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Original Article

A study on the correlation of extravascular lung water index and blood lactate clearance rate with the prognosis of patients with sepsis

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Abstract: Objective: To explore the clinical significance of dynamic changes in extravascular lung water index (EVLWI) and blood lactate clearance rate (LCR) in assessing the prognosis in patients with sepsis. Methods: The clinical data of 81 patients with sepsis receiving treatment in our hospital from January 2016 to January 2017 were analyzed retrospectively. The patients were divided into survival group and death group according to the survival condition on the 28th day after they were diagnosed with sepsis. The dynamic changes in EVLWI and LCR on the 1st day, the 2nd day and the 3rd day of the two groups of patients were analyzed to evaluate the clinical values of EVLWI and LCR in assessing the prognosis in patients with sepsis. Results: Among the 81 patients with sepsis included in this study, 47 patients survived and 34 patients died on the 28th day after they were clearly diagnosed with sepsis. The difference in basic information between the survival group and the death group was not statistically significant (P>0.05). EVLWI in the survival group was lower than that in the death group, while the LCR in the survival group was higher than that in the death group. The differences were statistically significant (P<0.05). The results of multivariate logistic regression analysis showed that EVWLI and LCR on the 3rd day after the patients were admitted to intensive care units (ICU) were the factors affecting the prognosis in the patients (P<0.001). The correlation analysis showed that the two indexes were negatively correlated (P<0.001). The analysis of receiver operating characteristic (ROC) curves indicated that when 9.29 mL/kg was taken as the threshold of EVLWI, the sensitivity was 91.2%, and the specificity was 83.0%; when 10.98 was taken as the threshold of LCR, the sensitivity was 95.7%, and the specificity was 85.3%. The sensitivity of the two combined indexes was 93.6%, and the specificity of them was 88.2%. Conclusion: The dynamic changes in EVLWI and LCR are closely related to the prognosis in patients with sepsis.

Keywords: Sepsis, extravascular lung water index, blood lactate clearance rate, prognosis

Introduction

Sepsis is a systemic inflammatory response syndrome in patients caused by bacteria (or other microbes such as fungi). It can induce systemic multiple organ dysfunction and even cause death in patients [1]. At present, there are over 35 million cases of severe sepsis in the world with a case fatality rate of 37.8%-45.8% [2]. As a common test index in clinical practice, extravascular lung water index (EVLWI) can timely reflect the change of pulmonary edema in the patients and assess the impact of sepsis on the lungs of the patients. EVLWI also plays an important role in predicting the case fatality rate and the disease progression of the patients [3]. As a metabolic marker of cell hypoxia, lactic acid is commonly used to assess the tissue perfusion state and the oxygen metabolism in the body, especially for patients prone to imbalance between oxygen supply and oxygen consumption [4]. The detection of lactic acid is of great significance. The effective dynamic monitoring of lactate clearance rate (LCR), an index reflecting the level of lactic acid, is more likely to help grasp the progression of sepsis in patients [5]. Currently, it has been found that a variety of biomarkers can be used for the early diagnosis of sepsis and used as important indexes to evaluate the prognosis [6-9]. However, the individual clinical test indicator has limited value in disease evaluation and is easy to be influenced by external environmental factors. Therefore, it is of great significance to carry out diagnosis and treatment of sepsis and evaluate the prognosis in

Table 1. Clinical characteristics and basic information of patients with sepsis

Factor	Survival group	Death group	Statistics	*P* value
Gender			X^2=0.045	0.832
Male (case)	26	18		
Female (case)	21	16		
Age (year)	59.08±15.51	57.44±18.51	t=0.433	0.666
Height (cm)	165.55±9.56	165.54±6.47	t=0.008	0.994
Body weight (kg)	66.18±10.28	67.63±10.88	t=-0.661	0.543
BMI (kg/m^2)	24.41±4.83	24.74±4.15	t=-0.325	0.746

Note: BMI, body mass index.

Table 2. Expressions and dynamic changes of EVLWI and LCR in the patients with sepsis

Factor	Time	Survival group	Death group	t value	*P* value
EVLWI	1d	11.53±3.38	13.89±3.24	-3.158	<0.001
	2d	9.36±3.63	15.02±4.58	-5.963	<0.001
	3d	7.44±3.44	15.29±4.22	-9.210	<0.001
LCR	1d	15.88± 6.26	14.50±4.79	-3.770	<0.001
	2d	19.52±6.60	8.62±4.48	-6.085	<0.001
	3d	21.84±5.91	7.13±7.01	10.219	<0.001

Note: EVLWI, extravascular lung water index; LCR, lactate clearance rate.

combination with various clinical indexes. In this study, we retrospectively studied the data of patients with sepsis in our hospital and analyzed the relationship between the combined indexes (EVLWI and LCR) and the prognosis in patients with sepsis. Now it is reported as follows.

Methods and materials

Clinical data

A total of 81 patients with sepsis treated in Intensive Care Units (ICU) of Jining NO.1 People's Hospital from January 2016 to January 2017 were selected. Inclusion criteria: Patients who met the diagnostic criteria for sepsis in the guidelines for the treatment of severe sepsis and septic shock in 2012; patients with clear evidence of bacterial culture; patients with complete clinical data; patients receiving the detection of EVLWI and LCR on the 1st, 2nd and 3rd day after they were admitted to ICU according to standard methods. Exclusion criteria: Patients who died within 3 days after admitted to ICU or patients who died of other causes; patients with irreversible chronic diseases or advanced cancer; patients aged less than 18 years old; patients with severe liver or kidney dysfunction, rheumatism, tuberculosis or diabetes; patients with autoimmune diseases; patients with thrombotic diseases; patients with chronic renal failure or long-term hemofiltration; patients with acute coronary syndrome or congestive heart failure; patients with other diseases that can severely affect the measurement of EVLWI and LCR; patients with incomplete clinical data. The patients were divided into survival group and death group according to the survival condition of the patients on the 28th day after they were clearly diagnosed with sepsis.

Standard methods for index detection

Detection of EVLWI: The patients lay in a supine position. Central venous catheters were connected to the monitor and the pressure transducer. The central venous pressure (CVP) was measured after the instrument was zeroed. The pulse indicator continuous cardiac output (PiCCO) catheter was placed in the femoral artery and connected to a monitor (Pulsion, Germany). The PiCCO temperature probe was connected to the subclavian catheter, and EVLWI was monitored and recorded. The measurement was conducted for at least three times, and the average was taken.

Calculation of LCR: A total of 1.5 mL arterial blood was taken from the patients at the bedside, and mixed rapidly. The value of lactic acid in the arterial blood was determined by whole blood lactic acid detection method with Siemens blood gas analyzer. The LCR dynamic value was calculated according to the formula for LCR.

Observation indexes

The prognostic values of EVLWI and LCR in patients with sepsis within 3 days after the patients were admitted to ICU were observed.

Statistical methods

SPSS 20.0 software was adopted for statistical analysis. The measurement data were expressed as mean ± standard deviation ($\bar{x}$ ± sd) using

Table 3. Correlation of logistic regression with the death of patients

Parameter	Regression coefficient	Standard error	Statistic	*P* value	OR value after the adjustment	95% CI of OR	
3d EVLWI	-0.424	0.084	25.491	<0.001	0.655	0.555	0.772
3d LCR	0.239	0.045	28.679	<0.001	1.270	1.163	1.386

Note: EVLWI, extravascular lung water index; LCR, lactate clearance rate.

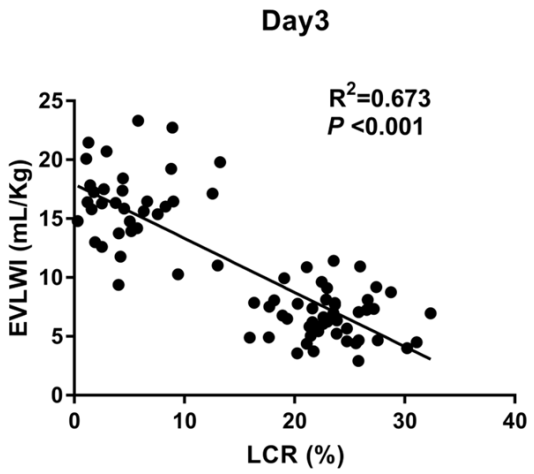

Figure 1. Correlation analysis of EVLWI and LCR. EVLWI, extravascular lung water index; LCR, lactate clearance rate.

independent-sample t test. The enumeration data were expressed as number (percentage) using chi-square test. The receiver operating characteristic (ROC) curve was established to analyze the area under the working curve of each index for predicting the death. The multivariate logistic analysis was used to analyze the correlation of EVLWI and LCR with the prognosis in patients on Day 1-3. Spearman was used for the correlation analysis. P<0.05 suggested that the difference was statistically significant.

Results

Clinical characteristics and basic information of patients with sepsis

A total of 81 patients were included in this study, including 44 males (taking up 54.3%) and 37 females (accounting for 45.7%) with an average age of 58.39±16.74 years old. Among them, 47 patients survived (the survival rate was 58.0%), and 34 patients died (the case fatality rate was 42.0%) on the 28th day after they were clearly diagnosed with sepsis. The gender, age, height, body weight and body mass index (BMI) of the patients were compared, and there were no statistically significant differences (P>0.05). The data were comparable. See **Table 1**.

Detection of the expressions and changes of EVLWI and LCR in the two groups of patients

EVLWI and LCR were detected on Day 1-3 after the patients were admitted to ICU. The levels of EVLWI of the patients in the survival group was decreased gradually with the prolonging of treatment time (P=0.004, P=0.000 and P=0.010, respectively for 1d EVLWI vs. 2d EVLWI, 1d EVLWI vs. 3d EVLWI and 2d EVLWI vs. 3d EVLWI), while those of the patients in the death group were mildly increased without statistical significance (P=0.246, P=0.143 and P=0.829, respectively for 1d EVLWI vs. 2d EVLWI, 1d EVLWI vs. 3d EVLWI and 2d EVLWI vs. 3d EVLWI). The levels of EVLWI in the death group were higher than those in the survival group at different time points, and the differences were statistically significant (all P<0.001).

The levels of LCR in the survival group were increased continuously with the prolonging of the admission time (P=0.010, P=0.067 and P=0.000, respectively for 1d LCR vs. 2d LCR, 1d LCR vs. 3d LCR and 2d LCR vs. 3d LCR), while those in the death group were decreased gradually (P=0.000, P=0.000 and P=0.302, respectively for 1d LCR vs. 2d LCR, 1d LCR vs. 3d LCR and 2d LCR vs. 3d LCR). The levels of LCR in the survival group were higher than those in the death group at different time points, and the differences were statistically significant (all P<0.001). See **Table 2**.

Multivariate logistic analysis

The multivariate logistic regression analysis with 28-day prognosis in patients (death or survival) as the outcome variables, and EVLWI and LCR on Day 1-3 of hospitalization as the independent variables showed that 3d EVLWI and 3d LCR were taken as the selected indexes

Table 4. Assessment on the effects of EVLWI, LCR and combined EVLWI and LCR on the prognosis in patients with sepsis

Methods	AUC	*P* value	AUC 95% CI	Critical value	Sensitivity (%)	Specificity (%)
EVLWI	0.912	<0.001	0.841-0.984	9.29	91.2	83.0
LCR	0.896	<0.001	0.814-0.978	10.98	95.7	85.3
Joint index	0.905	<0.001	0.826-0.984	NA	93.6	88.2

Note: EVLWI, extravascular lung water index; LCR, lactate clearance rate; AUC, area under the curve; CI, confidence interval.

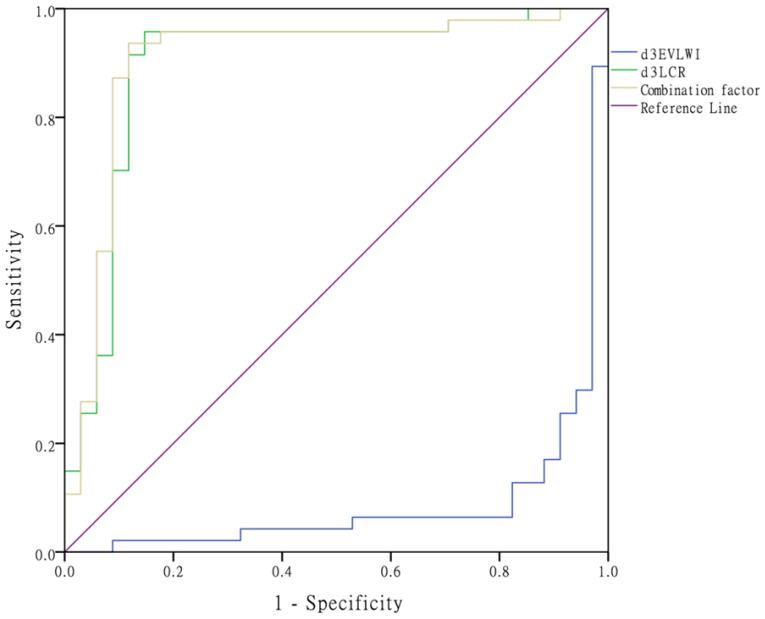

Figure 2. ROC working curve of EVLWI LCR and its combined indicators.

which were significantly correlated with death. The difference was statistically significant (P<0.001). See **Table 3**.

Correlation analysis of indexes

A correlation analysis was conducted for EVLWI and LCR on Day 3 after the patients were admitted to ICU based on the aforementioned logistic regression analysis results, which showed that LCR and EVLWI exhibited obviously negative correlation (R^2=0.673). The difference was statistically significant (P<0.001). See **Figure 1**.

Analysis of the diagnostic values of EVLWI and LCR in the prognosis with ROC curve

The survival condition on the 28th day after the patients were diagnosed with sepsis was taken as the outcome index. EVLWI, LCR and the combined EVLWI and LCR on Day 3 after the patients were admitted to ICU were used for analysis of prognosis. Both EVLWI>9.29 and LCR> 10.98 were the critical values. The sensitivities of EVLWI, LCR and combined EVLWI and LCR were 91.2%, 95.7% and 93.6%, respectively, and the specificities were 83.0%, 85.3% and 88.2%, respectively. The ROC curve was used to evaluate the diagnostic values of EVLWI, LCR and combined EVLWI and LCR in the prognosis in patients with sepsis. The area under the ROC curve was 0.912, 0.896 and 0.905, respectively; the differences were statistically significant (P<0.001). See **Table 4** and **Figure 2**.

Discussion

Sepsis results in extensive acute damage to pulmonary capillary endothelial cells, leading to increased permeability and exudation with the fluids predominantly distributed in cells, interstitial lungs, and alveoli [10]. At present, PiCCO is often used clinically to dynamically and hemodynamically monitor the state of the hemodynamics, which can effectively and accurately evaluate the patient's blood volume [11]. As the main index of PiCCO test, EVLWI can timely reflect the amount of extravascular fluid in the lung tissue. Some study has shown that EVLWI can be used as an independent risk factor to predict the disease severity and prognosis in patients [12]. The retrospective analysis of the clinical data of 105 patients with sepsis conducted by Wang et al. showed that the higher the EVLWI was, the higher the death rate would be [13]. The value of EVLWI is related to the risk rate and the death rate. EVLWI can be used as an independent factor for predicting 28-day prognosis in patients with sepsis. A prospective study of the EVLWI and other markers of lung injury in 19 patients with acute respiratory distress syndrome conducted by Phillips et

al. showed that EVLWI of the patients in the death group on the 1st day was significantly higher than that in the survival group, and EVLWI was increased gradually with the extension of hospital stays [14]. The study on the clinical data of 67 patients with sepsis conducted by Chung et al. showed that the level of EVLWI in patients with multiple organ dysfunction syndrome (MODS) was obviously higher than that in patients without MODS on Day 1 and Day 3 after the patients were admitted to ICU, suggesting that EVLWI may increase the death rate in patients with sepsis-induced MODS [15]. The results of this study showed that the level of EVLWI of the patients in the survival group was decreased significantly on Day 1-3 after the patients were admitted to ICU, and that of the patients in the death group was increased significantly with the time. EVLWI in the death group was notably higher than that in the survival group, suggesting that EVLWI may have some relationship with the prognosis of patients.

The main reason for the increase in blood lactate level is the imbalance between oxygen consumption and oxygen supply. During the occurrence and development of sepsis, the elevated lactate level is caused by the insufficient tissue perfusion, decreased LCR and oxygen utilization disorders [16]. At present, studies have shown that the detection of the level of lactic acid in arterial serum can effectively determine the prognosis and death of patients [17, 18]. When the initial level of lactic acid is greater than 4 mmol/L, the risk and probability of death will increase. The main mechanism of LCR, one of the indexes reflecting the level of lactic acid, is that the level of blood lactate is increased due to liver and kidney dysfunction, lactate cycle imbalance and abnormal LCR caused by the induced inflammatory response. Researchers have found that LCR can be used to predict patient prognosis more effectively than the value of lactate [19]. LCR can dynamically reflect changes in the level of lactate and patient's response to the treatment, and is of great value to assess the severity of the disease, treatment effects and prognosis in patients. LCR can be used to assess the prognosis in patients more sensitively and accurately. Meanwhile, in the first 24 hours of hospitalization, LCR is the best index to predict the 28-day case fatality rate in patients [20]. In this study, by observing the dynamic changes in LCR, we found that the value of LCR on Day 3 in the survival group was higher than those on Day 1-2, while it was decreased gradually with the increase in the hospitalization time. The value of LCR in the survival group was higher than that in the death group. The difference was statistically significant ($P<0.05$). Therefore, it is believed that the early dynamic changes in LCR in patients with sepsis are related to the prognosis in patients. The reason for the change in LCR may be related to the tissue perfusion and the recovery of oxygenation.

The results of this study showed that EVLWI was negatively correlated with LCR on Day 3 after the patients were admitted to ICU, suggesting a certain relationship between them, which may have a certain value to assess the prognosis in patients. The analysis of ROC curves indicated that when 9.29 mL/kg was taken as the threshold of EVLWI, the sensitivity was 91.2%, and the specificity was 83.0%; when 10.98 was taken as the threshold of LCR, the sensitivity was 95.7%, and the specificity was 85.3%. In order to clarify the value of the two combined indexes in assessing the prognosis, it was discovered that the sensitivity of the two combined indexes was 93.6%, and the specificity of them was 88.2%. The results implied that EVLWI and LCR have relatively high value in predicting the prognosis in patients with sepsis.

In conclusion, EVLWI is negatively correlated with LCR on the third day after the patients were admitted to ICU, and both of them have a relatively high value in predicting the 28-day prognosis in patients with sepsis. EVLWI and LCR can be dynamically monitored in clinical practice to provide guidance in the treatment of patients. However, the sample size of this study is small, and the observation time of EVLWI and LCR is relatively short. Therefore, it is necessary to increase the sample size, extend the time for monitoring the indexes and combine with the clinical practice for further study.

Disclosure of conflict of interest

None.

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