and chronic health status. It is widely applied in the assessment of critically ill patients, and is also a commonly used scoring system to judge the severity of acute pancreatitis[18,19]. An APACHE II score > 15 indicates a poor prognosis, and patients with higher scores have severe disease[20]. Greenberg *et al*[21] showed that the higher the APACHE II score within 72 h of admission in SAP patients, the higher the death rate. The findings of the present research indicated that patients in the AGI group had higher APACHE II scores than those in the non-AGI group. It is suggested that SAP patients with AGI are more critically ill and have a higher risk of death. The complexity of gastrointestinal function also lies in its internal dynamic changes. Disorder and translocation of intestinal flora is another potential mechanism for the occurrence of AGI. Intestinal flora activate the immune response through the lymphatic system, leading to the occurrence and even deterioration of MODS[22]. This research found a higher percentage of patients with AGI than with non-AGI, which was similar to the findings of Laterre *et al*[23]. It is suggested that MODS is closely related to SAP complicated by AGI.

From the interaction study of risk factors, it was found that there was a statistically positive interaction between the APACHE II score and CRE level in SAP patients with AGI. The RERI of the interaction effect between high APACHE II score and elevated

CRE level was 220.059, indicating that the risk of AGI increased by 220.059 times. The API was 0.678% and S was 3.123, indicating that 0.678% of AGI in these patients was caused by the coexistence of increased APACHE II score and increased CRE level, and the coexistence of both was 3.123 times that of AGI induced by the existence of either factor alone. Therefore, APACHE II score > 15 and CRE level > 100 μmol/L can lead to AGI in SAP patients. The changes in gastrointestinal function should be closely monitored, and timely and effective treatment should be provided to control the development of the patient's disease, reduce the body's inflammatory response, and avoid the involvement of other organs.

The present research was conducted to investigate the risk factors of SAP complicated by AGI and analyze the interaction between these risk factors. In this way, measures to prevent the incidence of AGI were implemented to improve the prognostic outcome of patients with SAP. However, the sample size in this study was limited, and the results may be biased to some extent. It is necessary to expand the sample and conduct a multicenter study to further confirm the risk factors of AGI in SAP patients.

CONCLUSION

An APACHE II score > 15 and CRE level > 100 μmol/L are both independent risk factors for SAP complicated with AGI, and there is a positive interaction between them. Therefore, in SAP patients with AGI, attention should be paid to managing the risk factors of AGI in SAP patients, and timely and effective interventions should be carried out to reduce the incidence of AGI and to improve the prognosis of SAP patients.

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Figure 1 Receiver operating characteristic curve analysis of acute physiological and chronic health scoring system II, creatinine and joint detection. APACHE II: Acute physiological and chronic health scoring system II.

Table 1 Comparison of clinical and laboratory data between the two groups, *n* (%)

Influencing factors	AGI group (*n* = 64)	Non-AGI group (*n* = 104)	χ^2/t value	*P* value
Gender			0.464	0.496
Male	31 (48.44)	56 (53.85)		
Female	33 (51.56)	48 (4 6.15)		
Age (mean ± SD, yr)	50.16 ± 7.56	49.42 ± 8.12	0.583	0.560
Hypertension			0.168	0.682
Yes	31 (48.44)	47 (45.19)		
No	33 (51.56)	57 (54.81)		
Diabetes			0.101	0.751
Yes	33 (51.56)	51 (49.04)		
No	31 (48.44)	53 (50.96)		
Coronary heart disease			0.008	0.927
Yes	34 (53.13)	56 (53.85)		
No	30 (46.87)	48 (46.15)		
Smoking			0.059	0.809
Yes	32 (50.00)	54 (51.92)		
No	32 (50.00)	50 (48.08)		
MODS			21.263	< 0.001
Yes	43 (67.19)	32 (30.77)		
No	21 (32.81)	72 (69.23)		
APACHE II score (mean ± SD)	17.45 ± 4.74	10.79 ± 3.95	-9.836	< 0.001
Leukocytes (mean ± SD, × 10^9/L)	15.12 ± 3.03	13.87 ± 2.27	-2.834	0.006
Hemoglobin (mean ± SD, g/L)	140.87 ± 14.93	144.50 ± 15.87	1.470	0.143

Creatinine (mean ± SD, μmol/L)	115.15 ± 12.18	93.07 ± 10.22	-12.116	< 0.001
Amylase (mean ± SD, U/L)	761.43 ± 73.90	751.20 ± 70.95	-0.894	0.373
Total bilirubin (mean ± SD, μmol/L)	22.09 ± 3.68	21.78 ± 3.61	-0.529	0.597

AGI: Acute gastrointestinal injury; MODS: Multiple organ dysfunction syndrome; APACHE II: Acute physiological and chronic health scoring system II.

Table 2 Factor assignment for logistic regression analysis

Influencing factors	Assignment of factors
Presence or absence of AGI	0 = Non-AGI group, 1 = AGI group
MODS	0 = no, 1 = yes
APACHE II	≤ 15 points = 0, > 15 points = 1
Creatinine	≤ 100 μmol/L = 0, > 100 μmol/L = 1
Leukocytes	Original value input

AGI: Acute gastrointestinal injury; MODS: Multiple organ dysfunction syndrome; APACHE II: Acute physiological and chronic health scoring system II.

Table 3 Logistic regression analysis of severe acute pancreatitis patients with acute gastrointestinal injury

Influencing factors	B value	SE value	Wald value	*P* value	OR value (95%CI)
APACHE II	1.716	0.613	7.820	0.005	5.560 (1.671-18.502)
MODS	-0.398	0.598	0.442	0.506	0.672 (0.208-2.169)
Leukocytes	0.196	0.101	3.769	0.052	1.216 (0.998-1.482)
Creatinine	3.380	0.553	37.366	< 0.001	29.365 (9.936-86.788)

MODS: Multiple organ dysfunction syndrome; APACHE II: Acute physiological and chronic health scoring system II.

Table 4 Interaction of creatinine and acute physiological and chronic health scoring system II score on acute gastrointestinal injury in severe acute pancreatitis patients

APACHE II	Creatinine	AGI group	Non-AGI group	OR	95%CI	RERI	API	S
–	–	1	79	1.00	–	220.059	0.678	3.123
+	–	5	4	98.75	9.228-1056.778			
–	+	21	12	138.25	16.998-1124.444			
+	+	37	9	0.024	0.002-0.314			

AGI: Acute gastrointestinal injury; APACHE II: Acute physiological and chronic health scoring system II.

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