

## Original Article

# Abdominal paracentesis drainage (APD) attenuates acute pancreatitis-associated lung injury in patients with ascitic fluids: a retrospective study

Jing Zhou, Zhu Huang, Long Cheng, Ning Lin, Weihui Liu, Hongyu Sun, Lijun Tang

General Surgery Center of PLA, Chengdu Military General Hospital, Chengdu, Sichuan, China

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**Abstract:** Objectives: Recently, we have demonstrated that abdominal paracentesis drainage (APD) benefits patients with acute pancreatitis (AP). However, the therapeutic efficacy of APD against AP-associated lung injury remains unclear. Methods: Consecutive patients with fluid collections ( $\geq 100$  ml) in the abdominal or pelvic cavity, who were admitted to our hospital within 48 h of the onset of AP, were included in this retrospective study. These patients were divided into two groups: APD group and non-APD groups. The prevalence of acute respiratory distress syndrome (ARDS), the details of mechanical ventilation and the mortality rate were first investigated. Subsequently, the clinical and laboratory parameters, lung injury severity index and infection-related parameters were also evaluated. Results: Of the 184 involved patients, 99 were in the APD group, and 85 were in the non-APD group. The mortality rate was significantly lower in the APD group (5.0%) than in the non-APD group (14.1%;  $P < 0.05$ ). But no significant differences were found in the prevalence of ARDS between the two groups ( $P > 0.05$ ). Importantly, APD group showed an obvious decrease in lung injury severity and the recovery time compared with the non-APD group ( $P < 0.05$ ). Additionally, the APD group displayed a lower incidence of pulmonary infection compared with the non-APD group ( $P < 0.05$ ). Conclusions: Treatment with APD benefits patients with lung injury in the early stage of AP.

**Keywords:** Acute pancreatitis, pancreatitis-associated lung injury, pancreatitis-associated ascitic fluid, abdominal paracentesis drainage

## Introduction

Pancreatitis-associated lung injury (PALI) is characterized by varying degrees of acute respiratory distress syndrome (ARDS). It occurs in approximately one third of patients in the early phase of moderately severe or severe acute pancreatitis (SAP), which accounts for 60% of all deaths of pancreatitis within the first week [1]. These data show that PALI is a significant health problem and that developing an efficient strategy to treatment the patients with PALI is essential.

PALI is a consequence of the systemic inflammatory response syndrome (SIRS), which is characterized by inflammation and immune system activation in the early stage of AP. Numerous reports have shown that inflammatory mediators play a key role in the pathogenesis of ALI, such as IL-1 $\beta$ , IL-6, IL-10, TNF- $\alpha$  and free fatty acids (FFAs). These mediators can contrib-

ute to the damage of the alveolar epithelial and endothelial barriers in lung [2, 3] and cause an increase in the permeability of the alveolar-capillary barrier. These events will make protein-rich edematous fluid influx into air spaces, thereby resulting in the dysfunction of gas exchange and ventilation of lung [4, 5]. To reduce inflammation and lung damage caused by SIRS during pancreatitis, various therapeutic endeavors have been proposed, however, no effective strategies for PALI have been developed thus far. Currently, mechanical ventilation still remains the main supportive method of treatment for PALI [6]. Therefore, it is essential to develop effective interventions to reduce and promote recovery of lung damage during pancreatitis [7].

Pancreatitis-associated ascitic fluids (PAAFs) are common complications in the early stages of pancreatitis. PAAFs, which appear in the

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abdominal or the pelvic cavity of patients, have been shown to be rich in toxic factors, including ILs, TNF- $\alpha$ , FFAs and other cytokines. These mediators can amplify the inflammation course of pancreatitis and ultimately result in the failure of distant organ [8, 9]. Therefore, we asked whether drainage of PAAFs can benefit patients with SAP. To explore this issue, in our previous studies [10, 11], we have developed a new therapeutic strategy, abdominal paracentesis drainage (APD), in order to remove PAAFs, and we have preliminarily evaluated the value of APD in pancreatitis patients. We found that treatment with APD decreased the mortality rate and rapidly normalized the laboratory variables. Meanwhile, we found that treatment with APD in patients with PAAFs did not increase the infection risk [12]. However, the other effects and underlying mechanism of APD have not been explored in detail. Especially, it is uncertain whether APD have the efficacy on patients with PALI. Therefore, it is necessary to further determine the effectiveness of APD on PALI.

In the present study, as an extension of our previous studies, we aimed to determine the prophylactic and therapeutic effects of APD on lung injury in the early stage of SAP.

### Patients and methods

#### *Study population*

We retrospectively reviewed our hospital records between October 2010 and September 2013. The approval of the Ethics Committee of Chengdu Military General Hospital was obtained (No. 2010034), and this study was performed according to the principles of the Declaration of Helsinki (2000 revision). SAP and MSAP (moderately severe acute pancreatitis) patients (>18 years old) with a volume of fluid collections of  $\geq 100$  ml in the abdominal or pelvic cavity, who were admitted to our hospital within 48 h of disease onset, were included in the study. Diagnoses of AP were based on clinical signs, serum amylase levels, and the computed tomography severity index (CTSI) per the revised Atlanta Classification [13]. The exclusion criteria included the following: 1. patients who underwent abdominal puncture or exploratory laparotomy for acute abdominal distresses before admission; 2. patients with AP subsequent to a second disease for which endoscopic retrograde cholangiopancreatography were

performed; 3. patients with a medical history of immune deficiency or chronic lung disease. All patients were followed for one year from inclusion in the study or until death.

#### *Grouping*

Patients were categorized into two groups according to whether they underwent APD treatment within 48 h after admission (the APD and non-APD groups).

#### *Intervention for the APD group*

As soon as the fluid ( $\geq 100$  ml) was detected by ultrasound within 48 h after admission, a pig-tail drainage tube (usually 14-16 F) was placed in the abdominal or pelvic cavity for continuous drainage of ascites to eliminate the fluid collections. An ultrasound guide was used in the puncture process to ensure optimal drainage placement and safety. In the treatment phase, replacement or additional placement was conducted if the initial APD was insufficient. Drainage of less than 10 ml/day for two consecutive days or no residual fluid collection on ultrasound was considered as an indication for removal of the tube. Ascites bacterial cultures were conventionally produced after APD each week. When a fever appeared, leukocytes increased or purulent sputum was present, blood culture and sputum culture results were obtained.

#### *Definition and treatment of lung injury*

According to the definition of ARDS (the Berlin definition, 2012) [14], the patients were divided into four categories based on their degree of hypoxemia: no ARDS ( $\text{PaO}_2/\text{FiO}_2 > 300$  mmHg) and mild, moderate or severe ARDS (200-300 mmHg, 100-200 mmHg, and  $< 100$  mmHg, respectively). Chest radiography or CT results were independently evaluated by two radiologists for the presence or absence of bilateral lung infiltrates. Cardiogenic pulmonary edema was excluded based on the assessment of echocardiograms.

For patients with ARDS, oxygen inhalation therapy and noninvasive or invasive mechanical ventilation have been adopted depending on the disease severity. The on and off times of ventilation were determined according to the practical guidelines for mechanical ventilation [15], which were decided jointly by two experi-

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enced specialists including an internal medicine physician. The ventilators were usually set at a tidal volume of 6-7 ml/Kg, continuous positive airway pressure (CPAP) or positive end-expiratory pressure (PEEP)  $\geq 10$  cmH<sub>2</sub>O and the minimal level of FiO<sub>2</sub> to maintain SO<sub>2</sub> above 90%. The end-inspiratory pressure was maintained below 30 cmH<sub>2</sub>O. The results of the extravascular lung water index (EVLWI) and the pulmonary vascular permeability index (PVPI) were measured using a transpulmonary thermodilution technique via a PICCO monitor (PC-8500, DE PULSION Corporation), were collected if the tests were performed. Finally, the results were obtained from 25 patients in the APD group and 27 patients in the non-APD group, and showed that all 52 included patients developed ARDS.

### *Treatment protocols*

All patients received conservative treatment such as rigorous fluid resuscitation, antibiotics, and gastrointestinal decompression according to the UK/International Association of Pancreatology guidelines. Nasojejunal enteral feeding was employed if necessary. Thoracentesis was conducted when pleural effusion was greater than 3 cm deep and a safety pathway existed. Abdominal ultrasound was performed if necessary. Abdominal contrast-enhanced CT was performed at admission and the disease severity was evaluated every 7-14 days thereafter if the patient's condition allowed. The vital signs and biochemical indexes, including inflammatory factor and blood gas levels, were closely monitored in all patients. The acute physiology and chronic health evaluation II (APACHE II) score, the Ranson score and the Murray lung injury score (MLIS) were collected on admission and each day for one week after admission.

During follow-up treatment, which was typically initiated 4 weeks after disease onset, patients who did not show any improvement or even deterioration (as evidenced by persistent fever, increased leukocyte count/increasing trend in the leukocyte count, worsening or new-onset organ failure, or diagnosis with infected necrotizing pancreatitis based on CT or fine needle aspiration results) during routine treatment accepted percutaneous catheter drainage (PCD). Surgeries such as endoscopic debridement or necrosectomy were performed at our center on

those people who had indications, such as persistent or worsening sepsis symptoms after PCD, worsening or new-onset organ failure, inadequate drainage (<10 ml/day) of fluid collections and necrosis, and bowel complications caused by ongoing necrosis (such as obstruction or uncontrolled fistula).

### *Data collection*

Data on the following parameters were collected: Prevalence and details of ARDS, mechanical ventilation, and disease-specific mortality. Demographic information and severity scores (APACHE II, Ransom, and MLIS) before and after APD for all patients. Serum levels of inflammatory cytokines (CRP, TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and IL-10) and FFAs, leukocyte count, respiratory rate (RR), and oxygenation index (PaO<sub>2</sub>/FiO<sub>2</sub>) before and after APD. ELWI and PVPI before and after APD in 25 patients in the APD group and 27 patients in the non-APD group. Prevalence of pneumonia, bacteremia and abdominal infection.

### *Statistical analysis*

The statistical calculations were performed using SPSS version 19.0 for Windows (IBM Corporation, Somers, NY, USA). Normally distributed data were described as the means  $\pm$  SD and were compared using Student's *t* test. Alternatively, non-normally distributed data were reported as the medians (interquartile range) and were compared using the Mann-Whitney test. Repeated-measures ANOVA followed by Scheffe post hoc analysis was used to compare data for the two groups at different time points. Categorical and qualitative data were presented as proportions and frequencies and were compared using a chi-squared test or Fisher's exact test. A *p* value <0.05 was considered to be statistically significant.

## **Results**

Of the 245 patients with sufficient fluid collections in the abdominal or pelvic cavity on admission for study inclusion, 61 patients were excluded from the study for the following reasons: 4 patients accepted endoscopic retrograde cholangiopancreatography before admission; 2 patients underwent laparotomy of the acute abdomen before admission and were intra-operatively diagnosed with SAP; 11 had a

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**Table 1.** Characteristics of 184 patients enrolled in this study on admission

Characteristic	Non-APD Group	APD Group	<i>p</i>
Number of patients	85	99	
Demographic data			
Age	49.3±10.8	50.0±11.5	0.085
Male:Female	44:41	52:47	1.000
Etiology (%)			0.960
Gallstone	38 (44.7)	46 (46.5)	
Hyperlipemia	25 (29.4)	29 (29.3)	
Alcohol abuse	17 (20.0)	20 (20.2)	
Others	5 (5.8)	4 (4.0)	
Classification			0.658
MSAP (79)	38	41	
SAP (105)	47	58	
Laboratory variables			
CRP (mg/L)	132.7±57.2	131.8±48.1	0.906
IL-6 (pg/ml)	360.6±155.9	354.5±97.4	0.696
IL-1β (pg/ml)	14.3±4.8	13.2±4.1	0.122
IL-10 (pg/ml)	128.1±72.1	129.6±58.1	0.875
TNF-α (pg/ml)	23.3±7.2	22.8±7.8	0.664
FFAs (mmol/L)	1.66±0.41	1.64±0.48	0.744
PH<7.2 (%)	8 (9.4)	9 (9.1)	0.645
PaO <sub>2</sub> /FiO <sub>2</sub> at admission	262.9±80.2	283.5±80.8	0.111
RR at admission (Time/min)	26.7±3.9	26.3±5.4	0.636
Severity scores			
APACHE II (mean ± SD)	17.8±11.7 (8-64)	17.6±10.1 (7-62)	0.942
Ranson score (mean ± SD)	3.3±1.5 (1-8)	3.2±1.4 (1-8)	0.535
MLIS (mean ± SD)	3.1±1.9 (0-8)	3.4±2.1 (0-9)	0.337
Indexes of medical economics (median ± interquartile range)			
Days in hospital	62.3±31.24	61.4±35.2	0.065
Total cost during hospitalization (dollars)	10,015.2±3,047.3	9,613.5±2678.3	0.052

APD = abdominal paracentesis drainage; APACHE II = acute physiology and chronic health evaluation II; MLIS = modified lung injury score; APD group = patients in this group treated with APD; Non-APD group = patients in this group treated without APD; CRP = C-reaction protein; FFAs = free fatty acids; PaO<sub>2</sub>/FiO<sub>2</sub> = oxygenation index; IL = interleukin.

medical history of immune deficiency or lung disease, such as respiratory tract infection, asthma or chronic obstructive lung disease; and 44 lacked complete information regarding the main endpoints (≥3 terms). Of the remaining 184 patients, in addition to conventional treatment, APD was performed on 99 patients within 48 hours after admission (APD group), while others were not (non-APD group). The total number of catheters used in the 99 patients in the APD group was 113. Of the 85 patients in the non-APD group, only 3 patients accepted APD beyond 48 hours after admission. The median duration of APD was 8.4 days. In addition, 61 patients in the APD group were managed with PCD after APD, and 4 patients

required endoscopic debridement or necrosectomy. Moreover, 62 patients in the non-APD group received PCD, and 6 were treated via endoscopic debridement or necrosectomy.

### Baseline data

The demographic data (age, sex, and etiology) were comparable between the non-APD and APD groups (Table 1). The main cause of AP attributed to bile duct problems (44.7% in the non-APD group and 46.5% in the APD group), followed by hyperlipidemia (29.4% in the non-APD group and 29.3% in the APD group). Aside from the demographic data, the levels of initial laboratory parameters (CRP, IL-6, IL-1β, IL-10,

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**Table 2.** Clinical Outcomes between two groups

Variable	Non-APD Group	APD Group	<i>p</i>
Number of patients	85	99	
Mortality (%)	12 (14.1)	5 (5.0)	0.042*
Patients without ARDS (%)	36 (42.4)	52 (52.5)	0.185
Prevalence of ARDS (%)			0.028*
Mild	23 (27.1)	35 (35.4)	
Moderate	14 (16.5)	8 (8.1)	
Severe	12 (14.1)	4 (4.0)	
Prevalence of pulmonary edema on Chest radiograph (%)	32 (37.6)	24 (24.2)	0.055
Patients treated with ventilator (%)	39 (45.9)	40 (40.4)	0.460
Duration of ventilator (d)	5.5±2.1	3.0±1.2	0.010*
The recovery of RR (d)	5.0±2.4	2.5±1.7	<0.001*
Organ failure (%)			0.016*
No organ failure	20 (23.5)	43 (43.4)	
Single organ failure	34 (40.0)	32 (32.3)	
Multiple organ failure	31 (36.5)	24 (24.2)	
Patients with thoracentesis (%)	15 (17.6)	19 (19.2)	0.850
Average volume of pleural drainage (ml)	416±52	395±48	0.247

APD = abdominal paracentesis drainage; APD group = patients in this group treated with APD; Non-APD group = patients in this group treated without APD; ARDS = acute respiratory distress syndrome; RR = respiratory rate. \*Significant difference.

**Table 3.** Laboratory and clinical parameters between two groups 4d after Admission (48 h after APD)

Variable	Non-APD Group	APD Group	<i>p</i>
Number of patients	85	99	
Laboratory variables			
FFAs (mmol/L)	1.44±0.40	0.49±0.23	<0.001*
CRP (mg/L)	124±52.1	55.0±22.8	0.012*
IL-6 (pg/ml)	338.4±108.2	133.2±51.4	0.023*
IL-10 (pg/ml)	120.1±65.7	45.0±19.2	0.021*
IL-1β (pg/ml)	12.0±3.9	8.3±2.4	0.017*
TNF-α (pg/ml)	19.9±6.9	12.7±4.1	0.021*
PH<7.2 (%)	4 (4.7)	5 (5.0)	0.241
Severity scores			
APACHE II (mean ± SD)	15.2±10.6 (0-64)	9.6±8.6 (0-61)	0.021*
Ranson (mean ± SD)	2.9±1.2 (1-6)	1.7±1.1 (1-6)	0.027*
MLIS (mean ± SD)	2.9±2.2 (0-8)	2.1±1.5 (0-8)	0.038*

APD = abdominal paracentesis drainage; APACHE II = acute physiology and chronic health evaluation II; MLIS = modified lung injury score; APD group = patients in this group treated with APD; Non-APD group = patients in this group treated without APD; CRP = C-reaction protein; FFAs = free fatty acids; IL = interleukin. \*Significant difference.

TNF-α and FFAs), RR and PaO<sub>2</sub>/FiO<sub>2</sub> were not different between the two groups at admission. The APACHE II scores, Ranson scores, and MLISs were similar between the two groups. There were no significant differences in the total cost during hospitalization and the num-

ber of days in the hospital (*P*>0.05; **Table 1**).

### Outcomes

Mortality and lung injury. The disease-specific mortality rate in the APD group was 5.0% (5/99 patients) which was significantly lower than that in the non-APD group (14.1%) (12/85 patients; *P*<0.05). There was no significant difference in the prevalence of ARDS or pulmonary edema (*P*>0.05). However, we found that the non-APD group exhibited a higher proportion of patients with moderate or severe ARDS than the APD group (*P*<0.05; **Table 2**). A similar number of patients were treated via mechanical ventilation (non-invasive or tracheal intubation) between the non-APD group (45.9%) and the APD group (40.4%; *P*>0.05). The patients in the APD group required a significantly shorter duration on the ventilator and exhibited a shorter recovery time from an abnormal breathing rate than the patients in the non-APD group (*P*<0.05). No significant difference was found in

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**Table 4.** Lung injury parameters between two groups before APD

Variable	Non-APD Group	APD Group	<i>p</i>
Number of patients	85	99	
Patients without ventilator therapy (%)	46 (54.1)	59 (59.6)	0.460
Ventilator therapy (%)			0.330
Non-invasive	26 (30.6)	32 (32.3)	
Tracheal intubation	13 (15.3)	8 (8.1)	
PaO <sub>2</sub> /FiO <sub>2</sub>	262.9±80.2	283.5±80.8	0.111
PVPI <sup>#</sup>	4.2±0.7	4.0±0.4	0.269
EVLWI (ml/kg) <sup>#</sup>	19.9±6.3	19.7±5.6	0.451

APD = abdominal paracentesis drainage; APD group = patients in this group treated with APD; Non-APD group = patients in this group treated without APD; PaO<sub>2</sub>/FiO<sub>2</sub> = oxygenation index; PVPI = pulmonary vascular permeability Index; EVLWI = extravascular lung water index. <sup>#</sup>25 patients in the APD group and 27 patients in the non-APD group were tested.

**Table 5.** Lung injury parameters between two groups 4d after admission (approximately 48 h after APD)

Variable	Non-APD Group	APD Group	<i>p</i>
Number of patients	85	99	
Patients without ventilator therapy (%)	49 (57.6)	69 (69.7)	0.093
Ventilator therapy (%)			0.048*
Non-invasive	23 (27.1)	25 (25.3)	
Tracheal intubation	13 (15.3)	5 (5.0)	
PaO <sub>2</sub> /FiO <sub>2</sub>	280.9±71.8	294.7±73.8	0.051
PVPI <sup>#</sup>	4.0±0.7	3.4±0.5	<0.001*
EVLWI (ml/kg) <sup>#</sup>	18.8±5.8	12.7±6.6	<0.001*

APD = abdominal paracentesis drainage; APD group = patients in this group treated with APD; Non-APD group = patients in this group treated without APD; PaO<sub>2</sub>/FiO<sub>2</sub> = oxygenation index; PVPI = pulmonary vascular permeability Index; EVLWI = extravascular lung water index. \*Significant difference. <sup>#</sup>25 patients in the APD group and 27 patients in the Non-APD group were tested.

the number of patients treated via thoracocentesis and the average volume of pleural drainage between the two groups ( $P>0.05$ ; **Table 2**).

Clinical and laboratory parameters. The clinical and laboratory parameters were collected approximately 4 days after admission (approximately 48 hours after APD). The APACHE II scores, Ranson scores, and MLISs were significantly higher in the non-APD group than those in the APD group ( $P<0.05$ ; **Table 3**). Although the levels of laboratory parameters (FFAs, CRP, TNF- $\alpha$ , IL-6, IL-1 $\beta$ , IL-10, and TNF- $\alpha$ ) declined somewhat in both groups, APD led to a significant decrease in these parameters ( $P<0.05$ ; **Table 3**). These results were consistent with the findings of our previous study.

Lung injury parameters. Within 2 days of admission (before APD), the number of patients treated via non-invasive or tracheal intubation, ven-

tilation or PaO<sub>2</sub>/FiO<sub>2</sub> showed no significant differences between the two groups. Lung injury severity indexes, including PVPI and EVLWI, which were assessed in 25 patients in the APD group and 27 patients in the non-APD group, showed no significant differences between the groups (**Table 4**). Approximately 4 days after admission (approximately 48 h after APD), there remained no significant difference in the number of patients treated via ventilation between the two groups ( $P>0.05$ ). However, the proportion of patients who received tracheal intubation was significantly higher in the non-APD group than that in the APD group ( $P<0.05$ ; **Table 5**). Although PaO<sub>2</sub>/FiO<sub>2</sub> showed no significant differences between the two groups, the lung injury severity indexes indicated that the more severe lung injury was observed in the non-APD group compared with the APD group. For example, the PVPI and EVLWI were (4.0±0.7) and (18.8±5.8) ml/Kg, respectively, in the 27 assessed patients in the non-APD group while those in the APD group were (3.4±0.5) and (12.7±6.6) ml/Kg, respectively, in the 25 assessed patients ( $P<0.05$ ; **Table 5**).

Five days after admission (approximately 72 h after APD), the percentage of patients not receiving mechanical ventilation in the APD group (83/99, 83.8%) was higher compared with that in the non-APD group (60/85, 70.6%;  $P<0.05$ ). Fewer patients underwent tracheal intubation in the APD group (2/99, 2.0%) than in the non-APD group (11/85, 12.9%;  $P<0.05$ ). PaO<sub>2</sub>/FiO<sub>2</sub> was (329.2±60.7) in the APD group, and this ratio was higher than that in the non-APD group (294.4±61.2;  $P<0.05$ ). All of the lung injury severity index scores showed greater improvement in the APD group; PVPI and

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**Table 6.** Lung injury parameters between two groups 5 d after admission (approximately 72 h after APD)

Variable	Non-APD Group	APD Group	<i>p</i>
Number of patients	85	99	
Patients without ventilator therapy (%)	60 (70.6)	83 (83.8)	0.034*
Ventilator therapy (%)			0.045*
Non-invasive	14 (16.5)	14 (14.1)	
Tracheal intubation	11 (12.9)	2 (2.0)	
PaO <sub>2</sub> /FiO <sub>2</sub>	294.4±61.2	329.2±60.7	0.008*
PVPI <sup>#</sup>	3.7±0.6	2.2±0.9	0.003*
EVLWI (ml/kg) <sup>#</sup>	15.2±5.6	7.1±2.6	<0.001*

APD = abdominal paracentesis drainage; APD group = patients in this group treated with APD; Non-APD group = patients in this group treated without APD; PaO<sub>2</sub>/FiO<sub>2</sub> = oxygenation index; PVPI = pulmonary vascular permeability index; EVLWI = extravascular lung water index. \*Significant difference. <sup>#</sup>25 patients in the APD group and 27 patients in the non-APD group were tested.

**Table 7.** Infection-related parameters between two groups

Variable	Non-APD Group	APD Group	<i>p</i>
Number of patients	85	99	
Prevalence of abdominal infection (%)			0.804
No infection	38 (44.7)	40 (40.4)	
Polymicrobial infections	43 (50.6)	53 (53.5)	
Monomicrobial infections	4 (4.7)	6 (6.1)	
The prevalence of pulmonary infections (%)	21 (24.7)	12 (12.1)	0.034*
The prevalence of bacteremia (%)	11 (12.9)	10 (10.1)	0.644
WBC count (×10E9/L)			
At admission	13.6±3.6	13.3±3.6	0.574
The recovery of WBC (d)	19.2±7.9	15.6±5.4	0.043*

APD = abdominal paracentesis drainage; APD group = patients in this group treated with APD; Non-APD group = patients in this group treated without APD; WBC = white blood cell. \*Significant difference.

EVLWI were (2.2±0.9) and (7.1±2.6) ml/Kg, respectively, in the APD group, and were (3.7±0.6) and (15.2±5.6) ml/Kg, respectively, in the non-APD group (*P*<0.05; **Table 6**). These results indicated that APD shortened lung injury recovery time.

Infection-related parameters. At admission, the mean white blood cell (WBC) count showed no significant differences between the two groups. However, recovery of the WBC count took longer in the patients in the non-APD group (19.2±7.9 days) compared with those in the APD group (15.6±5.4 days; *P*<0.05; **Table 7**). The incidence of pulmonary infection was higher in the non-APD group (21/85, 24.7%) than in the APD group (12/99, 12.1%; *P*<0.05), and most cases of pulmonary infection occurred in patients receiving tracheal intubation (26/33, 78.8%). Additionally, there were no significant

differences in the prevalence of abdominal infection between the non-APD group (47/85, 55.2%) and the APD group (59/99, 59.6%; *P*>0.05). The prevalence of bacteremia was similar between the two groups. Bacterial isolates were identified in the ascites of 4 patients, all of whom developed bacteremia. These results indicated that APD significantly reduced incidence of pneumonia but did not increase the risk of abdominal infection or bacteremia.

### Discussion

In this study, we establish evidence that treatment with APD benefits patients with AP-associated lung injury. The important findings are that (i) APD significantly reduced the serum levels of inflammatory factors; (ii) APD attenuated the lung injury severity indexes and

shortened lung injury recovery time. (iii) APD decreased the incidence of pneumonia in SAP patients.

In the past few years, in our institution, we demonstrated that ultrasound-guided APD is an beneficial minimally invasive step for patients with pancreatitis, which reduces inflammatory factors and postpones further interventions, although the efficacy of APD against PALI had not been elucidated [10]. As a further research step, we retrospectively analyzed the characteristics of lung injury in 184 MSAP/SAP patients with or without APD intervention treatment. We found that treatment with APD could attenuate PALI in patients with fluid collections. The findings offer new insight into the mechanisms for APD effectiveness, which has significant implications for the clinical management of AP-associated lung injury.

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The critical period of lung injury is between the first and fourth day during the course of AP [16, 17], and the severity of lung injury varies from mild hypoxemia without clinical or radiologic abnormalities to severe ARDS. All of these forms of damage have been associated with the magnitude of systemic inflammatory response syndrome (SIRS) caused by pancreatic inflammation in the early stage of AP [18, 19]. Thus, inflammatory factors play an important role in the AP-associated lung injury. Our research showed that treatment with APD at an early stage of AP significantly reduced the levels of cytokines, including CRP, TNF- $\alpha$ , IL-6, IL-1 $\beta$ , and IL-10, which was consistent with the findings of our previous study. These alterations may contribute to reduce pulmonary vascular permeability and alveolar epithelial injury.

PVPI and EVLWI, which are measures of the interstitial, alveolar and lymphatic fluid content of lungs, are early markers of acute lung injury [20-22]. Once the AP-associated lung injury occurs, the pulmonary microvasculature will suffer damage and the permeability of the endothelial membrane increases, resulting in capillary leakage and elevated PVPI and EVLWI. In this study, treatment with APD showed clear improvements in PVPI and EVLWI within 48 hours in SIRS patients, thereby reducing the lung injury severity. These results indicated that APD protected the alveolar epithelial and endothelial barrier and alleviated the vascular permeability caused by pancreatitis.

Some other reasons may also be responsible for the beneficial effects of APD on AP-associated lung injury. First, during the AP, pancreatic lipase is released by the inflamed pancreas into the peritoneal cavity, and may cause abdominal fat digestion, leading to the production of large amounts of FFAs [23], and FFAs could cause oxidative stress damage in lung [24]. Second, APD may reduce abdominal pressure by removing ascites and relieving visceral edema secondary to SIRS [25]; these effects may alleviate breathing difficulty and pulmonary atelectasis secondary to the diaphragm lift caused by increased intra-abdominal pressure [26]. Finally, APD may reduce the incidence of ventilator-associated lung injury by shortening the mean duration of mechanical ventilation and avoiding tracheal intubation [27].

Pulmonary infection is a common complication, particularly following mechanical ventilation, which has a significant impact on the mortality of patients with AP [28]. In our study, we found treatment with APD did not result in an evident increase in the prevalence of bacteremia or abdominal infection, which is consistent with the results of our previous study [12]. Importantly, we found that the APD group less frequently experienced pulmonary infection. Two reasons may explain why early APD may avoid additional pulmonary infections. First, APD may remove nutritional factors present in fluid collections, such as hematin, which favor bacterial growth [29]. Second, APD was correlated with accelerated recovery time from organ failure, including lung injury [10], and this effect may shorten the duration of ventilation, thereby avoiding the occurrence of ventilator-associated pneumonia.

There are some limitations in our study. First, this is a retrospective study, and some important data are lacking in a substantial number of patients. Second, because APD as a new step in the novel step-up approach treatment of pancreatitis remains in the initial stage at our institution, a lower rate of procedure-related complications may have occurred. Third, some patients had pleural effusion together with ascites, and the condition of pleural puncture may also impact pulmonary function; however, simplified studies were performed due to the limited number of patients available for investigation. Finally, all of the APD treatments in this study were performed within one week of disease onset, but APD may be performed at any time within four weeks of disease onset. The timing of APD and the characteristics of patients receiving APD are issues that need to be considered further. Therefore, further prospective multicenter studies need to be carried out to confirm the therapeutic efficacy of APD.

In conclusion, implementing APD is beneficial for patients with AP-associated lung injury in the early stage of MSAP/SAP. Furthermore, treatment with APD decreases the incidence of pneumonia in SAP patients.

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## Disclosure of conflict of interest

None.

**Address correspondence to:** Lijun Tang and Hongyu Sun, General Surgery Center of PLA, Chengdu Military General Hospital, Chengdu 610083, Sichuan, China. Tel: 0086-28-86571251; Fax: 0086-28-86571251; E-mail: 1328226428@qq.com (LJT); shongyu2008@163.com (HYS)

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