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Acute lung injury in patients with severe acute pancreatitis

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Background/aims: *Severe acute pancreatitis can result in acute lung injury. This study aims to investigate the clinical characteristics and possible prediction index of acute lung injury in severe acute pancreatitis.* ***Materials and Methods:*** *We retrospectively evaluated 184 patients with severe acute pancreatitis admitted between April 2007 and July 2010. There were 51 patients who developed acute lung injury with a rate of 27.7% (51/184). Clinical data of the acute lung injury and non-acute lung injury patients were compared, and the characteristics of acute lung injury were also analyzed. Meanwhile, we validated a few possible prediction indexes to identify the patients at high risk for acute lung injury at the time of hospital admission.* ***Results:*** *The severity index, hospital day, and the incidence of infectious complications were significantly higher in the acute lung injury patients than in the non-acute lung injury patients ($p<0.05$). The differences between the non-acute lung injury and acute lung injury groups in mortality (3% vs. 11.8%, $p<0.05$), operation (5.3% vs. 15.7%, $p<0.05$), and incidence of renal failure (15.8% vs. 33.3%, $p<0.05$), cardiovascular failure (3.8% vs. 15.7%, $p<0.05$), and pancreatic cyst (18% vs. 37.3%, $p<0.05$) were statistically significant. The patients with higher level of severity index score, acidosis, tachypnea, smoking history, and obesity were prone to develop acute lung injury.* ***Conclusion:*** *Acute lung injury occurrence in patients with severe acute pancreatitis varies according to predisposing conditions and independently carries poor prognosis.*

Key words: Pancreatitis, acute lung injury, clinical study, prediction

Ciddi akut pankreatit hastalarında akut akciğer hasarı

Giriş ve Amaç: *Ciddi akut pankreatit, akut akciğer hasarına neden olabilmektedir. Bu çalışmada ciddi akut pankreatitli hastalarda akut akciğer hasarının klinik özelliklerini araştırmak ve risk faktörlerini bulmak amaçlanmıştır.* ***Gereç ve Yöntem:*** *Nisan 2007'den Temmuz 2010'a kadar 184 ciddi akut pankreatitli hasta retrospektif olarak tespit edildi. Bunların 51 tanesinde (% 27.7) akut akciğer hasarı gelişmişti. Akut akciğer hasarı ve akut olmayan akciğer hasarı olan hastaların klinik özellikleri karşılaştırıldı ve akut akciğer hasarının özellikleri ayrıca analiz edildi. Aynı zamanda hastaneye yatışta akut akciğer hasarı açısından prediktif indeks oluşturmak için validasyon çalışması yapıldı.* ***Bulgular:*** *Ciddiyet indeksi, yatış süresi ve infeksiyöz komplikasyon varlığı akut akciğer hasarı olan olgularda, akut olmayan akciğer hasarı olan olgulara göre daha fazla idi ($p<0.05$). Akut akciğer hasarı olan ve akut olmayan akciğer hasarı olan hastalarda mortalite (3% vs. 11.8%, $p<0.05$), operasyon (5.3% vs. 15.7%, $p<0.05$), ve böbrek yetmezliği insidansı (15.8% vs. 33.3%, $p<0.05$), kardiyovasküler yetmezlik (3.8% vs. 15.7%, $p<0.05$), pankreatik kist (18% vs. 37.3%, $p<0.05$) aralarındaki farklar istatistiksel açıdan anlamlıydı.* ***Sonuçlar:*** *Ciddi akut pankreatitli olgularda akut akciğer hasarı gelişmesi altta yatan faktörlere göre değişmekte ve diğer faktörlerden bağımsız olarak kötü prognoz belirlemektedir.*

Anahtar kelimeler: Pankreatit, akut akciğer hasarı, klinik çalışma, tahmin

INTRODUCTION

Severe acute pancreatitis (SAP) commonly leads to systemic inflammatory response syndrome (SIRS) and distant organ complications (1). Acute lung injury (ALI) is one of the most common organ failures and approximately 30% of patients with ALI develop its more severe form, acute respiratory distress syndrome (ARDS). It is the first cause of patients' death during the early stage (2-4).

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Any intervention decreasing the incidence of ALI will significantly impact the mortality, complications, and need of intensive care unit (ICU) admission associated with this syndrome (5). Preventing the development of ALI and early intervention may be more effective in improving outcomes. Although no specific intervention has been shown to prevent ALI in patients at risk, determination of SAP patients at high risk for developing ALI should receive enough attention (6). Recent studies have identified several risk modifiers that may alter the likelihood of ALI development in patients with predisposing conditions. These include alcohol abuse, hypoalbuminemia, tachypnea, oxygen supplementation, obesity, and diabetes mellitus, however, whether these factors are independent of one another is unclear (7-11).

The aim of the present study was to investigate the clinical characteristics and possible prediction index of ALI in SAP.

METHODS

Selection of Patients

The medical records of West China Hospital of Sichuan University from April 2007 to July 2010 were reviewed and a cohort of patients consecutively admitted with a diagnosis of AP was identified. Hospitalized patients (>18 years of age) with a confirmed diagnosis of SAP were enrolled.

The diagnosis of AP was based on history of typical abdominal pain associated with at least a two-fold increase in serum lipase values and was confirmed by contrast-enhanced computer tomography (CT). The diagnostic criteria formulated for SAP at the 2002 Bangkok World Congress of Gastroenterology in Thailand were adopted (12): Ranson's score ≥3, or Acute Physiology and Chronic Health Evaluation (APACHE II) score≥8, or Balthazar's CT score ≥7, or local involvement (necrosis, abscess, pseudocyst), or organ failure. Patients were included within 72 h after the onset of the symptoms. Patients were excluded if they died during the three days after admission.

Clinical Treatment and Parameters Measurement

During the hospital stay, standardized comprehensive treatments and monitoring were implemented in SAP patients as follows (12,13): intensive care, fasting, and gastrointestinal decompression as well as inhibition the pancreatic secretion, measurement of central venous pressure via central venous catheter (CVC), fluid resuscitation, maintenance of adequate intravascular volume as well as homeostasis of electrolyte and acid base, prophylactic antibiotics, nutritive support, oxygen inhalation or respirator usage if respiratory failure developed, and symptomatic treatment.

The diagnostic criteria for organ failure are shown in Table 1 (15,16). ALI was defined according to

Table 1. Definitions of the primary and secondary end-points

End Point	Definition
Major complication	
New-onset multiple-organ failure or systemic complications	New-onset failure (i.e., not present at any time in the 24 h before first intervention) of two or more organs or occurrence of two or more systemic complications at the same time
Organ failure	
Pulmonary failure	ALI: *PaO_2/FIO_2<300;ARDS: PaO_2/FIO_2 <200, or need for mechanical ventilation
Circulatory failure	Hypotension, heart rate ≤54 bpm, or >130 bpm, mean arterial pressure ≤6.5 kPa (49 mmHg) despite adequate fluid resuscitation, or need for inotropic catecholamine support
Renal failure	Creatinine level >177 μmol/L after rehydration or new need for hemofiltration or hemodialysis
Hepatic failure	Serum bilirubilin ≥34 μmol/L, alanine aminotransferase >2 times of the upper normal limit
Systemic complication	
Disseminated intravascular coagulation	Platelet count <100×10^9/L
Severe metabolic disturbance	Calcium level <1.87 mmol/L

*FIO_2 denotes fraction of inspired oxygen, and PaO_2 partial pressure of arterial oxygen.

the standard American-European Consensus Conference (AECC) definition (14) as the development of acute, bilateral pulmonary infiltrates and hypoxemia in the absence of clinical signs of left atrial hypertension as the main explanation for pulmonary edema. Cardiovascular failure was considered in case of hypotension, heart rate ≤54 bpm, or >130 bpm, mean arterial pressure ≤6.5 kPa despite adequate fluid resuscitation, or need for inotropic catecholamine support. Renal failure was considered in case of urinary volume <480 mL/24 h, serum creatinine ≥177 μmol/L (2 mg/dL) after rehydration or new need for hemofiltration or hemodialysis; and development of hepatic failure was accepted in case of serum bilirubilin ≥34 μmol/L and alanine aminotransferase >2 times of the upper normal limit.

Study Methods

Based on whether the patients were either complicated by ALI or/and ARDS or not during the course of SAP, patients were accordingly divided into ALI group and non-ALI group, respectively. The following parameters were evaluated: age, gender, etiology of pancreatitis, severity of the illness [Ranson's criteria and Balthazar's CT classification, 24-h APACHE II score]. The primary end-points were mortality, length of hospital stay, incidence of operative necrosectomy, and pancreatic pseudocyst during the hospital stay for SAP. The secondary end-points were incidence of infectious complications and major organ complications.

Meanwhile, ALI risk indexes including alcohol abuse, acidosis, tachypnea, oxygen supplementation, blood glucose, smoking and obesity, were collected at the time of hospital admission.

Statistical Analysis

Statistical analysis was performed with the SPSS for Windows package of statistical programs. The qualitative variables, such as etiology, complications, overall surgery, and mortality, were presented as percentages. The quantitative variables were presented as mean with standard deviations if the distribution was normal and as median (interquartile range) if the distribution was abnormal. The study of the qualitative variables was processed with the chi-square test and Fisher's exact test. The comparison of two independent samples was evaluated with student's t-test where the distribution was normal. Two-tailed p-values <0.05 were considered statistically significant.

RESULTS

Clinical Profiles of the Patients

Of 184 patients with SAP who were included in this study, 51 (27.7%, 15 with ALI-only, 36 with ARDS) were in the ALI group and 133 (72.3%) were in the non-ALI group. The two groups had similar gender and age distribution as well as etiologic factors (p>0.05, Table 2). In ALI group, ventilation has been used in 43 (84.3%) patients; the average usage days were 15.7±10.9.

ALI Risk Index and Predisposing Conditions

The frequency of ALI varied according to predisposing conditions (Table 3). The index was collected at the time of hospital admission. The comparison of severity index showed that the ALI group had higher Ranson's scores (4.5±1.4 vs. 3.7±1.3, p<0.05) and 24-h APACHE II score (11.1±5.3 vs. 8.1±4.5, p<0.05) compared with the non-ALI group, but Balthazar's CT scores (5.9±1.8 vs. 5.5±1.3, p>0.05) in the two groups was not significantly different. The higher rate of ALI occurred after smoke inhalation (p<0.01) and in obese patients (p<0.01), but there was no significant difference in alcohol abuse between the two groups, though it is an important cause of acute pancreatitis.

Respiratory rate (RR) as a direct marker of respiratory symptom was evaluated in the study. RR at the time of hospital admission in the ALI group was higher compared to that in the non-ALI group (p<0.05). RR was more than 30 in 18 patients in the ALI group (35.3%) and in 13 patients (9.8%) in the non-ALI group (p<0.001). Meanwhile, oxygen saturation by pulse oximetry (SpO_2) and fraction

Table 2. Comparison of demographics and etiology between patients with severe acute pancreatitis in the non-ALI and ALI groups

	non-ALI (n=133)	ALI (n=51)
Age, years (mean±SD)*	45.1±10.6	47.4±11.1
Gender, n (%)**		
Male	74 (55.6)	31 (60.9)
Female	59 (44.4)	20 (39.2)
Etiology, n (%)**		
Gallstones	24 (18)	11 (21.6)
Hyperlipidemia	59 (44.4)	24 (47)
Alcohol	43 (32.3)	16 (31.4)
Idiopathic	7 (5)	0 (0)

Differences in gender and age distribution as well as etiologic factors between the non-ALI and ALI groups were not statistically significant, p>0.05.* Unpaired student's t-test. ** χ^2-test
ALI: Acute lung injury.

of inspired oxygen (FiO_2) were also significantly different in the two groups ($p<0.05$). PH in the ALI group was lower than in the non-ALI group ($p<0.05$). In the two groups, serum C-reactive protein (CRP) was remarkably beyond the upper normal limit on the first day of admission, but there was no significant difference in the level of CRP between the two groups ($p>0.05$). Although the level of blood glucose and calcium are used in the determination of the severity index of SAP, there was also no significant difference between the two groups regarding these parameters ($p>0.05$).

Comparison of Clinical Courses Between the non-ALI Group and the ALI Group

The comparison of clinical courses is shown in Table 4. The hospital days and the incidence of infection were significantly higher in the ALI group than in the non-ALI group (30.6±14.2 vs. 21.2±9.4,$p<0.05$; 52.9% vs. 22.5%, $p<0.001$, respectively). The differences between the non-ALI and ALI groups in mortality (3% vs. 11.8%, $p<0.05$), operation (5.3% vs. 15.7%, $p<0.05$), and in the incidence of renal failure (15.8% vs. 33.3%, $p<0.05$), cardiovascular failure (3.8% vs. 15.7%, $p<0.05$),

Table 3. ALI predisposing conditions in SAP patients

Variable	Total (184)	Non-ALI (133)	ALI (51)	p
Ranson's score (mean±SD)*	\	3.7±1.3	4.5±1.4	0.01
24-h APACHE score (mean±SD)*	\	8.1±4.5	11.1±5.3	0.01
Balthazar's CT score (mean±SD)*	\	5.5±1.3	5.9±1.8	NS
Smoking, n (%)**	76 (41.3)	46 (25.0)	30 (58.8)	0.003
Alcohol abuse, n (%)**	89 (48.4)	60 (45.1)	29 (56.9)	NS
Obesity, n (%)**	79 (42.9)	43 (32.3)	36 (70.6)	0.000
Respiratory rate, median (range)***	20 (18,22)	20 (18,22)	22 (20,26)	0.01
Tachypnea (RR>30/min), n(%) **	31 (16.8)	13 (9.8)	18 (35.3)	0.000
SpO_2, median (range)***	94 (92, 98)	94 (93, 99)	92 (90, 96)	0.04
FiO_2, median (range)***	0.2 (0.2, 0.3)	0.2 (0.2,0.3)	0.4 (0.4, 1.0)	0.01
PH, median (range)***	7.39 (7.34, 7.43)	7.4 (7.34, 7.44)	7.34 (7.32, 7.41)	0.04
CRP, median(range)***	211.0 (158.5, 303.3)	213 (172.5, 302.5)	191 (120.312)	NS
Glucose (mean±SD)*	/	12.0±5.0	13.1±5.0	NS
Calcium level <1.87 mmol/L, n (%)**	84 (45.7)	56 (42.1)	28 (54.9)	NS
Platelet count< 100×10^9 /L, n (%)**	63 (34.2)	45 (33.8)	18 (35.2)	NS

ALI: Acute lung injury; APACHE: Acute Physiology and Chronic Health Evaluation; SpO^2: Oxygen saturation by pulse oximetry; FiO_2: Fraction of inspired oxygen. CRP: C-reactive protein. NS: Non significant
*Unpaired student's t-test. **χ^2-test. *** Rank-sum test.

Table 4. Comparison of clinical courses in SAP patients with and without ALI

	Non-ALI (n=133)	ALI (n=51)	p
Hospital day (mean±SD) *	21.2±9.4	30.6±14.2	0.001
Operation, n (%)**	7 (5.3)	8 (15.7)	0.02
Organ failure, n(%)**			
Renal failure	21 (15.8)	17 (33.3)	0.01
Hepatic failure	12 (9.0)	7 (13.7)	NS
Cardiovascular failure	5 (3.8)	8 (15.7)	0.005
Infection, n (%)**	30 (22.5)	27 (52.9)	0.000
Pancreatic cyst, n (%)**	24 (18.0)	19 (37.3)	0.006
Mortality, n (%)**	4 (3)	6 (11.8)	0.02

Differences between the non-ALI and ALI groups regarding mortality, incidence of organ complication (except hepatic failure), incidence of operative necrosectomy, and hospital stay were statistically significant ($p<0.05$, *unpaired Student's t-test,** χ^2-test).
SAP: Severe acute pancreatitis. ALI: Acute lung injury. NS: Non significant.

and pancreatic cyst (18% vs. 37.3%, p<0.05) were statistically significant.

DISCUSSION

ALI/ARDS has been considered to be the primary cause of death in the early stage of SAP (15). In our cohort of patients, the morbidity rate of ALI/ARDS was 22.7% and the total mortality rate was 5.4%. No significant differences were found between the groups in terms of age, gender, and etiology (Table 2).

At the time of hospital admission, the ALI patients had higher level of Ranson's score and 24-h APACHE II score compared with non-ALI patients, but there was no significant difference in Balthazar's CT score, thus the level of local pancreas damage possibly did not correspond to the severity of SIRS totally. Compared to the non-ALI patients, the ALI patients had more complicated clinical courses, i.e. hospital stay and infectious complications (p<0.001).

Infectious complications are still regarded as the most serious complications of SAP, representing the dominant cause of late mortality (16). Causative pathogens isolated from the infected organs in SAP patients are multi-bacterial (17). According to the results of our study, in the ALI group, 75% of the isolated strains were Gram-negative bacteria, including Acinetobacter baumannii (41.7%), Pseudomonas aeruginosa (8.3%), Escherichia coli (16.7%), few Enterobacter cloacae, Klebsiella pneumonia, and Xanthomonas maltophilia; fungi accounted for 25% and were combined with a small amount of Gram-positive bacteria. In the non-ALI group, the multi-bacterial isolates predominantly comprised Escherichia coli (45.5%) and Pseudomonas aeruginosa (18.2%), few Klebsiella pneumonia, Acinetobacter baumannii, and a small amount of fungi. The difference in the type of microorganisms in the ALI patients may possibly be linked to the long-term use of prophylactic antimicrobial agents and invasive mechanical ventilation (18).

Prevention of ALI may improve survival and long-term functional outcomes better than interventions aimed at reducing mortality after development of ALI (19). Accurate, early identification of patients with SAP at risk for developing ALI provides the opportunity to test and implement secondary prevention strategies (20). There are few studies focused on the risk factors of ALI development in SAP so far. In the present study, we validated a few possible prediction indexes to identify patients with SAP at high risk for ALI at the time of hospital admission. The patients with a higher level of Ranson's score and 24-h APACHE II score, acidosis, smoking history, and obesity were prone to develop ALI/ARDS. In presence of tachypnea (respiratory rate>30/min) at the time of hospital admission, which cannot be alleviate after fluid expansion, the SAP patients may have the high likelihood of ALI/ARDS development.

In the early stage of pancreatitis, the abnormal activation of trypsin leads to partial activation of cytokine, thus inducing over-expression of inflammatory media due to the cascade connection - "waterfall effect". The inflammatory media are released into the blood abundantly, leading to SIRS, aggravate the injuries of the pancreas and other organs (including the lungs), and may even cause MOF (21). Ranson's score and 24-h APACHE II score are the indicator of the severity of AP, being good predictors of ALI development.

Obese patients may more easily fulfill AECC criteria for ARDS because of their body habitus which may increase the likelihood of respiratory failure (22,23). However, it is unclear whether this accounts for the association between obesity and ALI/ARDS completely in this study. Smoking could have damaged the lung tissue and lung function, and patients with smoking history had high likelihood to develop ALI/ARDS. Previous study reported that alcohol abuse was a risk factor for ALI development (7), but in the present study, there was no significant difference between the two gro-

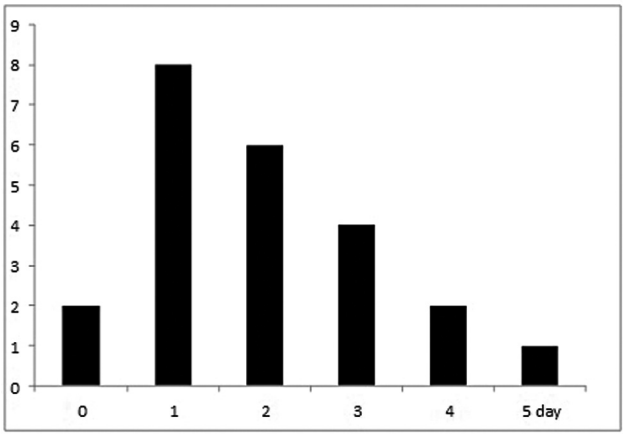

Figure 1. Timing of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) development during hospital stay.
The development of ALI/ARDS was concentrated on five days after onset of SAP. The day of admission is marked as Day 0 and the second day as Day 1.

ups. This may be because alcohol abuse is an important incentive for pancreatitis, and the patients included in this study mostly had alcohol abuse history (24). Timing of ALI/ARDS development was mainly concentrated in the five days after the onset of SAP in this study (Figure 1); this result is consistent with prior research (25). Thus, the risk prediction should be accomplished within 24 h after hospital admission; it is conducive to the prevention of ALI.

In conclusion, ALI/ARDS in SAP correlate to severe episodes in the initial stage and consequently complicate the clinical course of the disease. ALI development markedly increased the risk of infectious complications and death. Although no specific intervention has been shown to prevent ALI in patients at risk, applying a prediction model to identify high-risk patients may alert physicians to avoid specific "second-hit" hospital exposures, such as high tidal volume mechanical ventilation. A more accurate, early prediction model is needed to facilitate the identification of patients who can benefit from interventions to prevent disease progression.

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