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Screening study of peripheral blood biomarkers in sepsis-associated ARDS

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Abstract: Objective: Acute respiratory distress syndrome (ARDS) is a serious and rapidly progressive complication of sepsis with a very high mortality rate. Screening for reliable biomarkers can assist in the diagnosis and treatment of the disease, and the development of personalized immunotherapy regimens may provide great clinical benefit. Method: The clinical data of 110 patients with sepsis treated in our medical unit from November 2018 to January 2020 were reviewed through a single-center retrospective analytic study. Using the Statistical Package for Social Science (SPSS, version 26) and the software GraphPad Prism 7, statistical analyses were performed and graphs were generated. Mean (standard deviation [SD]) and median (interquartile range [IQR]) should be used for description of normally and non-normally distributed data, respectively. The normal and non-normal distributed quantitative variables were respectively assessed by independent T-test or Chi-square test. P-value <0. 05 noted statistical significance. Results: (1) Finally, 32 patients were enrolled in the study, among 32 patients with sepsis-associated ARDS, there were 13 cases in the survival group and 19 cases in the death group. There were 10 males and 3 females in the survival group, with an age of 61. 77±14. 296 years. There were 13 males and 6 females in the death group, with an age of 66. 11±11. 455 years. There was no statistically significant difference between the two groups in terms of age and gender (P>0. 05). (2) The difference in PaO2/FiO2 between the two groups was statistically significant (P<0. 05). Their AUC was 0. 8057, and the sensitivity and specificity were 89. 47% and 69. 23% respectively. (3) By comparison of median scatter plots, cytokines IL-6, IL-6/IL-10, admission NLR, and discharge NLR were higher in the death group compared with survival. IL-10 and IFN-γ were lower compared with survival. (4) The results of logistic regression analysis showed risk factors affecting the prognosis of sepsis-associated ARDS:PaO2/FiO2 (P=0. 019, OR:12. 289, 95% CI:1. 512 - 99. 8);Protective factor: IFN-γ(P=0. 03, OR:0. 161, 95% CI:0. 031 - 0. 834). Conclusion: (1) PaO2/FiO2 can be used to assess the prognosis of septic ARDS patients; (2) cytokine assay may be a guide to determine the prognosis of septic ARDS; (3) IFN-γmay be a protective factor in the course of septic ARDS patients.

1. Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection and is the leading cause of death due to infection [1]. ARDS is an acute respiratory failure syndrome caused by acute diffuse lung injury due to various intra- and extra-pulmonary pathogenic factors[2]. The causal mechanisms of sepsis-associated ARDS are still debated[3-4], and the means to prevent and treat sepsis-associated ARDS are even more limited, so that patients with sepsis-associated ARDS have a very poor prognosis and their mortality rate is as high as 30%[5]. Early identification and intervention in ARDS patients can significantly improve their prognosis[6], and to date, several potential biomarkers have been investigated[7-8], but no single biomarker has been identified that can specifically diagnose this disease. Therefore, we hope to screen for reliable biomarkers to help clinical early identification of patients with sepsis-associated ARDS and early intervention to improve prognosis.

The inflammatory response caused by sepsis is mediated by cytokines, of which the cytokines proven to be relevant to the pathogenesis are divided into pro- and anti-inflammatory factors, including tumour necrosis factor-α, interleukin-1, interleukin-6, interleukin-12, interleukin-8, interferon, macrophage migration inhibitory factor, interleukin 10, interleukin 4, and transforming growth factor β[9]. Alterations in cytokine expression and hypofunction of host defences mechanisms are closely associated with the development of sepsis, and there is heterogeneity in the etiology of ARDS, including inflammation, abnormal gas exchange (PaO2/FiO2), and sequential organ failure assessment (SOFA score) [10]. Therefore, in this study, the common peripheral blood biomarkers and PaO2/FiO2 and qSOFA scores in patients with sepsis-related ARDS were screened and studied to analyse their relationship with the prognosis of patients with sepsis-related ARDS and to provide a reference to assist in the diagnosis and treatment of the disease.

2. Materials and Methods

2.1. Materials

2.1.1. Study subjects

One hundred and ten patients with sepsis-related ARDS who were hospitalized in this treatment unit from October 2018 to January 2020 were selected as the study subjects, and the study subjects were strictly screened according to the inclusion and exclusion criteria.

2.1.2. Relevant diagnostic criteria and scoring table (omitted)

2.1.3. Inclusion criteria

(1) Age≥18 years; (2) The latest diagnostic criteria for sepsis were used: patients with infection or suspected infection when the sepsis-related sequential organ failure (SOFA) score increased ≥ 2 points from baseline; (3) Meeting the diagnostic criteria for acute respiratory distress syndrome; (4) Having intrapulmonary or extrapulmonary primary disease causing sepsis-related ARDS; (5) All patients completed cytokines, blood routine, biochemistry, and blood gas within 24 hours after admission routine, coagulation function, blood gas analysis, brain natriuretic peptide, chest CT or chest radiograph, cardiac ultrasound and other examinations were completed within 24 hours of admission in all patients, and the medical history was complete.

2.1.4. Exclusion criteria

(1) Presence of malignant tumors; (2) recent use of hormones or immunosuppressants; (3) combined hematologic disorders; (4)combined autoimmune system diseases; (5)positive human immunodeficiency virus (HIV) antibodies; (6)combined liver cirrhosis; (7)pregnant and lactating women; (8)incomplete data collection.

2.2 Research method

2.2.1. Data collection

The following data of septic patients were collected through the electronic medical record system of the hospital.

General data: gender, age, body temperature, respiratory rate, pulse rate, blood pressure, and state of consciousness.

Laboratory and imaging tests: IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, neutrophil count, lymphocyte count, platelet count, procalcitonin (PCT), blood gas analysis, brain natriuretic peptide, chest CT or chest radiograph, cardiac ultrasound, oxygenation index (PaO2/FiO2), qSOFA and SOFA score 24 hours after admission. And neutrophil count and lymphocyte count on the day of discharge, and patient prognosis was recorded.

2.2.2. Subgroups

Survival group: defined as patients whose clinical symptoms resolved or disappeared within 30 days after admission.

Death group: defined as those who died of sepsis-related ARDS or other complications within 30 days after admission.

2.2.3. Cytokine detection method

Flow cytometry was used to quantify the levels of interleukin 2, interleukin 4, interleukin 6, interleukin 10, and tumour necrosis factor alpha in the samples by analysing the fluorescence intensity of the complexes using the flow microsphere array method.

2.2.4. Conventional treatment methods

Routine anti-infection, fluid management, and a combination of respiratory, nutritional, metabolic, and other organ support.

2.3 Statistical methods

Graphpad Prism 7. 0 software was used for processing, and all data were tested for normality before analysis. The measurement data conformed to normal distribution was expressed as mean (standard deviation [SD]), and independent sample t-test was used for comparison between two groups, and chi-square test was used for comparison of count data. If the measurement data were non-normally distributed they were expressed as median (interquartile range [IQR]). The distribution of each blood biomarker concentration in patients was drawn as a scatter plot with the median. Logistic regression analysis was performed using the SPSS26. 0 system to find factors that may affect the prognosis of patients with sepsis-related ARDS. P-value <0. 05 noted statistical significance.

3. Results

3.1. Inclusion process of patients with sepsis-related ARDS

There were 110 patients who met the diagnostic criteria of Sepsis 3. 0, of which 50 patients met the Berlin criteria. Seventeen cases were excluded (4 patients with malignancy, 2 patients after cardiopulmonary resuscitation, 3 patients with cirrhosis, 4 patients with HIV-positive individuals, 2 patients with autoimmune system diseases, and 2 patients with hematologic diseases). Among the remaining 32 patients with sepsis-related ARDS, there were 13 patients in the survival group and 19 patients in the death group. There were 10 males and 3 females in the survivor group, aged 61. 77 ±14. 296 years. There were 13 males and 6 females in the death group, with an age of 66. 11 ± 11. 455. There was no significant difference between the two groups in terms of age and gender for comparison (P > 0. 05). (Figure 1).

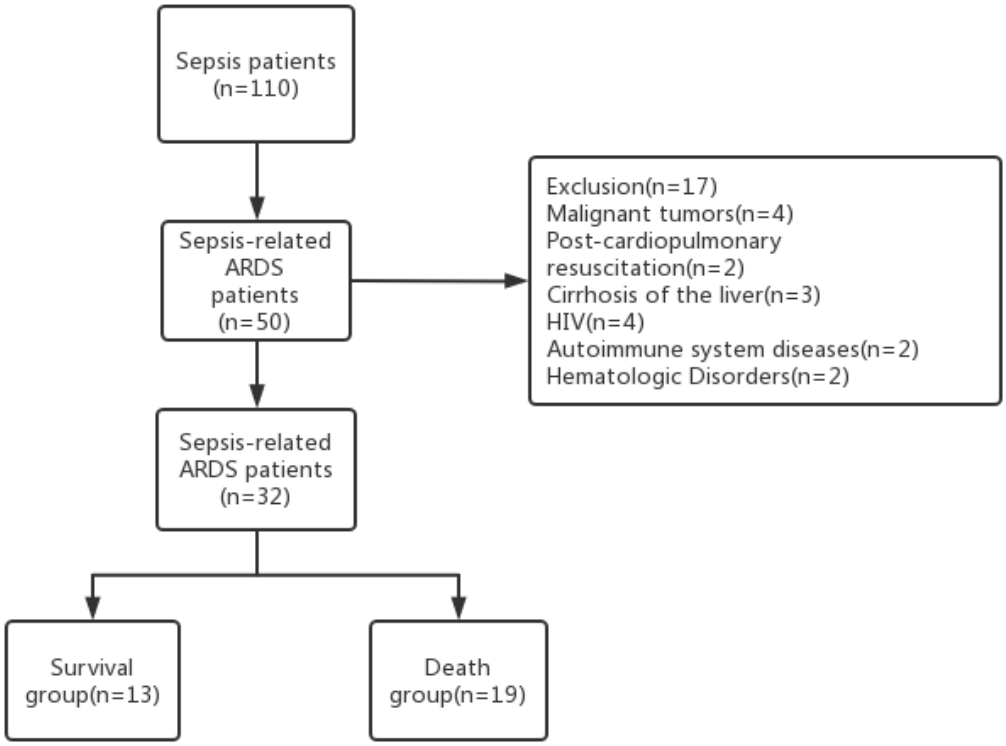


Figure 1: Flow of inclusion of patients with sepsis-related ARDS

3.2. Comparison of clinical data between two groups of patients

Peripheral blood biomarkers, qSOFA, and SOFA scores measured within 24 hours of admission to the EICU were tested for normality in both groups of patients with sepsis-related ARDS. T-lymphocyte percentage, neutrophil count at admission, qSOFA score, PaO2/FiO2, T-lymphocyte count, SOFA, and centrophil count at discharge were normally distributed. A t-test was performed to yield no significant differences in T-lymphocyte percentage (P>0. 05), neutrophil count at admission (P > 0. 05), qSOFA score (P> 0. 05), T-lymphocyte count (P> 0. 05), and SOFA (P> 0. 05) between the two groups of patients with sepsis-related ARDS. The differences in PaO2/FiO2 and central granulocyte count at discharge between the two groups were statistically significant (P< 0. 05). (Table

1).

Table 1: Comparison of clinical data of ARDS associated with sepsis

Date	Survival group	Death group	P value
T-lymphocyte percentage	61. 16 ± 14. 000	55. 79 ± 14. 179	0. 2986
Admission Neutrophil	10. 5 ± 6. 584	11. 89 ± 7. 567	0. 5951
qSOFA Rating	1. 615 ± 0. 650	1. 632 ± 0. 597	0. 9425
PaO2/FiO2	182. 4 ± 66. 486	114. 6 ± 38. 040	0. 0009
T-lymph	441. 4 ± 277. 6	329. 9 ± 283. 3	0. 278
SOFA	6. 23 ± 2. 83	6. 95 ± 2. 63	0. 469
Discharge neutrophil	5. 27 ± 2. 90	14. 90 ± 13. 80	0. 020
Age	64. 77 ± 14. 30	66. 11 ± 11. 45	0. 349
Gender			
Man	10	3	
Female	13	6	

3.3. ROC curve analysis of PaO2/FiO2 for assessing the prognosis of patients with sepsis-related ARDS

The ROC curve was plotted by using PaO2/FiO2 to assess the prognosis level of patients with sepsis-related ARDS. The results showed that the area under the curve (AUC) of PaO2/FiO2 was 0. 8057 (95% CI 0. 6356 - 0. 9757). Its optimal operating point (OOP) was 153. 7, suggesting that the prognosis of patients with sepsis-related ARDS is predicted by this optimal OOP. (Figure 2, Table 2)

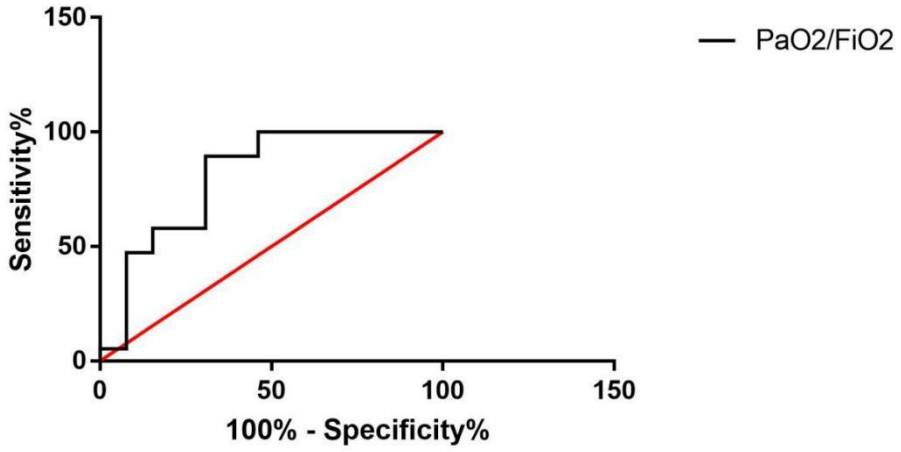


Figure 2: ROC curve analysis for PaO2/FiO2 assessment of prognosis in patients with sepsis-related ARDS

Table 2: ROC curve analysis for PaO2/FiO2 assessment of prognosis in patients with sepsis-related ARDS. (Note: a compared with area under the ROC curve = 0. 5)

Projects	AUC (95% CI)	*P* Value[a]	Optimal critical value (mmHg)	Sensitivity (%)	Specificity (%)
PaO2/FiO2	0. 8057 (0. 635-0. 975)	0. 003	153. 7	89. 47	69. 23

3.4. Comparison of non-normally distributed clinical profiles in sepsis-associated ARDS

The concentrations of cytokines (pg/ml), admission and discharge NLR and SOFA scores were compared in median scatter plots for patients with sepsis-related ARDS with different disease prognosis. As shown in Table 3, Figure 3, 5, 7 and 8: cytokines (IL-6, IL-6/IL-10), admission NLR, and discharge NLR were higher in the death group compared to the survivors. As shown in Table 3 and Figure 4, 6 cytokines (IL-10, IFN-γ) were lower in the death group compared to survival.

Table 3: Survival and Death Group Median of clinical data

Group (Number)	IL-6 Median (Range)	IL-10 Median (Range)	IL6/IL10 (Range)	IFN-γ Median (Range)	Admission NLR Median (Range)	Discharge NLR Median (Range)
Survival (13)	239 (114. 8-1014)	27 (6. 1-241. 2)	8. 85 (2. 99-47. 04)	5. 6 (0. 8-9)	17. 04 (5. 49-22. 94)	4. 99 (2. 225-7. 93)
Death(19)	339. 4 (187. 8-1463)	18. 8 (8. 2-42. 9)	13. 69 (9. 03-25. 24)	2. 45 (1. 275-4. 925)	17. 48 (15. 56-24. 43)	17. 62 (10. 36-35. 32)

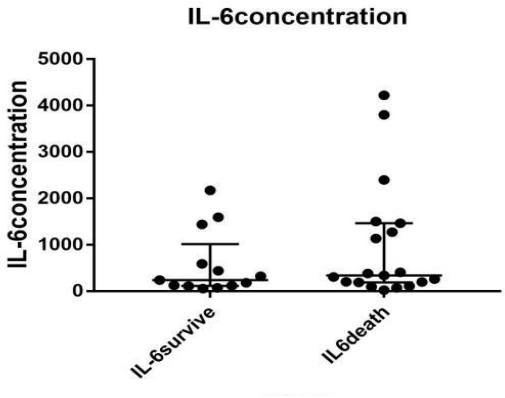


Figure 3: IL-6 concentration (pg/ml)

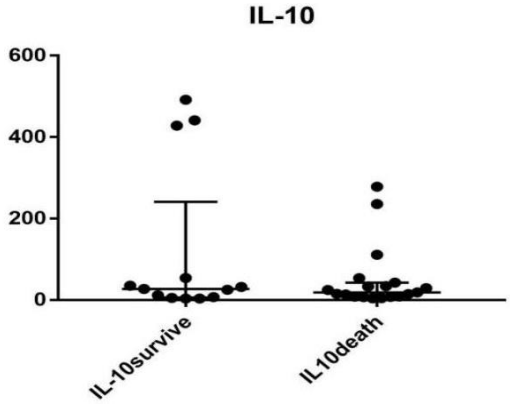


Figure 4: IL-10 concentration (pg/ml)

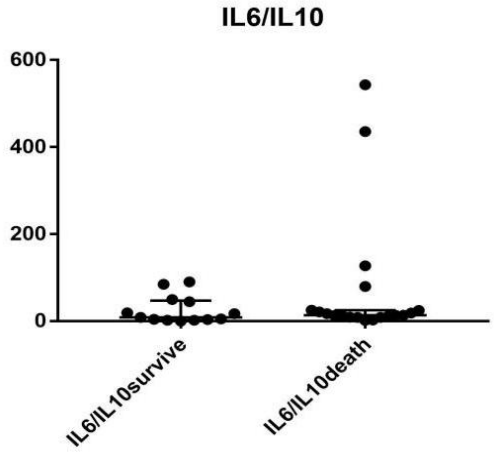


Figure 5: IL-6/IL-10 Ratio

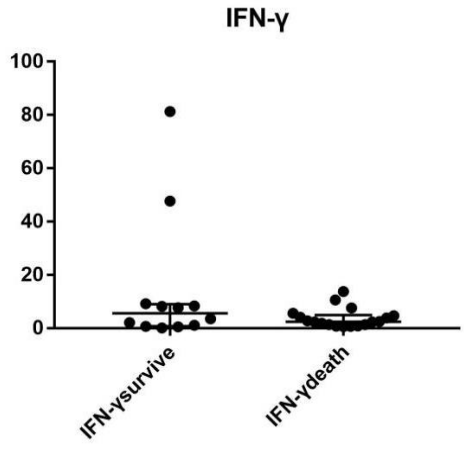
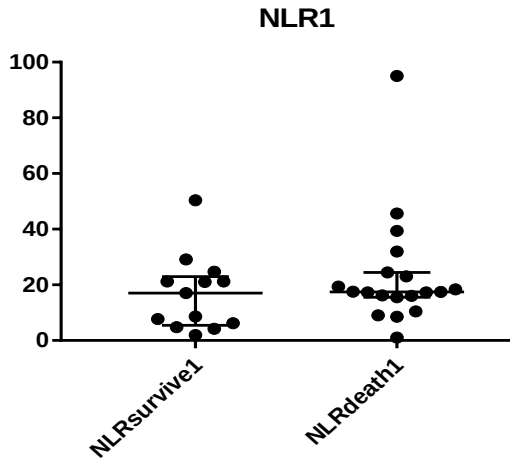


Figure 6: IFN-γconcentration (pg/ml)



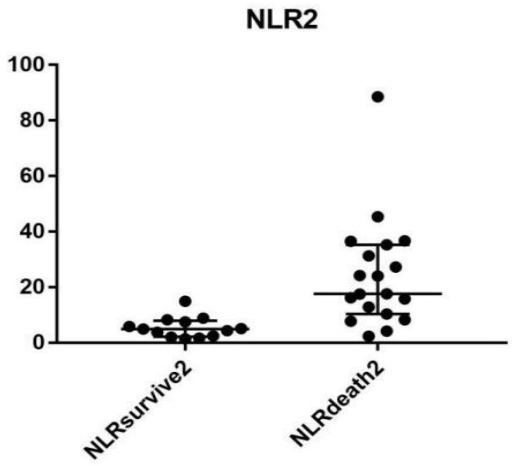
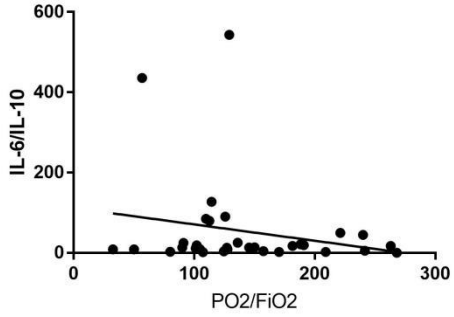


Figure 7: Admission NLR Figure 8: Discharge NLR

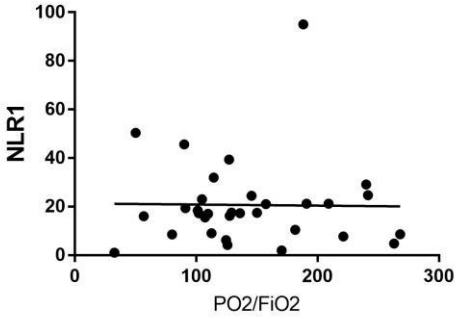
Linear correlation analysis was performed between IL6/IL10, admission NLR (NLR1), discharge NLR (NLR2) and PaO2/FiO2 of patients with sepsis-related ARDS. It was concluded that there was a linear correlation between discharge NLR and PaO2/FiO2(r value：-0. 5028 P < 0. 05). (Figure 9, Table 4).

Table 4: Correlation analysis of IL6/IL10, admission NLR (NLR1), discharge NLR (NLR2) and PaO2/FiO2 rows in patients with sepsis-related ARDS

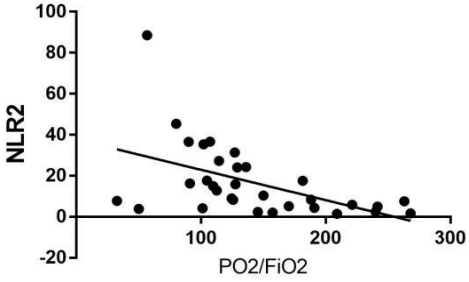
	IL6/IL10		Admission NLR		Discharge NLR	
Indicators	rvalue	Pvalue	rvalue	Pvalue	rvalue	Pvalue
PaO2/FiO2	-0. 208	0. 2533	-0. 0152	0. 9342	-0. 5028	0. 0034



(a)



(b)



(c)

Figure 9: Linear correlation analysis of IL6/IL10, admission NLR (NLR1), discharge NLR (NLR2) and PaO2/FiO2 rows in patients with sepsis-related ARDS

3.5. Influencing factors of sepsis-related ARDS: one-way logistic regression analysis

Logistic regression analysis was performed to determine the factors affecting the prognosis of patients with sepsis-related ARDS, with gender, age, IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ, oxygenation index score, and qAOFA score as covariates. Patient 30-day prognosis was used as the dependent variable for analysis. The results showed that INF-γ and oxygenation index score were associated with the prognosis of sepsis-related ARDS. (Table 5)

Table 5: Logistic regression analysis of the influencing factors of sepsis-related ARDS

	Regression coefficient	P Value	OR	OR95%CI
Gender (female/male)	-0. 431	0. 601	0. 65	0. 13-3. 26
Age	0. 028	0. 34	1. 029	0. 971-1. 09
IL-2	-0. 863	0. 321	0. 422	0. 077-2. 321
IL-4	-0. 069	0. 926	0. 933	0. 218-3. 999
IL-6	0. 311	0. 53	1. 365	0. 518-3. 597
IL-10	-0. 443	0. 366	0. 642	0. 246-1. 678
TNF-α	-0. 492	0. 517	0. 611	0. 138-2. 708
IFN-γ	-1. 828	0. 03	0. 161	0. 031-0. 834
PaO2/FiO2	2. 5	0. 019	12. 289	1. 512-99. 8
qSOFA	0. 045	0. 94	1. 046	0. 322-3, 398

4. Discussion

4.1. The prognostic value of PaO2/FiO2 in patients with sepsis-associated ARDS

In this study, the oxygenation index of patients with sepsis related ARDS in the survival group was higher than that in the death group within 24 hours after admission (P<0. 01), and the difference was statistically significant. PaO2/FiO2 values were significantly lower in patients with sepsis-associated ARDS in the death group compared with those in the survival group. It indicates that the prognosis of sepsis-associated ARDS may be related to Pa02/Fi02 values. In order to explore the value of PaO2/FiO2 in evaluating the prognosis of sepsis related ARDS patients, logistic regression analysis showed that PaO2/FiO2 is the prognostic factor of sepsis related ARDS patients. The ROC curve analysis of PaO2/FiO2 shows that the larger the area under the curve, the higher its predictive value. In conclusion, PaO2/FiO2 is related to the prognosis of sepsis-related ARDS, and it can be used as a reliable indicator to evaluate the prognosis of these patients. The oxygenation index can directly reflect the oxygenation of the organism and indirectly reflect the degree of lung injury. Patients with higher PaO2/FiO2 ratios had higher value of superoxide dismutase (SOD) and increased antioxidant capacity. Conversely, patients with low PaO2/FiO2 ratios indicate less free oxygen, which is associated with increased oxidative activity [11]. The use of SOD in the treatment of ARDS has been demonstrated previously[12]. Jia et al. studied the predictive value of oxygenation index measured at different times for the 28-day prognosis of ARDS patients, and believed that early oxygenation index could initially determine the prognosis of patients, and oxygenation index measured after mechanical ventilation had a higher value, so it was recommended to use oxygenation index measured at 6 hours of mechanical ventilation to evaluate the prognosis of ARDS patients[13]. Therefore, some scholars have pointed out that oxygenation index is the most appropriate parameter for predicting mortality of ARDS patients[14]. In conclusion, we believe that PaO2/FiO2 is feasible to evaluate the prognosis of patients with sepsis-associated ARDS. However, due to the small sample size and single-center study,

it is necessary to further expand the sample size and combine multi-center studies for verification

4.2. The prognostic value of IFN-γ in patients with sepsis-associated ARDS

IFN-γ also belongs to a multifunctional class of cytokines whose immune functions include up-regulation of pathogen recognition, antigen processing and presentation, and immunomodulation [15]. Low dose of IFN-γ can enhance the immune function of the body. Conversely, excessive NK cell activation and IFN-γ production in the early stages of sepsis patients can amplify the systemic inflammatory response, which leads to physiological dysfunction and aggravation organ damage. Eventually, it leads to immune suppression and decrease of IFN-γ levels in the middle and late stages of the organism, resulting in deterioration of the disease and seriously affecting the prognosis of patients. Studies in animal models suggest that IFN-γ production is reduced in severe sepsis [16]. Jekarl et al. found a clear negative correlation between IFN-γ and the severity of sepsis, which is consistent with the results of the present study[17]. In conclusion, it can be concluded that IFN-γ levels are different in different periods of sepsis and can reflect the condition and prognosis of patient. The subjects of this study were patients with sepsis-associated ARDS in the middle and late stages. A slight increase in IFN-γ may enhance the immune function of patients, improve the immunosuppression and prognosis of the organism.

In this study, the median scatter plot showed that the level of IFN-γ in patients with sepsis-associated ARDS was higher in the survival group than in the death group and logistic regression analysis showed that IFN-γ level could affect the prognosis of patients with sepsis-related ARDS (OR=0. 161). Therefore, it can be speculated that IFN-γ may be a protective factor in the course of sepsis-associated ARDS. It has been suggested that the impaired secretion of IFN-γ by NK cells is a marker of sepsis-induced immunosuppression[18]. It has also been shown that the production of IFN-γ by T cells is significantly reduced during sepsis. Treatment that simultaneously restores IFN-γ production by T cells has been shown to improve survival in animal models of sepsis[19]. Therefore, the results of this study are consistent with the results of foreign studies, which can assist clinical development of different treatment strategies. At present, the mortality rate of patients with sepsis-associated ARDS is still very high after active anti-infection, lesion removal, organ support and other treatments. Immunotherapy around sepsis has also become a research hotspot[20]. The study by Zhao et al. found that treatment of a rat model of sepsis with recombinant IL-15 significantly increased the number of T and NK cells and the level of IFN-γ, improved immune function, and prolonged the survival of septic rats[21]. Similar studies have also shown that IL-33 administration can promote IFN-γ production and reduce mortality in septic mice[22]. Venet et al. showed that IFN-γ can reverse the level of immunosuppression in patients with sepsis[23]. At the same time, some studies have shown that mitochondrial dysfunction may be related to the pathogenesis of sepsis, and IFN-γ can reverse mitochondrial dysfunction[24]. IFN- therapy may be beneficial only in patients with sepsis who exhibit immunosuppression, but if it is administered during the proinflammatory phase of sepsis, it should be alert to the risk of developing a severe inflammatory storm that may cause damage to the organism.

Screening specific biomarkers for patients with sepsis-associated ARDS can help clinicians to identify specific patient populations and assist in the diagnosis and treatment of the disease. At the same time, it can also be used as a target for the treatment of diseases, drug development, testing and application. Closely monitoring the levels of patient-specific biomarkers and developing personalized treatment plans may bring great clinical benefits.

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