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Original Article

The change and predictive value of extravascular lung water index in sepsis-associated respiratory distress syndrome

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Abstract: Objective: To investigate the change and predictive value of extravascular lung water index (EVLWI) in patients with sepsis-associated respiratory distress syndrome. Methods: A total of 92 patients with sepsis-associated respiratory distress syndrome were enrolled. According to the oxygenation index levels, ARDS patients were divided into three groups: mild, moderate and severe. Furthermore, all patients were divided into the survival group and the death group based on their survival status. The patients EVLWI and oxygenation index (PaO_2/FiO_2) were measured, and the acute physiology and chronic health evaluation II (APACHE II) score were assessed to observe the EVLWI levels in different patients and its predictive value for disease prognosis. Results: The EVLWI and APACHE II scores of patients with sepsis complicating severe ARDS were notably higher than those of patients with sepsis complicating moderate and mild ARDS; the scores of the sepsis combined with moderate ARDS group was higher than mild ARDS group, and both had statistically significant differences (all $P<0.001$). The 28-day mortality rate of the sepsis combined with severe ARDS group was the highest, and there was a statistical difference compared with the mild ARDS group ($P<0.05$). EVLWI in the survival group was significantly lower than that in the death group, which was statistically different ($P<0.001$). Both the sensitivity and specificity of the ROC curve of EVLWI were high, which was of high value for prognosis and diagnosis of the disease. Conclusion: The extravascular lung water index has a good predictive value for the severity of disease and prognosis of patients with sepsis complicating acute respiratory distress syndrome. Hence, it is worthy of clinical application.

Keywords: Extravascular lung water index, sepsis, respiratory distress syndrome, predictive value

Introduction

Sepsis is a clinically common severe infection symptom with a high incidence, which is also one of the common causes of hospitalization and death in ICU [1-3]. Acute respiratory distress syndrome (ARDS) is an acute hypoxic respiratory failure syndrome caused by various pathogenic factors, and its mortality rate can reach and maintain at 40% [4]. Some studies have found that sepsis can cause multiple organ failure, among which ARDS is the most common cause [5]. Clinically, patients with ARDS caused by sepsis often show insufficient effective blood volume. Early fluid resuscitation is particularly critical, but excessive fluid replenishment may lead to decreased oxygen supply in the body due to pulmonary edema, resulting in metabolism disorder of cell tissue in the state of hypoxia, which further aggravates the damage [6].

Therefore, early assessment of body fluid has a positive significance for the prognosis of patients. In previous studies, hemodynamic status is considered as an effective and important indicator for early fluid assessment [7], and the most commonly used parameter in clinical assessment of hemodynamic status is extravascular lung water index (EVLWI) [8]. Extravascular lung water can be interpreted in a narrow sense and a broad sense; in the broad sense, it refers to the water contained in tissues outside the pulmonary blood vessels, and in the narrow sense it refers to the water contained in lung interstitium [9]. The clinical gold standard for the determination of lung water content is the weighing method, but this method cannot be used in vivo and cannot be repeated, and therefore cannot be carried out effectively in clinical practice. As a result, other indicators are often used in clinic [10]. For example, the oxygenation index (PaO_2/FiO_2) and APACHE II scores are considered to be able to evaluate ARDS, but they have many influencing factors and are highly limited [11]. With the deepening of clinical research, the detection of EVLW level by PiCCO can objectively and accurately reflect the degree, condition and development trend of pulmonary edema in the early stage, which is of great significance in evaluating the therapeutic effect and prognosis [12, 13]. In another study, it was found that EVLWI could objectively and accurately reflect the entire pathological process of occurrence, development and evolution of pulmonary edema, which is of high value in guiding clinical treatment and evaluating the prognosis of patients [14].

In this study, we collected the clinical data of patients with ARDS caused by a single factor of sepsis, and monitored the EVLWI level in different patients and its prognostic value.

Materials and methods

The general information

The clinical data of 92 patients with sepsis-related respiratory distress syndrome who were admitted to the ICU of the Shengli Oilfield Central Hospital from January 2017 to December 2018 were collected, including 48 males and 44 females, aged 45-65 years old. All the included patients signed the informed consent, and this study was approved by the Ethics Committee of the Shengli Oilfield Central Hospital.

Inclusion and exclusion criteria

Inclusion criteria: All patients met the third international consensus definition of sepsis and septic shock (sepsis-3) in the 2016 European society of intensive care medicine and diagnosis of sepsis [2]; the diagnosis of ARDS was based on the new Berlin diagnostic criteria defined by the 2012 European society of intensive care medicine [15]; patients were under 75 years old; patients were excluded from ARDS caused by other diseases.

Exclusion criteria: The patients who lacked clinical data; patients with severe malnutrition, tumors, etc.; patients with severe cardiopulmonary disease or cerebrovascular disease; patients with mental illness who can not be cooperated with.

Methods

Determination of EVLWI: Catheterization was performed for each patient in their deep veins and femoral artery at the initial diagnosis and treatment, and then they were connected to the PICCO monitor (PULSION, Munich, Germany) to measure the patient's EVLWI and oxygenation index (PaO_2/FiO_2). According to the patient's oxygenation index level, ARDS was divided into three groups: mild, moderate and severe. Mild: 200 mmHg $\leq PaO_2/FiO_2 <$300 mmHg; moderate: 100 mmHg $\leq PaO_2/FiO_2$ <200 mmHg; severe: PaO_2/FiO_2 <100 mmHg.

Acute physiology and chronic health evaluation (APACHE) was used to score the general condition of all patients, which is the most authoritative critical illness evaluation system in clinical practice and has crucial application value for the assessment of condition and prognosis in critically ill patients [16]. Besides, the 28-day survival of patients was recorded, and the patients were divided into the survival group and death group according to their survival status.

Statistical analysis

The data were analyzed with SPSS17.0. Kolmogorov test was used to perform the normality test for continuous variables. The data with normal distribution are expressed as mean ± standard deviation ($\bar{x}$ ± sd), and those with homogeneity of variance were analyzed by the t test and expressed as t. Conversely, the data that did not conform to the normal distribution and the homogeneity of variance were analyzed by the rank sum test and denoted by F. One-way ANOVA was used to detect differences among groups, and LSD was further used for pairwise comparison. An independent t test was used for intragroup pairwise comparison. Count data were evaluated by the Pearson chi-square test and expressed as χ^2. The ROC diagnostic curve was used to evaluate the value of diagnosis. $P<0.05$ was considered statistically significant.

Table 1. General data and baseline data of patients in the three groups

Items	Sepsis combined with mild ARDS (n=25)	Sepsis combined with moderate ARDS (n=40)	Sepsis combined with severe ARDS (n=27)	χ^2/F	P
Gender (male:female)	16:9	26:14	18:9	0.042	0.979
Age (year)	62.6±10.3	64.3±8.2	62.5±8.7	0.440	0.645
Infection sites				1.012	0.985
Lung	10	18	12		
Abdomen	4	8	4		
Urinary system	3	5	4		
Traumatism	8	9	7		
Complicated diseases					
Hypertension				1.996	0.369
Yes	8	18	8		
No	17	22	19		
Diabetes				2.066	0.356
Yes	3	10	4		
No	22	30	23		
Cerebrovascular disease				3.024	0.221
Yes	2	8	2		
No	23	32	25		
COPD				5.505	0.064
Yes	4	12	2		
No	21	28	25		

Results

General information among the three groups of patients

There were no significant differences in gender, age, infection sites and complicated disease among the three groups, which were comparable (P>0.05). See **Table 1**.

Comparison of EVLWI and APACHE II scores among the three groups of patients

There were significant differences by statistical comparison in the EVLWI and APACHE II scores among the three groups (P<0.001). Patients with sepsis complicating severe ARDS had notably higher EVLWI and APACHE II scores than those with sepsis complicating mild and moderate ARDS, which was statistically significant (P<0.001). Besides, patients with sepsis combined with moderate ARDS had obviously higher EVLWI and APACHE II scores than those with sepsis combined with mild ARDS (P<0.001). See **Table 2** and **Figure 1**.

Comparison of 28-day survival status among the three groups of patients

After 28 days of treatment, the survival status of three groups was statistically different (P<0.05). The mortality of sepsis combined with severe ARDS group was the highest, and there was statistical difference compared with the sepsis complicated with mild ARDS group (P<0.05), but there was no difference compared with sepsis complicated with moderate ARDS group (P>0.05). See **Table 3**.

Comparison of oxygenation index, EVLWI and APACHE II scores between survival the group and the death group

According to whether the patients survived, they were further divided into a survival group (n=62) and a death group (n=30). There was no statistical difference between the survival group and the death group in PaO_2/FiO_2 and APACHE II score (P>0.05). Moreover, the EVLWI of the survival group was markedly lower than that of the death group, with a statistical sig-

Table 2. Comparison of EVLWI and APACHE II scores in the three groups

Groups	EVLWI (mL/kg)	APACHE II score (score)
Sepsis combined with mild ARDS (n=25)	9.30±1.86$^{\#,*}$	11.88±3.81$^{\#,*}$
Sepsis combined with moderate ARDS (n=40)	13.38±3.35$^{\#}$	17.42±6.32$^{\#}$
Sepsis combined with severe ARDS (n=27)	17.16±4.11	23.74±5.06
F value	37.204	31.747
P	<0.001	<0.001

Note: Compared with the sepsis combined with severe ARDS group, $^{\#}P<0.001$; compared with the sepsis with moderate ARDS group, $^{*}P<0.001$. EVLWI, extravascular lung water index; APACHE II, acute physiology and chronic health evaluation II.

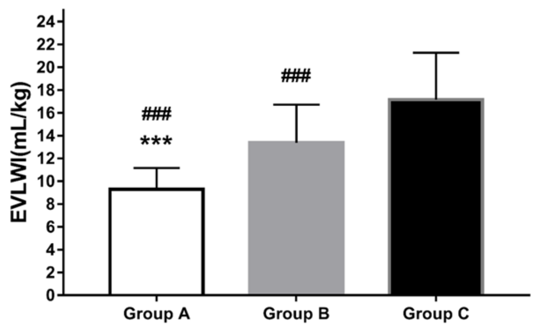

Figure 1. The Comparison of EVLWI among the patients in the three groups. A: Sepsis combined with mild ARDS; B: Sepsis combined with moderate ARDS; C: Sepsis combined with severe ARDS. Compared with the sepsis combined with severe ARDS group, $^{\#}P<0.001$; compared with the sepsis with moderate ARDS group, $^{*}P<0.001$. EVLWI, extravascular lung water index.

nificant difference (P<0.001), as shown in **Table 4**.

Comparison of PaO_2/FiO_2, EVLWI and APACHE II scores on the ROC curve for disease prognosis

The area under the ROC curve of PaO_2/FiO_2 was 0.576, 95% CI (45.1%-70.1%), the Youden index was 0.158, the sensitivity was 0.900, and the specificity was 0.258. The area under the ROC curve of EVLWI was 0.875, 95% CI (80.4-94.6%), the Youden index was 0.608, the sensitivity was 0.833, the specificity was 0.774, and the critical value was 14.75 mL/kg. The area under the ROC curve of APACHE score was 0.663, 95% CI (54.6%-78.0%), the Youden index was 0.333, the sensitivity was 0.833, and the specificity was 0.500. See **Figure 2**.

Discussion

Sepsis causes inflammatory dysregulation in the host due to infection, resulting in dysfunction of important organs. It is often accompanied by a common complication of acute respiratory distress syndrome (ARDS), which increases the mortality rate of patients by about 10%-15% [17]. ARDS is mainly caused by the damage of pulmonary capillaries and alveolar cells under various etiological factors, resulting in alveolar edema and interstitial fibrosis. The pathology of ARDS shows that the rise of extravascular pulmonary fluid index (EVLWI) is often above 7.5 mL/kg.

Some studies have found that other clinical monitoring indicators, such as central venous pressure, cardiac index and average arterial pressure, are not effective in predicting the severity and prognosis of ARDS [18, 19]. Meanwhile, EVLWI is widely used to monitor pulmonary extravascular lung water [20]. Studies have shown that EVLWI is associated with the severity of ARDS, and the more severe the disease is, the higher EVLWI will be. They are positively correlated, which has a good predictive value for the occurrence of pulmonary edema and the prognosis of ARDS patients [21]. After grouping on the basis of the severity of concurrent ARDS, this study found that patients with severe ARDS had significantly higher EVLWI and APACHE II scores than those with moderate or mild ARDS, and the differences were statistically significant, indicating that EVLWI was related to the severity of concurrent ARDS, which was consistent with the above studies.

In a previous meta-analysis of prognosis of ARDS patients, 4188 cases of ARDS patients were selected to observe their survival status according to the severity of ARDS. The results showed that the mortality rates of patients with mild ARDS ranged from 24 to 30% while the moderate ARDS was 29-34% and the severe ARDS was 42-48%, and the mortality rate showed an increasing trend from mild to severe [22]. In this study, we observed the 28-day mor-

Table 3. Comparison of survival status after 28 days of treatment in the three groups

Items	Sepsis combined with mild ARDS (n=25)	Sepsis combined with moderate ARDS (n=40)	Sepsis combined with severe ARDS (n=27)	X^2	P
Survival group (n, %)	20 (80.0%)	28 (70.0%)	14 (51.8%)*	6.327	0.042
Death group (n, %)	5 (20.0%)	12 (30.0%)	13 (48.2%)*		

Note: Compared with the sepsis combined with mild ARDS group, *P<0.05. ARDS, acute respiratory distress syndrome.

Table 4. Comparison of oxygenation index, EVLWI and APACHE II scores between the survival group and the death group

Groups	PaO_2/FiO_2 (mmHg)	EVLWI (mL/kg)	APACHE II score (score)
Survival group (n=25)	162.50±64.25	11.50±3.47	18.52±6.87
Death group (n=40)	147.23±58.08	17.27±3.49	20.37±6.50
t	1.101	7.467	1.545
P	0.274	<0.001	0.145

Note: EVLWI, extravascular lung water index; APACHE II, acute physiology and chronic health evaluation II.

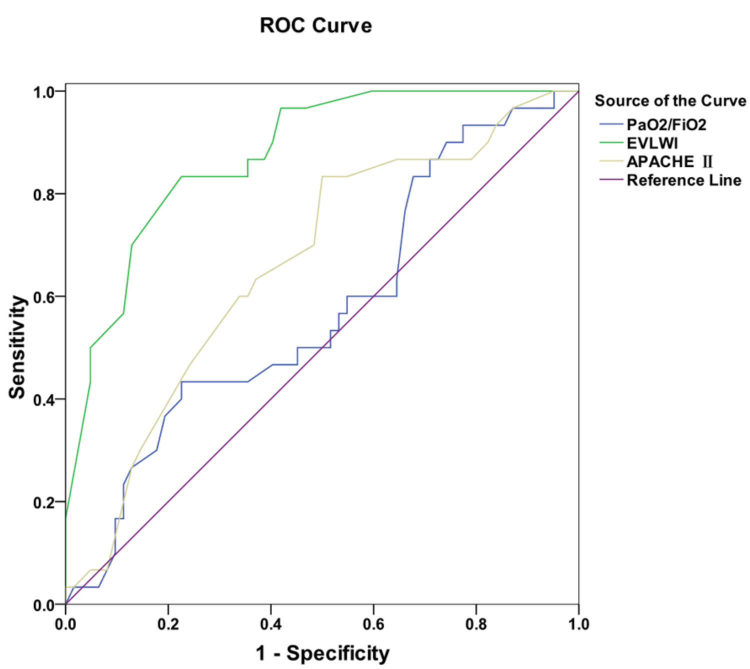

Figure 2. Comparison of PaO_2/FiO_2, EVLWI and APACHE II scores on the ROC curve. EVLWI, extravascular lung water index; APACHE II, acute physiology and chronic health evaluation II.

tality after grouping sepsis with different severity of ARDS. The results showed that the mortality rates of mild, moderate, and severe ARDS were 20.0%, 30.0%, and 48.2%, respectively, and the mortality of patients with severe ARDS was different from that of patients with mild ARDS, which were in agreement with the above findings. Patients with sepsis complicating severe ARDS suggest a poor prognosis and high mortality.

Regarding the predictive value of EVLWI for disease, in a previous study, 29 patients with sepsis were monitored for EVLWI. The final study found that the EVLWI level of patients who died was notably increased, and there was a significant difference in EVLWI level between the patients who died and those who survived [23]. Another study involving 373 cases of sepsis found that the mortality rate of patients with EVLWI above 15 mL/kg could be as high as 65%, while the mortality rate of patients with EVLWI below 10 mL/kg was markedly reduced to 33% [24]. In a study based on whether sepsis was combined with ARDS, it was found that the EVLWI level of patients with ARDS was apparently higher than that of patients without ARDS. Besides, patients death rate was increased with the rise of EVLWI levels, and the lower the EVLWI level was, the higher the survival rate would be for patients with ARDS [25]. In another study, it was found that EVLWI was closely related to the prognosis of patients with lung injury. When EVLWI was higher than 16 mL/kg and was used to predict the mortality of ICU patients with acute lung injury, its sensitivity and specificity reached 75-78% [26]. There were no statistical differences in PaO_2/FiO_2 and APACHE II scores between the survival group and the death group in this study. However, in the case of EVLWI, the survival group was significantly lower than the death group, which was statistically different. The area under the ROC curve of EVLWI was 0.875, and the critical value was 14.75 mL/kg. As a result, the predictive value of EVLWI for disease prognosis is better than PaO_2/FiO_2 and APACHE II scores, which has higher sensitivity and specificity.

The shortcoming of this study was that it was a single-center retrospective study with a small sample size, so multi-center prospective studies with a larger sample size are needed for further research.

In summary, the extravascular lung water index has a good predictive value for the severity of disease and prognosis of patients with sepsis complicating acute respiratory distress syndrome, which is worthy of clinical application.

Disclosure of conflict of interest

None.

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