Int J Clin Exp Med 2017;10(2):3445-3453
www.ijcem.com /ISSN:1940-5901/IJCEM0038793

Original Article

Analysis of risk factors of secondary pulmonary edema during fluid resuscitation in sepsis patients

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Received August 25, 2016; Accepted November 27, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: Background: Sepsis patients are likely to develop non-cardiogenic pulmonary edema. This study was to identify the risk factors of secondary pulmonary edema in sepsis patients presenting with tissue hypoperfusion undergoing fluid resuscitation. Methods: Adult sepsis patients with a serum lactate level >2 mmol/L were enrolled. Patients with a decline of PaO2/FiO2 (P/F) and diagnosed with pulmonary edema were assigned into the P/F decline group. The level of lactate, P/F, procalcitonin (PCT), central venous pressure (CVP) and acute physiology and chronic health evaluation II (APACHE II) and sequential organ failure assessment (SOFA) scores were evaluated. The risk factors of secondary pulmonary edema were analyzed. Results: A total of 195 cases of sepsis were recruited including 94 in the P/F decline group and 101 in the P/F non-decline group. APACHE II, SOFA scores, serum albumin, serum creatinine, PCT, NT-proBNP and CVP levels were subject to uni- and multi-variate logistic regression analysis. The results demonstrated that APACHE II, SOFA scores and PCT were the risk factors of secondary pulmonary edema in sepsis patients undergoing fluid resuscitation. Conclusion: APACHE II, SOFA scores and PCT are the risk factors of secondary pulmonary edema in patients with sepsis during the fluid resuscitation.

Keywords: Sepsis, fluid resuscitation, pulmonary edema, risk factor

Introduction

Sepsis is a life-threatening syndrome that arises when the host immunoreaction to the infection injures the organs [1]. The incidence of tissue hypoperfusion in sepsis patients may aggravate the severity of disease and accelerate the incidence and progression of organ dysfunction. Systemic circulation and perfusion should cater to tissue metabolism, and attain the balance between oxygen supply and consumption. If oxygen supply-consumption imbalance arises, sepsis can evolve into multiple organ dysfunction syndrome (MODS) with a significantly high mortality rate. Early and effective interventions are required to decrease the mortality rate [2]. Early fluid resuscitation acts as a vital intervention for sepsis patients suffering from tissue hypoperfusion [3]. Based upon the Frank-Starling mechanism, fluid resuscitation should be administered if cardiac output (CO) could be enhanced by increasing venous return [4], maintain blood vessel interior capacity, improve tissue organ perfusion, decrease the risk of MODS and reduce the mortality rate, thereby improving clinical prognosis [5].

Sepsis patients are likely to develop non-cardiogenic pulmonary edema due to severe systemic inflammatory response, alveolar epithelial and capillary endothelial injury [6]. Therefore, the incidence of secondary pulmonary edema during fluid resuscitation is likely to provoke gas interchange disturbance, lead to respiratory failure and accelerate the progression into MODS [7]. Moreover, the fluid treatment for sepsis patients complicated with pulmonary edema is complicated [8] and the mortality rate will ascend [9]. In clinical practice, how to decrease the incidence of pulmonary edema during fluid resuscitation is of vital significance for sepsis patients complicated with tissue hypoperfusion.

Pulmonary edema can be divided into cardiogenic and non-cardiogenic pulmonary edema [10]. The focus of clinical therapy is to treat the

primary disease. For both types of pulmonary edema, conservative liquid therapy can shorten mechanical ventilation time, protect organ function and reduce the mortality rate.

Previous investigations have demonstrated that fluid resuscitation during hospitalization increases the incidence of ARDS in septic shock patients [11]. Excessive fluid load prolongs the duration of organ dysfunction and elevates the death rate [12]. In this retrospective study, the changes of P/F and the incidence or aggravation of pulmonary edema were observed during fluid resuscitation, aiming to explore the risk factors of secondary pulmonary edema, identify the sepsis patients with high-risk pulmonary edema and provide guidance to the fluid treatment in sepsis patients.

Materials and methods

Study subjects

Inclusion criteria: Sepsis patients admitted to the Department of Critical Care Medicine of Xiangya Hospital of Central South University between November 2013 and March 2016 were recruited according to the following criteria: those aged ≥18 years; those with serum lactate level >2 mmol/L (18 mg/dl) and those signed the informed consents. Sepsis is defined as systemic inflammatory response syndrome (SIRS) induced by bacteria or highly-suspected infectious lesions. SIRS patients present with at least two of the following manifestations: body temperature >38°C or <36°C; heart rate >90 beats/min; respiratory rate >20 times/min or $PaCO_2$ <32 mmHg; peripheral blood leukocyte count >12 × 10^9/L or <4 × 10^9/L or immature cells >10%.

Exclusion criteria: those with acute myocardial infarction, cardiogenic shock or heart failure heart failure with EF value <40%; those with pulmonary embolism and pericardial tamponade after cardio-pulmonary resuscitation; those with severe asthma, COPD and lung cancer; those with airway obstruction, moderate or high quantity of hydrothorax, pneumothorax and P/F≤100; pregnant woman; those refused to sign the informed consents; length of hospital stay <24 h.

Baseline data

Multiple parameters including medical history, age, gender, vital signs upon admission, respiratory rate, P/F, arterial serum lactate level, serum albumin, APACHE II and SOFA scores, PCT, NT-proBNP, arterial blood gas analysis, CVP, infection site, etiology test, adjuvant examinations, blood transfusion, intake and output volume of the first 24 h-fluid resuscitation (7:00 a.m. to 7:00 a.m. of the next day), total fluid intake and output volume during ICU stay, duration of mechanical ventilation, length of ICU stay and 28-d follow-up were closely monitored. Blood gas analysis was performed (GEM Premier 3000 blood gas analyzer, U.S.). Based upon the fluid resuscitation procedures, dynamic blood gas analysis was carried out. Routine blood test and liver and kidney function test were completed by the inspection department of Xiangya Hospital. NT-proBNP level was quantitatively analyzed by enzyme-linked fluoroimmunoassay (VIDAS PC, VIDASNT-proBNP kit, pg/ml, France). PCT level was measured using enzyme-linked fluoroimmunoassay (VIDAS PC, VIDASPCT kit, ng/ml, France).

Experimental grouping

According to the Surviving Sepsis Campaign's (SSC) resuscitation bundle, fluid resuscitation compliance was assessed at 6 h after diagnosis of septic shock.

If arterial serum lactate level was improved, the standard reference of P/F decline complied with the Berlin ARDS Definition in 2012 [13]. During fluid resuscitation, patients with declining P/F and were diagnosed with pulmonary edema by three independent specialists were assigned into the P/F decline group, and those without P/F decline were allocated into the P/F non-decline group.

If serum lactate level was not improved, patients with declining P/F during fluid resuscitation, and were diagnosed with pulmonary edema by three independent specialists were assigned into the P/F decline group. The remaining patients without P/F decline continued to receive fluid therapy for 24 h. Those with P/F decline and were diagnosed with pulmonary edema by three independent specialists were allocated into the P/F decline group and others were assigned into the P/F non-decline group.

The diagnosis of pulmonary edema was confirmed by three clinicians according to medical history, clinical symptom, physical sign, labora-

Table 1. Comparison of baseline data between the P/F decline and P/F non-decline groups

Parameter	OI decline group	OI non-decline group	*P* value
No. of case (n)	94	101	
Gender (male/female)	61.7% (58/36)	58.4% (59/42)	0.66
Age (years)	57.5 ± 15.2	55.9 ± 14.2	0.45
Medical history			
Hypertension (Yes/No)	19.1% (18/76)	11.9% (12/89)	0.17
Coronary heart disease (Yes/No)	11.7% (11/83)	3.0% (3/98)	0.03
Diabetes mellitus (Yes/No)	13.8% (13/81)	8.9% (9/92)	0.37
Blood transfusion (Yes/No)	74.5% (70/24)	61.4% (62/39)	0.07
CRRT (Yes/No)	64.9% (61/33)	28.7% (29/72)	0.008
Duration of mechanical ventilation (h)	49.0 (17.0, 108.2)	8.1 (0, 44.0)	0.007
Length of ICU stay	112.6 (66.1, 188.4)	85.3 (55.2, 157.4)	0.12
Fluid balance at the first day (ml)	2858.0 ± 1980.8	1651.5 ± 1804.8	0.005
Total fluid balance (ml)	5725.5 ± 4941.1	2246.5 ± 4238.1	0.003
28-d mortality rate (%)	67% (63/31)	18.8% (19/82)	0.004

tory and accessory examinations including radiography, lung CT, ultrasound and/or PiCCO parameters.

Diagnostic criteria of pulmonary edema

Diagnostic criteria of cardiogenic pulmonary edema: On the basis of Framingham standard [14], clinical symptom, physical sign, laboratory examination (troponin, NT-proBNP), electrocardiogram, imaging test, echocardiography, hemodynamics test and therapeutic outcomes were considered.

Diagnostic criteria of non-cardiogenic pulmonary edema: based on the Berlin ARDS Definition [13], high-risk patients presented with de novo symptoms or aggravation, such as shortness of breath and respiratory distress; bilateral lung infiltration, unexplained by hydrothorax, pulmonary atelectasis or node; respiratory failure unexplained by heart failure or excessive fluid load; patients with PEEP ≥5 cmH_2O under mechanical ventilation were divided into the mild, moderate and severe types.

Statistical analysis

Data analysis was performed using SPSS 22.0 statistical software (SPSS, Chicago, IL, USA). If measurement data were not normally-distributed, relevant data were described by the median (interquartile range). Enumeration data were expressed as rate and percentage. The equality of variance between groups was analyzed by Levene test. If measurement data were normally-distributed, relevant data were statistically compared using independent sample t-test. If measurement data were not normally-distributed, relevant data were statistically analyzed by independent sample Mann-Whitney U test. Enumeration data were compared between groups using *chi*-square test. Except P/F, logistic regression analysis was used to analyze other parameters. A value of $P<0.05$ was representative as statistically significant and $P<0.01$ as extremely statistically significant.

Results

Clinical data

In total, 195 sepsis patients with elevated serum lactate level were recruited including 94 in the P/F decline group and 101 in the P/F non-decline group. No statistical significance was noted between two groups in terms of age, gender ratio, hypertension, diabetes mellitus, blood transfusion status and length of ICU stay (all $P>0.05$). History of coronary heart disease, duration of mechanical ventilation and whether CRRT was performed significantly differed between two groups (all $P<0.01$). In the P/F decline group, fluid balance at the first day and total fluid balance were significantly higher compared with those in the P/F non-decline group (both $P<0.01$). The 28-d mortality rate in the P/F decline group was considerably higher than that in the P/F non-decline group ($P<0.01$), as illustrated in **Table 1**.

Table 2. Comparison of site of infection between two groups by *chi*-square test

Parameter	P/F decline group	P/F non-decline group	*P*
Site of infection			
Abdominal cavity (Yes/No)	39.4% (37/57)	48.5% (49/52)	0.25
Urinary system (Yes/No)	14.9% (14/80)	25.7% (26/75)	0.08
Multiple sites (Yes/No)	18.1% (17/77)	9.9% (10/91)	0.15
Unknown sites (Yes/No)	19.1% (18/76)	9.9% (10/91)	0.07
Lung (Yes/No)	7.4% (7/87)	3.0% (3/98)	0.2
Skin soft tissue (Yes/No)	1.1% (1/93)	3.0% (3/98)	0.62

Abdominal cavity was the most common site of infection, followed by urinary system, unknown sites, multiple sites, lung and skin soft tissue. The site of infection did not significantly differ between two groups (all P>0.05), as described in **Table 2** in details.

Laboratory parameters

As illustrated in **Table 3**, P/F, serum albumin level and CVP did not significantly differ between two groups (all P>0.05). APACHE II and SOFA scores, serum creatinine level, PCT and NT-proBNP significantly differed between the P/F decline and P/F non-decline groups (all P<0.01).

Logistic regression analysis

Except P/F, laboratory parameters were subject to univariate logistic regression analysis. APACHE II and SOFA scores, serum albumin, serum creatinine, PCT, NT-proBNP and CVP were used as concomitant variable and the incidence or aggravation of pulmonary edema was utilized as dependent variable. Univariate logistic regression analysis revealed that APACHE II and SOFA scores, PCT and NT-proBNP were the risk factors of secondary pulmonary edema. In addition, the OR values of these parameters exceeded 1. Although serum creatinine yielded statistical significance, it was not a risk factor because the OR value within 95% confidence interval was 1, as shown in **Table 4**.

After inclusion of baseline parameters of age, gender and medical history, multi-variate logistic regression analysis demonstrated that APACHE II score, SOFA score and PCT were the risk factors of secondary pulmonary edema and the OR values exceeded 1, as illustrated in **Table 5**.

Comparison of different parameters in predicting pulmonary edema

The ROC curves of APACHE II score, SOFA score and PCT in predicting the incidence of pulmonary edema were lineated. The optimal threshold value of APACHE II score was calculated as 15.5, the sensitivity was 0.755, the specificity was 0.693 and the maximal area under curve (AUC) was 0.795, as revealed in **Figure 1**. In addition, the optimal threshold value of SOFA score was calculated as 15.5, the sensitivity was 0.543, the specificity was 0.871 and the maximal AUC was 0.707. The predicting values of APACHE II and SOFA scores were higher compared with that of PCT (**Figure 1**).

Discussion

Early fluid resuscitation is regarded as the primary treatment of tissue hypoperfusion in sepsis patient. However, it is likely to provoke the incidence of pulmonary edema due to excessive fluid load. Secondary pulmonary edema not only causes respiration function deterioration and prolongs mechanical ventilation and length of ICU stay, but also accelerates the progression into MODS [7] and increases the mortality rate [9]. Based on the Starling formula [15], when the colloid osmotic pressure is low or the permeability of pulmonary capillary endothelium to water and protein is altered, the quantity of pulmonary extravascular fluid is increased, leading to pulmonary edema. Capillary endothelial permeability alteration induced by different types of injuries is likely to cause the formation of non-cardiogenic pulmonary edema. In this study, APACHE II and SOFA scores, serum albumin, serum creatinine, PCT, NT-proBNP and CVP were assessed to reflect the severity of diseases, plasma colloid osmotic pressure, inflammation response and heart function parameters, aiming to explore the risk factors of pulmonary edema during fluid resuscitation in sepsis patients.

The history of coronary heart disease did not significantly differ between two groups. Patients with coronary heart disease were compli-

Table 3. Comparison of laboratory parameters between the OI decline and OI non-decline groups

Parameter	P/F decline group	P/F non-decline group	*t* value
APACHE II score	19.4 ± 6.2	12.9 ± 4.9	2.70
SOFA score	11.5 ± 3.4	8.6 ± 3.0	2.72
P/F	298.1 ± 121.6	300.1 ± 143.4	1.12
Serum albumin (g/L)	25.0 ± 5.5	23.6 ± 6.9	1.25
Serum creatinine (umol/L)	171.7 (119.7, 297.5)	129.2 (86.9, 209.7)	2.88
PCT (ng/ml)	52.9 (20.2, 179.1)	16.7 (2.4, 58.6)	2.96
NT-proBNP (pg/ml)	4984.5 (2252.0, 18589.8)	2610.5 (775.8, 6626.8)	2.78
CVP (mmHg)	7.0 ± 5.0	6.0 ± 3.9	1.02

Table 4. Univariate logistic regression analysis of APACHE II score, SOFA score, serum creatinine, PCT and NT-proBNP

Parameter	B	SE	Wald	*P*	OR value	95% CI
APACHE II score	0.216	0.035	38.118	<0.01	1.241	1.159-1.329
SOFA score	0.299	0.056	28.882	<0.01	1.348	1.209-1.504
Serum creatinine	0.002	0.001	5.111	0.024	1.002	1.000-1.004
PCT	0.009	0.002	15.886	<0.01	1.009	1.005-1.014
NT-proBNP	0.006	0.002	10.253	0.001	1.006	1.002-1.009

Table 5. Multi-variate logistic regression analysis of all parameters

Parameter	B	SE	Wald	P	OR value	95% CI
APACHE II score	0.175	0.047	13.994	<0.01	1.191	1.087-1.305
SOFA score	0.239	0.084	8.014	0.005	1.270	1.076-1.498
PCT	0.009	0.003	7.305	0.007	1.009	1.002-1.016

Note: Baseline data including age, gender and medical history were adjusted prior to multivariate logistical regression analysis.

cated with coronary artery lesions and the sepsis exerted an inhibitory effect upon the myocytes [16], leading to cardiac function failure and cardiogenic pulmonary edema. Due to the limited sample size, the sites of infection did not significantly differ between two groups. However, pulmonary infection has been validated as the risk factor of the incidence of ARDS, which directly injures the alveolar epithelial cells and indirectly leads to capillary endothelial cell injury mediated by inflammation response, thereby provoking the incidence of non-cardiogenic pulmonary edema [17]. Although no statistical significance was observed in blood transfusion between two groups, blood transfusion has been considered as a risk factor of the incidence of pulmonary edema. It may affect the lung capillary permeability through leukocyte antibody and biological active substances, making protein enter into the pulmonary stroma and alveolus and leading to the occurrence of pulmonary edema [18]. In the P/F decline group, the serum creatinine level and PCT were significantly higher and the inflammatory response was more severe compared with those in the P/F non-decline group. Therefore, the percentage of patients undergoing CRRT was higher in the P/F decline group. In this study, the fluid balance at the first day and total fluid balance in the P/F decline group were significantly higher compared with those in the P/F non-decline group. Patients diagnosed with sepsis are likely to suffer from fluid leakage and pulmonary edema due to capillary leakage and fluid tolerance [11]. For sepsis patients, P/F decline can cause respiration function deterioration, prolong mechanical ventilation duration and increase the incidence of lung injury and ventilator associated pneumonia. Hence, the duration of mechanical ventilation significantly differed between two groups.

APACHE II and SOFA scores are commonly adopted in ICU center. APACHE II score is utilized to evaluate and quantify the severity of diseases in critically ill patients, which offers objective evaluation of the possibility or organ failure or death [19]. It is of predictive value for the clinical prognosis of patients, which is the most frequently used parameter in ICU settings [20]. SOFA score is used to assess the severity

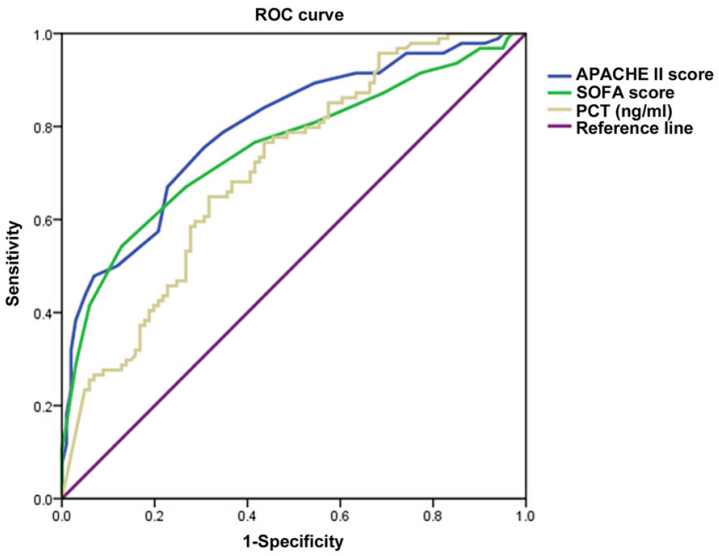

Figure 1. Comparison of ROC curves of APACHE II score, SOFA score, PCT in predicting the incidence of pulmonary edema.

of organ dysfunction from the slight to severe severity of organ dysfunction [21]. Vincent et al. [22] found that SOFA score in sepsis patients is closely correlated with the mortality rate. Previous studies [23] also demonstrated that APACHE II and SOFA scores can be utilized to predict the incidence of ARDS in critically ill patients. In this study, both APACHE II and SOFA scores are the risk factors of secondary pulmonary edema during fluid resuscitation in sepsis patients complicated with elevated serum lactate level. The higher the APACHE II and SOFA scores, the more severe the disease and the higher risk of pulmonary edema.

PCT is not only a sensitive marker of systemic inflammatory response, but also a parameter of lung inflammatory response [24]. Both infectious and non-infectious inflammatory responses can cause injuries to alveolar epithelial cells and pulmonary capillary, increase capillary permeability and lead to the formation of pulmonary edema after proteins entering into the lung stroma and pulmonary alveolus [25]. Therefore, PCT is able to reflect the lung capillary permeability to certain extent. In this investigation, we also found that PCT is associated with the incidence of pulmonary edema and serves as a risk factor of secondary pulmonary edema in sepsis patients. Nobre et al. [26] revealed that approximately 19.1% of patients with serious sepsis possess low levels of PCT, whereas PCT is correlated with the severity of systemic and lung inflammatory response and can reflect the capillary permeability of the lung. In this study, PCT is proven to be associated with the incidence of pulmonary edema.

In this study, no significant correlation was observed between the serum albumin level and the incidence of pulmonary edema. Nevertheless, based upon the Staling principle [15], the decline of plasma colloid osmotic pressure may accelerate the fluid effusion into tissue space, whereas 75% to 80% of colloid osmotic pressure originates from serum albumin. Therefore, hypoalbuminemia patients are more inclined to suffering from tissue space and tissue edema [27]. Much attention should be paid to the low plasma colloid osmotic pressure in hypoalbuminemia patients during fluid treatment, which functions prevent the aggravation of pulmonary edema. SAFE [28] experiments [29] have demonstrated that use of albumin could terminate the application of mechanical ventilation and blood pressure medication, and bring clinical benefits to patients diagnosed with serious sepsis [30].

BNP and NT-proBNP are commonly used biomarkers for rapid diagnosis of heart failure [31]. Previous research [32] revealed that NT-proBNP, as a widely recognized biomarker of heart failure, is of significant value for the diagnosis of cardiogenic dyspnea or respiratory failure. NT-proBNP is primarily metabolized through the kidney [33]. Critically ill patients are frequently complicated with acute kidney injury, which may affect the detection of NT-proBNP level. Therefore, NT-proBNP fails to offer accurate assessment of cardiac function and capacity for critically ill patients. The findings in this study are insufficient to support the role of NT-proBNP in the prognosis of secondary pulmonary edema. Subsequent investigations with a large sampling size are urgently required.

At present, CVP is widely applied in the ICU center and emergency outpatient. In this study, the CVP did not significantly differ between two groups. Since CVP mainly affects the right

heart function, whereas cardiogenic pulmonary edema is induced by left heart dysfunction or excessive cardiac load. Hence, no significant association can be noted between CVP and the incidence or aggravation of pulmonary edema, which is consistent with the findings of present investigation. Although 8-12 mmHg of CVP is recommended as the resuscitation target by the septic shock treatment guidelines [3], recent investigations [34] have demonstrated that it is likely to lead to excessive fluid load and the formation of pulmonary edema. Therefore, it is not feasible to use the CVP alone to evaluate the circulation status. Alternative parameters, such as medical history, dynamic change of CVP and hemodynamics indexes should also be considered to provide accurate guidance for fluid resuscitation [35].

In this investigation, the serum creatinine levels significantly differed between two groups, whereas no apparent correlation was documented between the serum creatinine and the incidence or aggravation of pulmonary edema. Previous investigations [36] have demonstrated that lung interacts with the kidney in critically ill patients. ARDS is capable of accelerating the occurrence and development of renal injury. Acute kidney injury can up-regulate the production of inflammatory factors, alter leukocyte transportation and influence lung capillary permeability. Therefore, renal function should be cautiously evaluated during the course of treatment, which avoids the possibility of excessive fluid load and reduces the risk of pulmonary edema.

In present investigation, the percentage of patients with secondary pulmonary edema was 48.2% and the total mortality rate was calculated as 42.1%. The mortality rate in the P/F decline group was up to 67%, three times of 18.8% in the P/F non-decline group. Iscimen et al. [37] found that the incidence of pulmonary edema in patients diagnosed with septic shock was 44.4%, 25% in a study by Chang et al. [8]. SAOP research demonstrated that the mortality rate of septic shock patients was 54.1% [38]. Another study found that the mortality rate of septic shock patients reached as high as 61.2% [39]. The disparity among multiple studies is probably due to the ICU and patients' conditions. Otero et al. [40] conducted a retrospective study and concluded that severe infection patients are inclined to organ functional injury during the course of medical treatment, thereby significantly enhancing the mortality rate. Similar findings were equally obtained in current study. The occurrence of secondary pulmonary edema during fluid resuscitation subsequently evolved into MODS and significantly increased the mortality rate. Hence, the risk factors related to the incidence of pulmonary edema should be identified and corresponding measures should be taken as early as possible in sepsis patients, aiming to reduce the risk of pulmonary edema.

The findings in this investigation have demonstrated that APACHE II, SOFA scores and PCT act as the risk factors of the incidence of secondary pulmonary edema in sepsis patients. Meantime, alternative clinical parameters should be incorporated to provide guidance for fluid resuscitation, which significantly decreases the risk of pulmonary edema.

Study limitations

The decline in P/F probably results from multiple causes. The observation time in this investigation is limited. Hence, the influence of other confounding factors may not be excluded. This study is a single center retrospective study. Multi-center studies with a larger sampling size are urgently required.

Conclusion

Taken together, APACHE II and SOFA scores and PCT are the risk factors of the incidence or aggravation of secondary pulmonary edema during fluid resuscitation in sepsis patients, which is of certain significance for guiding the clinical therapy.

Disclosure of conflict of interest

None.

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