

## Clinical Characteristics of Patients with Acute Pancreatitis Coexisting with Organ Failure: A Retrospective Cohort Study

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### Abstract

**Purpose:** Acute pancreatitis is a systemic disease, and is usually closely associated with organ failures. This study was to investigate the pattern of organ failure in the course of acute pancreatitis.

**Recent Findings:** A total of 783 severe acute pancreatitis (SAP) and moderately severe acute pancreatitis (MSAP) patients who were sequentially treated in Department of Surgery, Ruijin Hospital from January 2001 to December 2008 were retrospectively analyzed. All the patients were divided according to their outcomes into two groups: deceased group and survival group. The relationship between the happening of organ failure and outcome of the patients were observed. Then peripheral blood level of endotoxin core antibody and TNF- $\alpha$  between SAP and MSAP groups were compared. Among the 783 patients, the numbers of MSAP patients and SAP patients were 573 and 210 respectively. Overall, 698 patients were survived, which represents 89.1% of the total patients. Furthermore, 273 patients or 34.9% of the total were diagnosed with organ failure. There were 109 patients with single organ failure, 2 of which died; 81 and 60 patients with 2 organs failure and 3 organs failure respectively. In each group 30 patients died. Finally there were 23 patients with 4 or more organs failure and none of them survived. The rate is 15.3% (107/698) of the patients with single organ failure in survival group, while the corresponding number is only 2.4% (2/85) in deceased group. On the contrary, only 11.6% (81/698) patients in the survival group had multiple organ failure, while the number is 97.6% (83/85) in the deceased group. Respiratory, renal, cardiovascular, neurological, hematologic and hepatic failure occurred in 206, 80, 103, 92, 41, and 27 patients, with the incidence of 26.3%, 10.2%, 13.2%, 11.7%, 5.2%, and 3.4%; and the mortality rates were 38.8%, 63.8%, 49.5%, 37.0%, 53.7%, and 44.4% respectively. Peripheral blood levels of TNF- $\alpha$  and endotoxin core antibody in patients with SAP were significantly different with that of MSAP.

**Summary:** In the course of acute pancreatitis, respiratory and cardiovascular failure has the highest incidence, and renal, hematologic failure is associated with poorest prognosis.

**Keywords:** Acute pancreatitis; Organ failure; Prognosis; Endotoxin core antibody

### Introduction

In the course of acute pancreatitis (AP), single or multiple organ failure is often the primary cause of death in this disease [1]. According to "Classification of acute pancreatitis 2012: revision of the Atlanta classification and definitions by international consensus", Severity of the disease is categorized into 3 levels: mild, moderately severe, and severe. Mild acute pancreatitis lacks both organ failure (as classified by the modified Marshal scoring system) and local or systemic complications. Moderately severe acute pancreatitis has transient organ failure (organ failure of <48 h), local complications, and/or exacerbation of coexistent disease. Severe acute pancreatitis is defined by the presence of persistent organ failure (organ failure that persists for  $\geq$  48 h).

As mild acute pancreatitis has extremely low mortality and lacks organ failure, our study focus on moderately severe acute pancreatitis (MSAP) and severe acute pancreatitis (SAP). A retrospective analysis

was conducted for 783 MSAP and SAP patients treated in Ruijin Hospital from January 2001 to December 2008. The aim of this study was to investigate the pattern of organ failure in the course of acute pancreatitis and classify the severity of different types of organ failure.

### Patients and Methods

#### Patients

From January 2001 to December 2008, 783 MSAP and SAP patients admitted to the Department of Surgery, Ruijin Hospital affiliated to Shanghai Jiaotong University School of medicine.

The diagnosis of AP was established in cases with clinical presentations and biochemical findings (two of the following three features: abdominal pain consistent with acute pancreatitis; serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT) and less

commonly magnetic resonance imaging (MRI) or transabdominal ultrasonography).

The first diagnosis was established in the emergence room of our hospital. After admission, antibiotics were administered to patients for not more than 7 days, unless they had persistent clinical manifestations of sepsis.

Parenteral nutrition was initiated, and after the gastrointestinal tract function recovered from paralysis, the patients were fed by both enteral nutrition and parenteral nutrition. Patients who developed organ failure were treated in an intensive care unit (ICU).

Patients with infected necrosis were advised to receive surgical intervention and if possible, intervention was postponed until approximately 4 weeks after the onset of disease. Mild pancreatitis were excluded which were identified by the absence of organ failure or local or complications, and chronic or recurrent pancreatitis were excluded.

According to 2012 acute pancreatitis classification [2], these patients were further divided into MSAP and SAP, MSAP is characterized by the presence of transient organ failure or local or systemic complications in the absence of persistent organ failure, and SAP is characterized by persistent organ failure.

Transient organ failure is organ failure that is present for <48h. Persistent organ failure is defined as organ failure that persists for >48 h. Among these patients, 573 cases were MSAP patients and 210 cases were SAP patients. Of the 783 patients, 698 patients were cured and 85 patients died, the dead ones were all SAP cases.

For each patient the following demographic and clinical data were recorded: age, sex, etiology, hospitalization time, APACHE II score at admission, situation of organ failure. Etiology was divided into two groups: biliary group and non-biliary group.

A biliary etiology was confirmed by ultrasonography, CT scan, ERCP, MRCP and operation.

Pancreatic necrosis and abscess were defined by the findings on contrast-enhanced CT scan or in operation. Organ failure criteria to define MSAP and SAP are based on Modified Marshall scoring system.

The criteria of organ failure in this study: Because Modified Marshall scoring system only assess respiratory, cardiovascular and renal systems, we only use it to define MSAP and SAP, but in this study we choose SOFA score standard to determine the patients' organ failure (Table 1) [3,4].

organ	Criteria for the diagnosis of organ failure
Cardiovascular	Mean arterial pressure<70 mmHg or The application of vasoactive drugs
Respiratory	Oxygenation index (PaO <sub>2</sub> /FiO <sub>2</sub> )<200 mmHg
Renal	Serum creatinine 171 umol/L
Neurological	Glasgow score<13
Hepatic	Total bilirubin>101 mmol/L, albumin<28 g/L
Hematological	platelet<50 x 10 <sup>9</sup> /L

**Table 1:** Criteria for the diagnosis of organ failure.

## Grouping

The patients were divided according to their outcomes into two groups: deceased group and survival group. The relationships between the happening of organ failure and outcome of the patients were observed. The data recorded for each patient included age, gender, etiology, length of hospitalization and APACHE II score at admission.

## Test

Of the 783 patients, sixty ones from June 2006 to Feb 2007, whose peripheral blood level of endotoxin core antibody and TNF-α on their admission days were determined using ELISA, and 20 healthy controls were included. These biochemical factors of SAP and MSAP were compared. The test kit was obtained from Hycult biotechnology b.v., Edinburgh, Scotland, and samples were tested following the instruction of test kit.

## Ethics

All research have been approved by Ethics Committee of Ruijin Hospital Shanghai Jiaotong University School of Medicine, and all clinical investigation must be conducted according to the principles expressed in the Declaration of Helsinki.

## Statistics

Results were expressed as mean. Continuous data were evaluated by t test, and categorized data were analyzed by Chi-square test or Fisher's exact test. P<0.05 was considered statistically significant.

## Results

Of the 783 patients, 698 patients were cured and 85 patients died. The patients in the deceased group were significantly older and had a higher APACHE II score than those in the survived group. The length of hospitalization was significantly shorter in those with a fatal outcome. The survival group showed a significantly higher proportion (biliary/non-biliary) than the deceased group in etiology. There was no significant difference in gender (Table 2).

	Survival (698)	Deceased (85)	Total (783)
Mean age (yr)	54.3*	63.9	55.3
Gender (male/female)	317/381	36/41	353/430
Etiology (biliary/non-biliary)	357/341*	18/67	375/408
Hospitalization (d)	50.5*	29.1	48.2
APACHE II score	6.3*	12.5	7.0
*p<0.05 vs deceased group			

**Table 2:** Comparison of clinical characteristics.

The incidence of different organ failure: Respiratory failure is with the highest incidence of 26.3%; Second is Cardiovascular failure with the incidence of 13.2%; then is Neurological failure with the incidence of 11.7%, Renal failure with the incidence of 10.2%, Hematological failure with the incidence of 5.2%, Hepatic failure with the incidence of 3.4%. The last column shows the distribution of different organ failure in patients with MSAP and SAP (Table 3).

	Survival (698)	Incidence (100%)	Deceased (85)	Incidence (100%)	Total (783)	Incidence (100%)	MSAP/SAP
Respiratory	126	18.1%^	80	94.1%	206	26.3%	45/161
Renal	29	4.2%^	51	60.0%	80	10.2%	3/77
Cardiovascular	52	7.4%^	51	60.0%	103	13.2%	25/78
Neurological	58	8.3%^	34	40.0%	92	11.7%	5/87
Hematological	19	2.7%^	22	25.9%	41	5.2%	0/41
Hepatic	15	2.1%^	12	14.1%	27	3.4%	0/27

^p<0.01 vs deceased group

**Table 3:** The incidence of different organ failure.

The mortality of different organ failure: Renal failure is with the highest mortality of 63.8%; second is Hematological failure with the mortality of 53.7%; then is Cardiovascular failure with the mortality of 49.5%, Hepatic failure with the mortality of 44.4%, Respiratory failure with the mortality of 5.2%, Neurological failure with the mortality of 3.4% (Table 4).

	Survival (698)	Deceased (85)	Total (783)	Mortality (100%)
Respiratory	126	80	206	38.8%
Renal	29	51	80	63.8%
Cardiovascular	52	51	103	49.5%
Neurological	58	34	92	37.0%
Hematological	19	22	41	53.7%
Hepatic	15	12	27	44.4%

**Table 4:** The prognosis of different organ failure.

Compare with Tables 3 and 4, we found it present different trends in incidence and mortality of different organ failure in patients with acute pancreatitis. High incidence doesn't mean high mortality, and low incidence doesn't mean low mortality. The most typical example is Respiratory failure which experienced the highest incidence but lower mortality while renal failure experienced the highest mortality but lower incidence.

Comparison of the numbers of organ failure and prognosis: Of the 783 patients, 273 patients turned to organ failure, with the incidence of 34.9%. There were 109 patients with single organ failure, 2 patients died. There were 81 patients with 2 organs failure, 30 patients died. There were 60 patients with 3 organs failure, 30 patients died.

There were 23 patients with 4 or more organs failure, all patients died. There were 15.3% (107/698) patients with single organ failure in survival group while only 2.4% (2/85) patients in deceased group. There were 11.6% (81/698) patients with multiple organ failure in survival group while 97.6% (83/85) patients in deceased group (Table 5).

The number of failure organs	Survival (%)	Deceased (%)	Total (%)
1	107 (15.3%)^	2 (2.4%)	109 (13.9%)
2	51 (7.3%)^	30 (35.3%)	81 (10.3%)
3	30 (4.3%)^	30 (35.3%)	60 (7.7%)
4	0 (0.0%)	19 (22.4%)	19 (2.4%)
5	0 (0.0%)	2 (2.4%)	2 (0.3%)
6	0 (0.0%)	2 (2.4%)	2 (0.3%)
Total	188 (26.9%)	85 (100%)	273 (34.9%)

^p<0.01 vs deceased group

**Table 5:** Comparison of the numbers of organ failure and prognosis.

The distribution of single organ failure and multiple organ failure: The patients with single failure have only 2 dead cases, with the mortality of 1.83%, the patients with multiple organ failure have 83 dead cases, with the mortality of 50.61%. There are differences in distribution of the patients with multiple organ failure and with single organ failure (Table 6).

	Single organ failure n (%)		Multiple organ failure n (%)	
	Survival n=107	Deceased n=2	Survival n=81	Deceased n=83
Respiratory	66 (61.7%)	0 (0%)	60 (74.1%) ^	80 (96.4%)
Renal	2 (1.9%)	0 (0%)	27 (33.3%) ^	51 (61.4%)
Cardiovascular	26 (24.3%)	2 (100%)	26 (32.1%) ^	49 (59.0%)
Neurological	13 (12.1%)	0 (0%)	45 (55.6%) ^	34 (41.0%)
Hematological	0 (0%)	0 (0%)	19 (23.5%) ^^	22 (26.5%)
Hepatic	0 (0%)	0 (0%)	15 (18.5%) ^	12 (14.5%)

^p<0.01 vs deceased group, ^^p<0.05 vs deceased group

**Table 6:** The distribution of organ failure.

Peripheral blood level of endotoxin core antibody in patients with AP were significantly lower than that in control group ( $P < 0.01$ ), and the level of SAP group in admission day was significantly lower than that of MSAP group ( $P < 0.01$ ). Peripheral blood level of TNF- $\alpha$  in patients with AP were significantly higher than that in control group

( $P < 0.01$ ). The level of SAP group was significantly higher than that of MSAP group in admission days ( $P < 0.01$ ). The calcium level ( $P < 0.05$ ) and the level of polymorphonuclear neutrophil ( $P < 0.01$ ) in patients with SAP and MSAP had significant difference, but the other biochemistry index did not have difference (Table 7).

	Endotoxin core antibody (MMU/)	TNF- $\alpha$ (pg/ml)	Blood calcium (mmol/L)	Blood glucose (mmol/L)	Polymorphonuclear neutrophil (*10 <sup>9</sup> )	Blood amylase (U/L)
SAP	36.9 $\pm$ 9.8 <sup>^</sup>	18.12 $\pm$ 2.43 <sup>*</sup>	1.80 $\pm$ 0.26 <sup>^^</sup>	12.30 $\pm$ 5.43	13.60 $\pm$ 4.32 <sup>**</sup>	843 $\pm$ 575
MSAP	48.4 $\pm$ 9.6 <sup>^</sup>	14.09 $\pm$ 3.81 <sup>*</sup>	2.02 $\pm$ 0.14 <sup>^^</sup>	12.16 $\pm$ 5.46	9.42 $\pm$ 3.73 <sup>**</sup>	1031 $\pm$ 674

<sup>^</sup>, <sup>\*</sup>, <sup>\*\*</sup>  $p < 0.01$ , <sup>^^</sup>  $p < 0.05$

**Table 7:** The correlation between biochemical factors and severity of AP (2007).

## Discussion

Acute pancreatitis is a systemic disease, and is usually closely associated with organ failures [5-7]. In recent years, the treatment on AP has been improving steadily [8], significantly reducing the mortality associated with the disease. Currently, the major cause of death for AP patients is the multiple organ failures [9-11].

The clinical course of AP has 2 phases: early and late. The early phase, usually lasting during the first week, is characterized by the systemic inflammatory response syndrome (SIRS) as a result of the release of inflammatory mediators. This syndrome is often accompanied with organ failure and general derangements, including hypovolemia, hyperdynamic circulatory regulation, fluid loss from the intravascular space, and increased capillary permeability [12,13]. The definition of acute pancreatitis severity in the early phase depends on the presence of organ failure rather than necrosis [2]. The later phase, which can last from a few weeks to months, always has persistent systemic inflammations accompanied with the presence of the local complications [13,14]. Thus, the definition of acute pancreatitis severity in the late phase depends on the presence of organ failure and morphologic features [2].

Several cohort studies concentrated on the roles of organ failure in acute pancreatitis [15-21]. Most of these studies indicated that the presence of organ failure, particularly persistent organ failure, is significantly associated with mortality [15,16]. But rare study focused on the different types of organ failure affect the result of this disease. Particularly, because the definitions and classifications of acute pancreatitis have been updated and the treatment for AP has changed most previous studies are outdated or have a few inadequacies [22-25].

According to "Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus", Severity of the disease is categorized into 3 levels: mild, moderately severe, and severe. As a simple and practical clinical scoring system, a modified Marshall scoring system is recommended to stratify the severity of acute pancreatitis [2,26]. It aims to be able to early identification of potential serious patients and facilitate the patients with appropriate treatment.

Our study demonstrated that, in the course of acute pancreatitis, the number of organ failure is elevated accompanied the severity of the disease. Meanwhile, respiratory, cardiovascular and neurological failures have the highest incidence. Renal, hematologic and

cardiovascular failures are associated with the poorest prognosis. There appears to be different trends in the incidence and mortality of different organ failures. High incidence doesn't necessarily mean high mortality; similarly low incidence doesn't mean low mortality. The most typical example is respiratory failure, which has the highest incidence but relatively low mortality. On the other hand, renal failure has the highest mortality with a low incidence, suggesting more attention should be directed to the patients with acute renal failure. Furthermore, the risk factors that contribute to the acute renal failure, including insufficiency of circulation, IAH (intra-abdominal hypertension), and the use of nephrotoxicity drugs, etc., deserves more attention. Indicators related to renal function such as urine output, urine specific gravity, and creatinine level must also be aggressively monitored to identify the change of the renal function.

In order to reveal the effect of inflammatory factors and endotoxin on organ failures, this study also measured TNF- $\alpha$  and endotoxin core antibody in a group of patients. It demonstrated that Peripheral blood level of TNF- $\alpha$  and endotoxin core antibody in patients with SAP were significantly different with that of MSAP.

TNF- $\alpha$ , which is elevated in severe AP, is believed to activate neutrophils, increase capillary permeability, up-regulate endothelial adhesion molecules, and subsequently initiate or aggravate cellular toxic effects. TNF- $\alpha$  appears to act downstream by stimulating the release of other mediators (e.g., IL-6 and IL-8), thereby creating a vicious cytokine cascade promoting systemic inflammatory response syndrome and enhanced injury to the pancreas and distant organs [27].

Endotoxin is the major constituent of the wall of Gram-negative bacteria, its main components being the O-antigenic polysaccharide and lipid A [28]. Endotoxemia has been shown to be directly related to the severity of episodes of AP being more relevant in patients with SAP [29-32]. The Endocab IgM antibody titer is an indirect marker for endotoxin levels and endotoxemia peaks coincidentally with the lower levels of Endocab IgM antibody [33-35].

For AP cases, after the occurrence of various organ failures, the mortality increases from 37% to 63.8%, a very significant difference. As a result, a better understanding of organ failures offers great help for physicians to draw more accurate prognosis for each cases. Meanwhile, the varying fatality rates associated with different type of organ failures also enable physicians to choose the most effective treatment for each case, significantly improving the treatment effectiveness on AP cases.

Nonetheless, we acknowledge the limitations to our investigation. Our study was retrospective and from a single study center. In our study, the deceased group showed a significantly lower proportion (biliary/non-biliary) than the survival group in etiology. Based on this point in etiology, we need to consider an association between a cause of death and organ failure in further study.

In conclusion, our findings on the relationship between acute pancreatitis and organ dysfunction may promise to be a simple method to predict the severity of acute pancreatitis.

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