The risk factors for acute respiratory distress syndrome in patients with severe acute pancreatitis: a retrospective analysis

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Abstract
Acute respiratory distress syndrome (ARDS) is very common in patients with severe acute pancreatitis (SAP), the early interventions are essential to the prognosis of SAP patients. We aimed to evaluate the risk factors for ARDS in SAP patients, to provide insights into the management of SAP.

SAP patients treated in our hospital from June 1, 2018 to May 31, 2020 were included. The characteristics and lab test results were collected and compared, and we conducted the logistic regression analyses were conducted to identify the potential risk factors for ARDS in patients with SAP.

A total of 281 SAP patients were included finally, the incidence of ARDS in patients with SAP was 30.60%. There were significant differences on the respiratory rate, heart rate, APACHE II and Ranson score between 2 groups (all $P < .05$). And there were significant differences on the polymorphonuclear, procalcitonin, C-reactive protein, serum creatinine, albumin and PO2/FiO2 between 2 groups (all $P < .05$), and no significant differences on the K+, Na+, Ca+, white blood cell, neutrophils, urine and blood amylase, trypsin, lipase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, triglyceride, total cholesterol, total bilirubin, fasting blood glucose, and pH were found (all $P > .05$). Respiratory rate >30/min (odds ratio [OR]: 2.405, 95% confidence interval[CI]: 1.163–4.642), APACHE II score >11 (OR: 1.639, 95% CI: 1.078–2.454), Ranson score >5 (OR: 1.473, 95% CI: 1.145–2.359), polymorphonuclear >14 x 10⁹/L (OR: 1.316, 95% CI: 1.073–2.328), C-reactive protein >150 mg/L (OR: 1.27, 95% CI: 1.002–1.534), albumin <30 g/L (OR: 1.113, 95% CI: 1.005–1.489) were the independent risk factors for ARDS in patients with SAP (all $P < .05$).

The incidence of ARDS in SAP patients is relatively high, and it is necessary to carry out targeted early prevention and treatment for the above risk factors.

Abbreviations: ALB = albumin, ARDS = acute respiratory distress syndrome, CRP = C-reactive protein, PMN = polymorphonuclear, RR = respiratory rate, SAP = severe acute pancreatitis, SCr = serum creatinine.

Keywords: acute respiratory distress syndrome, management, pancreatitis, risk, treatment

1. Introduction
Acute pancreatitis is one of the common digestive system diseases worldwide.[1] It has the characteristics of rapid onset, severe disease, multiple complications, and high mortality, which brings physical and economic burdens to patients and their families.[2,3] At the same time, it also consumes a lot of medical resources, and the overall mortality can be as high as 5%.[4] The main cause of death of AP is the progression of severe acute pancreatitis (SAP) during the course of the disease.[5] When AP progresses to SAP, it often requires intensive care unit treatment. Acute respiratory distress syndrome (ARDS) is the most common direct cause of early death in SAP patients.[6] Therefore, the early detection and management of ARDS is vital to the prognosis of SAP patients.

ARDS is one of the serious complications of SAP. The main clinical manifestations are shortness of breath and refractory hypoxemia.[7] At present, the main measures for clinical treatment of ARDS are mechanical ventilation, high-concentration mask oxygen, and so on.[8,9] Although the survival rate of ARDS is improved to a certain extent, the treatment effect is still not satisfactory.[10] Therefore, clarifying the risk factors of ARDS...
complicated by SAP and early intervention are extremely important for the prevention and treatment of ARDS. In this present study, we aimed to assess the risk factors for ARDS in patients with SAP, to provide evidence for the clinical management of SAP.

2. Methods

2.1. Ethical issues

Our study was approved and verified by the ethical committee of our hospital (18029-5c), and written informed consents were obtained from all the participants.

2.2. Patients

The SAP patients treated in our hospital from June 1, 2018 to May 31, 2020 were included. The patients were included if they met following criteria:

(1) the first main symptom of disease was abdominal pain;
(2) the patients was admitted to our hospital within 24 hours since the onset of disease;
(3) the SAP diagnosis met the diagnostic criteria,[11,12] 2 of the following 3 characteristics must be met:
   ① Abdominal pain met the characteristics of acute pancreatitis (acute persistent, severe mid-upper abdominal pain often radiates to the back);
   ② Serum amylase or amylase is at least greater 3 times than the upper limit of normal level;
   ③ computed tomography or abdominal ultrasound and other imaging examinations found characteristic changes of acute pancreatitis.[4]

The patients were well informed and agreed to participate in this study. The patients were excluded if they met following exclusion criteria:

(1) pregnant women;
(2) patients with lung infections, heart failure, or malignant tumors, autoimmune system diseases
(3) patients with incomplete data records and disagreed to participant in this study.

The included patients were divided into ARDS group and no ARDS group based on whether they had been diagnosed as ARDS. The ARDS was diagnosed if patients met following diagnostic criteria[13,14]:

① acute or progressive dyspnea within 7 days after injury;
② chest radiograph or chest computed tomography showed that the lung infiltrated that were consistent with “pulmonary edema” could not be explained by pleural effusion, lung lobes or atelectasis a;
③ The source of pulmonary edema could not be explained by heart failure and respiratory failure with fluid overload;
④ the PO2/FiO2 was ≤300 mm Hg.

2.3. Data collection

Two authors collected and checked the records consistently. The clinical data of patients were collected including age, gender, personal history (hypertension, diabetes, hyperlipidemia). And the vital signs upon admission including heart rate, respiratory rate (RR). And related laboratory test results were also collected including electrolytes (Na+, K+, Ca+), white blood cell, polymorphonuclear (PMN), neutrophils, procalcitonin, C-reactive protein (CRP), serum creatinine (SCR), urine and amylase, trypsin, lipase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin (ALB), triglyceride, total cholesterol, total bilirubin, and pH. The related disease judgment index APACHE II score and Ranson score were also collected.

2.4. Statistical analysis

All the data were processed and analyzed with SPSS 22.0 software. The t test or Chi-square test were applied to analyze the characteristics and score differences, and the logistic regression analyses were conducted to identify the potential risk factors for ARDS in patients with SAP. And P < .05 was considered statistically significant in this study, all the tests were 2-sided.

3. Results

3.1. The characteristics of patients

A total of 281 SAP patients were included finally, of whom 86 patients were diagnosed with ARDS, the incidence of ARDS in patients with SAP was 30.60%. As presented in Table 1, there were significant differences on the RR, heart rate, APACHE II, and Ranson score between 2 groups (all P < .05), and no significant differences on the gender, age, hypertension, diabetes, and hyperlipidemia were found (all P > .05).

3.2. The lab test results comparison

As indicated in Table 2, there were significant differences on the PMN, procalcitonin, CRP, SCR, ALB, and PO2/FiO2 between 2

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### Table 1

| Items                  | ARDS group (n=86) | No ARDS group (n=195) | χ² | P     |
|------------------------|-------------------|-----------------------|----|-------|
| Male/female            | 41/45             | 90/105                | 1.216 | .118  |
| Age (yr)               | 52.04±10.17       | 51.95±9.89            | 8.179 | .085  |
| Hypertension           | 26 (30.23%)       | 66 (33.85%)           | 1.044 | .391  |
| Diabetes               | 11 (12.79%)       | 23 (11.79%)           | 1.128 | .294  |
| Hyperlipidemia         | 14 (16.28%)       | 29 (14.87%)           | 1.046 | .831  |
| RR (l/min)             | 34.59±8.31        | 25.03±5.11            | 4.479 | .035  |
| HR (l/min)             | 128.17±24.66      | 105.74±20.58          | 14.272 | .011  |
| APACHE II score        | 18.09±4.68        | 9.87±3.24             | 2.477 | .13   |
| Ranson score           | 5.54±1.35         | 4.16±1.02             | 1.845 | .388  |

ARDS = acute respiratory distress syndrome, HR = heart rate, RR = respiratory rate.
groups (all P < .05), and no significant differences on the K\(^+\), Na\(^+\), Ca\(^+\), white blood cell, neutrophils, urine and blood amylase, trypsin, lipase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, triglyceride, total cholesterol, total bilirubin, fasting blood glucose, and pH were found (all P > .05).

### 3.3. Logistic analyses on the risk factors for ARDS in patients with SAP

Table 3 indicated the variable assignment for the multivariate logistic regression analysis. And as presented in Table 4, RR > 30/ min (odds ratio [OR]: 2.405, 95% confidence interval [CI]: 1.163–4.642), APACHE II score > 11 (OR: 1.639, 95% CI: 1.078–2.454), Ranson score > 5 (OR: 1.473, 95% CI: 1.145–2.359), PMN > 14 × 10\(^9\)/L (OR: 1.316, 95% CI: 1.073–2.328), CRP > 150 mg/L (OR: 1.127, 95% CI: 1.002–1.534), ALB ≤ 30 g/ L (OR: 1.113, 95% CI: 1.005–1.489) were the independent risk factors for ARDS in patients with SAP (all P < .05).

### 4. Discussions

The ARDS is characterized as diffuse damage of pulmonary capillaries caused by pathogenic factors inside and outside the lungs, leading to pulmonary edema and acute progressive respiratory failure.[15] Exudative lesions is a main manifestation of lung imaging in patients with ARDS, and the patient often firstly has obvious symptoms of dyspnea, and are manifested as abnormal breathing frequency and amplitude, and the disease progresses rapidly.[16] Within 72 hours, it can progress to respiratory failure or even multiple organ failure. Previous studies[17–19] have shown that ARDS is one of the early serious complications of SAP and can increase the mortality of SAP patients. The incidence of ARDS in SAP varies from 25.44% to 59.21% in previous studies,[20,21] and the incidence of ARDS in SAP patients in our study is 30.60%. Therefore, it is extremely

### Table 2

| Items          | ARDS group (n = 86) | No ARDS group (n = 195) | t     | P   |
|---------------|--------------------|------------------------|-------|-----|
| K\(^+\) (mmol/L) | 4.32 ± 0.45        | 4.18 ± 0.39            | 1.504 | .167|
| Na\(^+\) (mmol/L) | 135.10 ± 21.14     | 132.55 ± 18.72         | 1.162 | .003|
| Ca\(^+\) (mmol/L) | 1.62 ± 0.27        | 1.70 ± 0.24            | 1.023 | .061|
| WBC (× 10\(^9\)/L) | 16.22 ± 5.39       | 15.19 ± 4.46           | 2.119 | .172|
| PMN (× 10\(^9\)/L) | 15.64 ± 4.04       | 12.29 ± 4.79           | 2.744 | .035|
| NEU-R (%)      | 86.06 ± 21.26      | 86.14 ± 20.18          | 9.169 | .102|
| CRP (mg/L)     | 11.48 ± 3.04       | 3.17 ± 1.20            | 2.207 | .024|
| PCT (ug/L)     | 167.42 ± 38.55     | 136.47 ± 33.86         | 11.142| .009|
| SCR (ummol/L)  | 152.38 ± 37.12     | 102.13 ± 29.95         | 10.225| .014|
| Urine amylase (U/L) | 3798.64 ± 755.08  | 3768.12 ± 713.19      | 366.064| 1.07|
| Blood amylase (U/L) | 895.55 ± 184.86  | 871.17 ± 113.67        | 60.179| .113|
| Trypsin (U/L)  | 775.13 ± 204.54    | 764.42 ± 201.19        | 66.260| .098|
| Lipase (U/L)   | 963.37 ± 295.50    | 981.18 ± 236.62        | 74.493| .133|
| ALT (U/L)      | 126.28 ± 41.16     | 125.84 ± 39.22         | 12.274| .182|
| AST (U/L)      | 155.68 ± 42.01     | 148.12 ± 40.25         | 18.407| .096|
| TB (g/L)       | 56.42 ± 17.25      | 59.16 ± 17.69          | 2.054 | .078|
| ALB (g/L)      | 28.49 ± 7.16       | 33.16 ± 8.62           | 5.503 | .006|
| TG (mmol/L)    | 5.02 ± 2.11        | 6.26 ± 2.64            | 1.117 | .104|
| TC (mmol/L)    | 5.99 ± 2.04        | 6.12 ± 1.99            | 1.148 | .002|
| TBL (ummol/L)  | 35.36 ± 8.21       | 34.18 ± 9.07           | 3.102 | .118|
| Fasting blood glucose (mmol/L) | 13.22 ± 5.14 | 13.49 ± 5.44 | 2.808 | .094|
| PO\(_2\)/FiO\(_2\) (mm Hg) | 190.38 ± 60.24 | 251.16 ± 80.62 | 19.271 | .001|
| pH             | 7.14 ± 0.19        | 7.31 ± 0.20            | 0.978 | .101|

ALB = albumin, ALT = alanine aminotransferase, ARDS = acute respiratory distress syndrome, AST = aspartate aminotransferase, CRP = C-reactive protein, NEU-R = neutrophils, PCT = procalcitonin, PMN = polymorphonuclear, SCR = serum creatinine, TB = total bilirubin, TC = total cholesterol, TG = triglyceride, WBC = white blood cell.

### Table 3

| Variable          | Assignment          | SE     | OR     | 95% CI          | P   |
|-------------------|---------------------|--------|--------|-----------------|-----|
| RR (min)          | ≤ 30               | 0.133  | 1.20   | 1.163–4.642     | .002|
| APACHE II score   | > 11               | 0.247  | 1.639  | 1.078–2.454     | .025|
| Ranson score      | > 5                | 0.431  | 1.473  | 1.145–2.359     | .012|
| PMN (× 10\(^9\)/L) | > 14              | 0.204  | 1.316  | 1.073–2.328     | .035|
| CRP (mg/L)        | > 150              | 0.350  | 1.127  | 1.002–1.534     | .039|
| SCR (ummol/L)     | > 120              | 0.359  | 1.113  | 1.005–1.489     | .041|

ALB = albumin, CRP = C-reactive protein, PMN = polymorphonuclear, RR = respiratory rate.
important to clarify the risk factors of SAP patients with ARDS and to intervene early for the prevention and treatment of ARDS in SAP patients.

The mechanism of ARDS in SAP patient should be considered. The release of a large amount of inflammatory transmitters after the onset of SAP can directly damage capillary endothelial cells, resulting in increased vascular permeability, and thus affecting lung tissue perfusion. Furthermore, a large amount of pancreatic produced by SAP enters the blood circulation and causes vascular dysfunction. The accumulation of body fluid in the third gap leads to a decrease in effective circulating blood volume and insufficient tissue perfusion. At the same time, a large amount of pancreatic can also activate coagulation and related complement to promote the production of bioactive substances such as histamine and serotonin, thereby constricting pulmonary blood vessels. Besides, the intestinal-derived endotoxin can activate macrophages and mononuclear phagocytes, release leukocytes and oxygen free radicals in large quantities, and cause microthrombosis and lung damage. However, the mechanism of ARDS complicated by SAP is not yet fully understood and still needs further investigations.

Previous studies have shown that risk factors such as smoking, alcohol abuse, hypoproteinemia, and diabetes can effectively predict the occurrence of ARDS. In addition, research results indicate that alcoholism, hypoproteinemia, APACHE II score, gender, SCR, etc. may be the risk factors to predicting the occurrence of ARDS. The results of our study have indicated that SAP patients with RR > 30/min, APACHE II score > 11, Ranson score > 5, PMN > 14 × 10^9/L, CRP > 150 mg/L and ALB < 30 g/L may have higher risks for ARDS, early alarm and interventions are needed for those patients. Previous studies have shown that APACHE II, Ranson score have great significance in evaluating the severity and prognosis of SAP. The APACHE II score used to assess the physiological state and criticality of critically ill patients has been widely accepted, and it has superiority in predicting organ failure. Studies have reported that the Ranson score has a better advantage in predicting the length of stay in SAP patients.

Current studies have found that when SAP occurs, inflammatory cells aggregate and activate accordingly, and inflammatory mediators are synthesized and released into the blood, which stimulates the cascade-like release of inflammatory mediators, and finally leads to systemic inflammatory response syndrome, which is the cause of ARDS. CRP is an inflammatory index widely used clinically, and the level of CRP can reflect the changes in the patient’s ARDS. When patients with septic shock develop ARDS, the level of CRP in the patient’s body is significantly increased, which is consistent with the results of this study. Studies have shown that PMN and its secretions play an important role in the pathogenesis of ARDS and is an important risk factor for the occurrence of ARDS. The uncontrolled inflammatory response caused by a large number of PMN aggregation, activation, and apoptosis is the fundamental cause of ARDS caused by various etiologies. The results of this study show that hypoproteinemia in severely infected patients is an independent risk factor for ARDS. It’s been found that hypoproteinemia is an independent risk factor for ARDS in patients with acute stroke. The possible mechanism is that a decrease in ALB causes a decrease in plasma colloidal osmotic pressure, which causes water in the blood to move more easily into the lung interstitium, leading to pulmonary edema, and with the gradual decrease of lung surfactants, lung injury is further aggravated. It’s been reported that correcting hypoproteinemia is beneficial to SAP patients and it can reduce the occurrence of ARDS. However, a study has found that ALB infusion can improve lung compliance in SAP patients, but the final result did not reduce the incidence of ARDS. Therefore, the role of ALB in the development of ARDS needs further investigations.

5. Conclusions

In conclusion, the incidence of ARDS in SAP patients is relatively high, and RR > 30/min, APACHE II score > 11, Ranson score > 5, PMN > 14 × 10^9/L, CRP > 150 mg/L, and ALB < 30 g/L are the risk factors for ARDS in SAP patients. Therefore, in clinical practice, for patients with those risk factors, the health care providers should be vigilant in the occurrence of ARDS and be active in the early-stage intervention to reduce the occurrence of ARDS and improve the prognosis of SAP patients.

Author contributions

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