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Original Article

Serum levels of TNF-α and IL-10 and prognostic risk factors in patients with transfusion-related acute lung injury

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Abstract: Objective: To investigate serum levels of Tumor necrosis factor alpha (TNF-α) and interleukin-10 (IL-10) in patients with transfusion-related acute lung injury (TRALI) and analyze the prognostic risk factors. Methods: 40 patients with TRALI, 42 patients with non-TRALI (acute lung injury caused by pulmonary infection or other reasons), and 40 healthy subjects were enrolled from our hospital. Results: TNF-α and IL-10 expressions in the healthy control group (HCG) and non-TRALI group was lower than that in the TRALI group, whereas the expressions in the non-TRALI group was higher than that in HCG ($P < 0.05$). In addition, the 48-hour survival rate in the TNF-α low-expression group (LEG) was higher than that in the high-expression group (HEG), whereas the 48-hour survival rate in the IL-10 LEG was lower than that in the HEG ($P < 0.05$). Further, TNF-α and IL-10 expressions are related to the amount of blood transfused, and IL-10 showed the best diagnostic efficacy with the biggest AUC while TNF-α showed the highest diagnostic sensitivity. Cox multiple-factor analysis results showed that the amount of blood transfusion was an independent prognostic risk factor for TRALI. Conclusions: TNF-α and IL-10 were risk factors of prognosis, but were not independent risk factors.

Keywords: TNF-α, IL-10, transfusion-related acute lung injury, expression, prognosis

Introduction

Transfusion-related acute lung injury (TRALI) is an acute non-cardiogenic lung injury caused by the human leucocyte antigen antibody or granulocyte specific antibody in blood within 6 h after transfusion. Antibody mediated TRALI is caused by passive transfusion of cognate antibodies and non-antibody mediated TRALI is caused by transfusion of aged cellular blood products. TRALI is one of the most common blood transfusion-related complications and the leading cause of transfusion-related death with 5%-14% mortality, and accounts for 38% of all transfusion-related deaths [1-4]. The pathogenesis of TRALI is not fully clear so far and there is no specific treatment. Prevention is the main measure to reduce the occurrence of TRALI.

TRALI may or may not be associated with other risk factors of acute lung injury (ALI). Its clinical features are very similar to those of aspiration pneumonia, pulmonary infection, and other diseases [5, 6]. Diagnosis of TRALI in accordance with the clinical features of patients has great limitations. Therefore, exploring relevant biological indexes, such as TNF-α and IL-10, and other objective measures to aid clinical judgment of TRALI is essential. ALI is usually associated with inflammatory reaction and release of a large number of inflammatory factors. It mainly occurs due to destruction of the endothelial barrier by leukocyte antigen and immune response activation. Thus, recruitment of inflammatory cells is promoted in ALI [7, 8]. TNF-α and IL-10 are important inflammatory factors, of which TNF-α is a pro-inflammatory factor. Previous studies have reported elevated TNF-α expression in the peripheral blood of patients with ALI. Limiting the release of TNF-α is an important strategy in treating ALI [9]. However, few studies have reported the significance of TNF-α expression in TRALI. IL-10 is an anti-inflammatory factor. Studies have reported significantly reduced IL-10 expression in mice with

TRALI. Exogenous injection of IL-10 can effectively inhibit the development of TRALI and reduce the associated mortality in mice [10]. However, the clinical significance of IL-10 expression in patients with TRALI is rarely reported.

Therefore, TNF-α and IL-10 expression in the peripheral blood of patients with TRALI was tested in this study and their relationship with prognosis was analyzed along with their clinical significance.

Materials and methods

Study subjects

In total, 40 patients with TRALI, 42 patients with non-TRALI (acute lung injury caused by pneumonia), and 40 healthy subjects were recruited from our hospital. They were 21-43 years old. The inclusion criteria were as follows: Patients with TRALI met the TRALI diagnostic criteria recommended by the National Heart, Lung and Blood Institute in 2005 [11]. There was no evidence of acute lung injury (ALI) before transfusion, ALI occurred within 6 hours of or after infusion of blood components, PaO_2/FiO_2 ≤300 mmHg, chest X-ray showed bilateral infiltration. No clinical evidence of elevated left atrial pressure was found. Patients with non-TRALI were diagnosed in accordance with the 2006 Guidelines for Diagnosis and Treatment of Acute Lung Injury-Acute Respiratory Distress Syndrome [12]. It occurred 12-48 hours after direct or indirect lung injury, PaO_2/FiO_2 ≤300 mmHg, Chest X-ray shows patchy shadows in both lungs. Hypoxemia is difficult to heal after routine oxygen inhalation. Except the patients in the healthy control group (HCG), none of the patients ever reported serious injury to any organ or previous ALI occurrence. The exclusion criteria were as follows: Patients with unidentified TRALI, unstable coronary heart disease, intermittent myocardial infarction, severe pulmonary hypertension, severe osteoarthropathy or fracture, hepatic and renal insufficiency, inherited metabolic disease, or endocrine system disease; patients who were transferred midway; patients or their family members did not cooperate with the treatment; and patients with malnutrition, tumor, or mental or learning dysfunction. The study was approved by the Ethics Committee of the First People's Hospital of Wenling, and the patients or their family members signed the informed consent form.

Outcome measures

Blood sampling is performed within 6 hours after the patient is diagnosed. Enzyme-linked immunosorbent assay (ELISA) was used to detect the serum levels of TNF-α and IL-10. Kaplan-Meier survival curve was generated to analyze the relationship between TNF-α and IL-10, and prognosis. Receiver operating characteristic (ROC) was introduced to analyze the efficacy of TNF-α and IL-10 in the differential diagnosis of TRALI and non-TRALI. COX regression analysis was applied to prognostic risk factors. TNF-α (BMS223-4) and IL-10 ELISA reagents (EHIL10) were purchased from Thermo Fisher, CVs were < 10%. Sensitivity was 2.3 pg/mL, and < 3 pg/mL, respectively.

Test methods

Two milliliters of peripheral venous blood from each subject was collected by nurses at our hospital, TNF-α and IL-10 were assayed by ELISA. Briefly, serum was separated from the peripheral blood after centrifugation for 10 min at 1000 rpm, and 50 μL of serum was added to an antibody coated 96-well plate. Then, 50 μL of biotin labeled antibody was added. After mixing well, the resulting solution was incubated for 60 min at 37°C. The plate was washed 3 times for not less than 30 s. After patting the liquid dry, 80 μL of affinity streptomycin-HRP was added, mixed well, and incubated for 30 min at 37°C. After washing 3 times, 50 μL of substrate A and B were respectively added and incubated in the dark for 10 min at 37°C. Finally, 50 μL of stop solution was added and absorbance at 450 nm was determined. Standard curves were also established. Three replicate wells were set up for each sample and standard at different concentrations.

Statistical analysis

SPSS19.0 (Asia Analytics Formerly SPSS China) was used for statistical analysis. The enumeration data are expressed as ratios. χ^2 test was used for comparing the ratios. Measurement data are expressed as mean ± sd. Analysis of variance was introduced for comparing among groups. The LSD test was applied for back testing. Survival curves were plotted using the

Table 1. Patient characteristics

	TRALI (n = 40)	Non-TRALI (n = 42)	Healthy control group (n = 40)	χ^2/t/F	P
Gender [n (%)]				0.781	0.677
Male	18 (45.00)	23 (54.76)	20 (50.00)		
Female	22 (55.00)	19 (45.24)	20 (50.00)		
Age (years)	38.33±8.47	36.59±9.62	38.19±10.53	0.421	0.658
Weight [n (%)]				0.587	0.746
≤60 kg	18 (45.00)	19 (45.24)	21 (52.50)		
> 60 kg	22 (55.00)	23 (54.76)	19 (47.50)		
Height [n (%)]				0.595	0.743
≤165 cm	21 (52.50)	22 (52.38)	18 (45.00)		
> 165 cm	19 (47.50)	20 (47.62)	22 (55.00)		
BMI (kg/m^2)	22.56±2.38	23.14±2.17	22.32±1.49	1.741	0.180
HLA antibody I [n (%)]				17.551	0.000
Yes	8 (20.00)	0 (0.00)*	0 (0.00)*		
No	32 (80.00)	42 (100.00)*	40 (100.00)*		
HLA antibody II [n (%)]				15.224	0.001
Yes	7 (17.50)	0 (0.00)*	0 (0.00)*		
No	33 (82.50)	42 (100.00)*	40 (100.00)*		
WBC count ($10^9/L$)	15.29±4.85	12.64±5.21*	6.34±1.39*,#	47.862	0.000
CRP (mg/L)	112.64±21.67	68.28±23.82*	4.37±1.25*,#	294.698	0.000
Neutrophil proportion (%)	88.64±6.48	82.67±7.94*	62.75±4.33*,#	177.117	0.000
Mean arterial pressure (mmHg)	86.4±7.2	88.4±8.2	85.5±3.8	2.022	0.137
Amount of blood transfusion (ml)	2637.59±875.66	1964.76±768.29		4.517	0.000
Total infusion volume (mL)	4256.41±1268.97	3429.56±1120.07		3.820	0.000
Mechanical ventilation [n (%)]				39.970	0.000
Yes	26 (65.00)	22 (52.38)	0 (0.00)*,#		
No	14 (35.00)	20(47.62)	40 (100.00)*,#		
Smoking history [n (%)]				5.681	0.058
Yes	18 (45.00)	14 (33.33)	8 (20.00)		
No	22 (55.00)	28 (66.67)	32 (80.00)		
Prognosis [n (%)]				36.086	0.000
Death	23 (57.50)	23 (54.76)	0 (0.00)*,#		
Survival	17 (42.50)	19 (45.24)	40 (100.00)*,#		

Note: *implies P < 0.05 compared with TRALI; #implies P < 0.05 compared with non-TRALI.

Kaplan-Meier method. ROC was used for analysis of diagnostic value. COX regression analysis was performed for prognostic risk factors of TRALI. P < 0.05 implied statistical significance.

Results

Patient information

In total, 40 patients were categorized in the TRALI group, including 18 males (45.00%) and 22 females (55.00%). They were 38.33 ± 8.47 years old. The non-TRALI group comprised 42 patients, including 23 males (54.76%) and 19 females (45.24%), who were 36.59 ± 9.62 years old. The HCG comprised 40 subjects, including 20 males (50.00%) and 19 females (50.00%), who were 38.19 ± 10.53 years old. There was no difference in gender and age among the 3 groups (P > 0.05). Other patient characteristics are shown in **Table 1**.

TNF-α and IL-10 expression

The expression levels of TNF-α and IL-10 in HCG and the non-TRALI group were lower than that

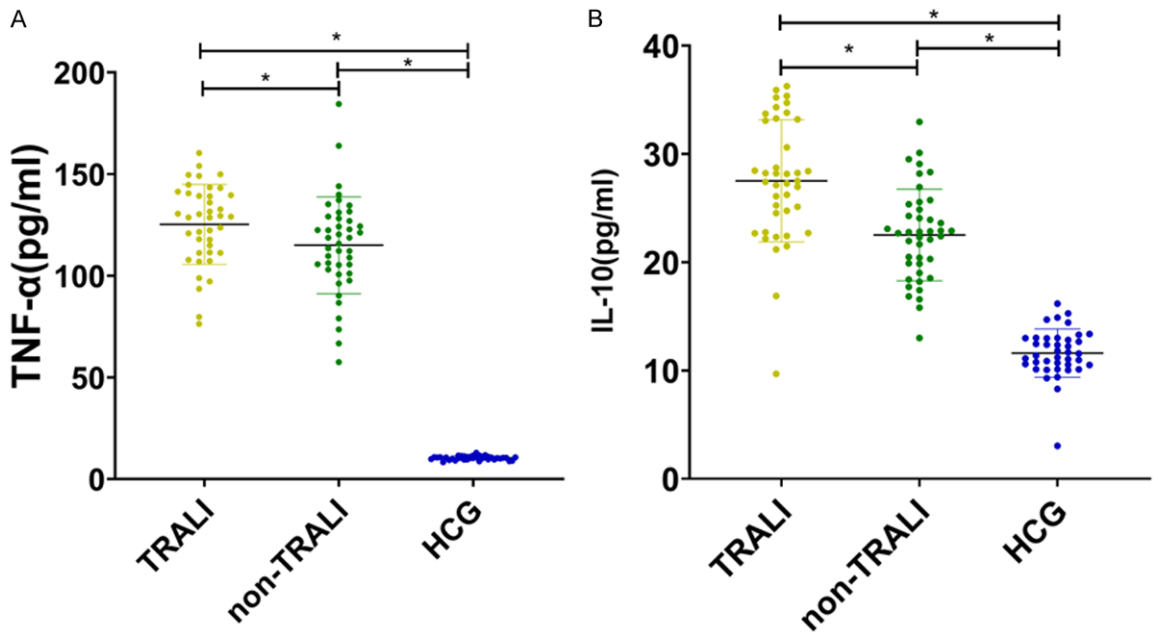

Figure 1. TNF-α and IL-10 expression. The expression levels of TNF-α and IL-10 in HCG and the non-TRALI group were lower than that in the TRALI group (P < 0.05). Expression in the non-TRALI group was higher than that in the HCG (P < 0.05). *indicated P < 0.05.

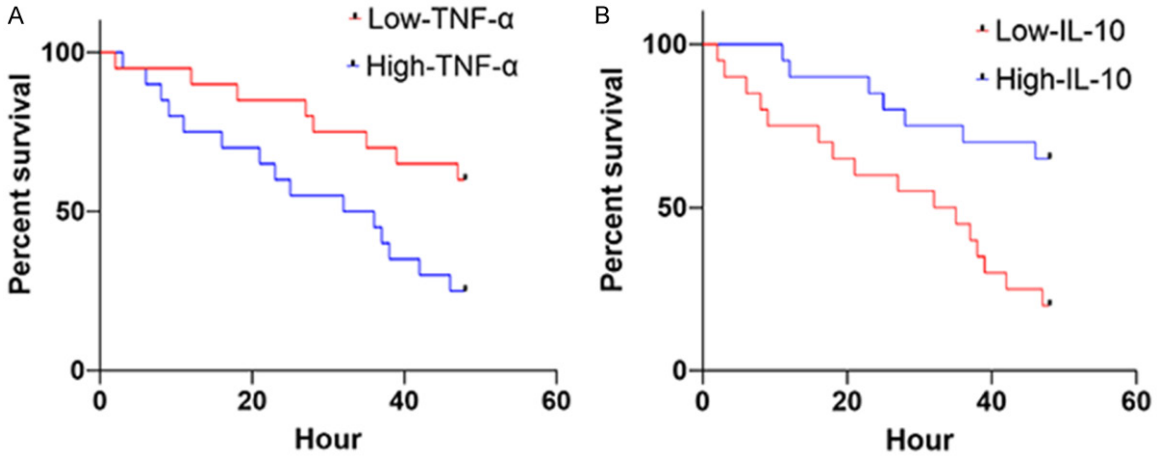

Figure 2. Relationship between TNF-α and IL-10, and prognosis of patients with TRALI. A. Relationship between TNF-α and prognosis. Kaplan-Meier survival analysis results showed that the 48-hour survival rate in the TNF-α low-expression group was higher than that in the high-expression group (P < 0.05). B. Relation between IL-10 and prognosis. The 48-hour survival rate in the IL-10 low-expression group was lower than that in the high-expression group (P < 0.05).

in the TRALI group (P < 0.05). Expression in the non-TRALI group was higher than that in the HCG (P < 0.05) (**Figure 1**).

Relationship between TNF-α, IL-10, and prognosis

The medians of TNF-α and IL-10 expression levels were 128.87 and 27.47, respectively. This median was considered the critical value. The patients were divided into a high-expression group (HEG) and low-expression group (LEG). Kaplan-Meier survival analysis showed that the 48-hour survival rate in the TNF-α HEG was 25.00% (5 cases) and was lower than 60.00% (12 cases) in the LEG (P < 0.05). The 48-hour survival rate in the IL-10 HEG was 65.00% (13 cases) and was higher than 20.00% (4 cases) in the LEG (P < 0.05) (**Figure 2**).

Table 2. Efficacy of TNF-α and IL-10 in differential diagnosis of TRALI and non-TRALI

	TNF-α	IL-10	TNF-α and IL-10 in combination
AUC	0.654	0.770	0.767
95% CI	0.535 to 0.773	0.667 to 0.873	0.664 to 0.871
Critical value	128.40 pg/mL	24.41 pg/mL	
Specificity	55.00%	75.00%	75.00%
Sensitivity	76.19%	73.81%	73.81%

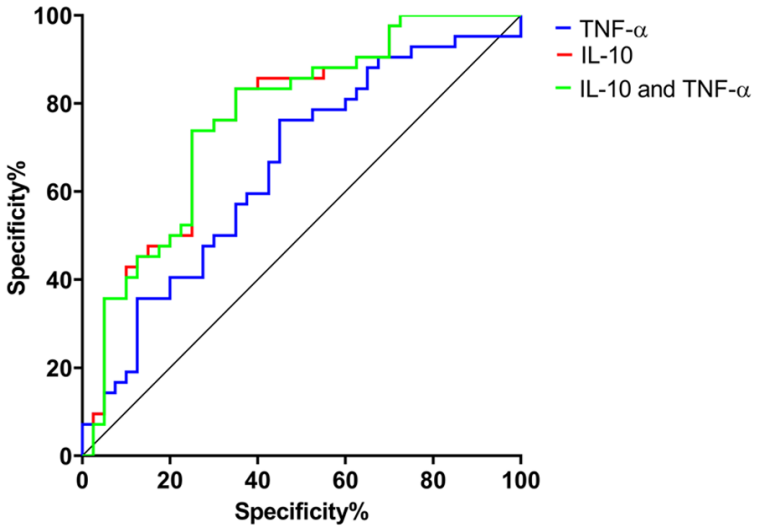

Figure 3. Efficacy of TNF-α and IL-10 in the differential diagnosis of TRALI and non-TRALI. AUC (TNF-α) = 0.654, AUC (IL-10) = 0.770, AUC (TNF-α combined IL-10) = 0.767.

Table 3. Assignment table

	Assignment
Gender	Male = 1, female = 0
Age	Continuous variable
Weight	≤60 kg = 1, > 60 kg = 0
Height	≤165 cm = 1, > 165 cm = 0
HLA antibody I	Yes = 1, No = 0
HLA antibody II	Yes = 1, No = 0
WBC count	Yes = 1, No = 0
CRP	Continuous variable
Neutrophil proportion	Continuous variable
Mean arterial pressure	Continuous variable
Amount of blood transfusion	Continuous variable
Total amount of blood transfusion	Continuous variable
Mechanical ventilation	Yes = 1, No = 0
Smoking history	Yes = 1, No = 0
Prognosis	Death = 1, survival = 0
TNF-α	Continuous variable
IL-10	Continuous variable

Efficacy of TNF-α and IL-10 in the differential diagnosis of TRALI and non-TRALI

The AUC, critical value, specificity, and sensitivity of TNF-α in the differential diagnosis of TRALI and non-TRALI were respectively 0.651, 128.40 pg/mL, 55.00%, and 76.19% and those of IL-10 were correspondingly 0.770, 24.41 pg/mL, 75.00%, and 73.81%. The AUC, specificity, and sensitivity of TNF-α and IL-10 in combination were 0.767, 75.00%, and 73.81%, respectively. IL-10 showed the best diagnostic efficacy with the biggest AUC whereas TNF-α showed the highest diagnostic sensitivity (**Table 2**; **Figure 3**).

Risk factor analysis for prognosis

Cox multiple-factor analysis results showed that the amount of blood transfusion was an independent prognostic risk factor for TRALI ($P < 0.05$) (**Tables 3-5**).

Discussion

Till date, the pathogenesis of TRALI has not been studied clearly. It is generally believed that TRALI is mainly caused by immune and non-immune factors. With respect to the immune factors, it is generally considered that leukocytes are activated by leukocyte antibodies in the blood, resulting in vascular endothelial cell injury. However, no leukocyte antibodies were detected in a large number of patients with TRALI. Tumor necrosis factor, interleukins, and other cytokines are important causes of lung edema in patients with TRALI [13-16]. Therefore, in this study, we investigated the relationship

Table 4. Single-factor risk analysis for prognosis

	B	SE	Wald	df	Sig.	Exp (B)	95.0% CI	
							Lower limit	Upper limit
Gender	-0.260	0.428	0.369	1	0.543	0.771	0.333	1.783
Age	-0.052	0.022	5.664	1	0.017	0.950	0.910	0.991
Weight	0.596	0.422	1.990	1	0.158	1.814	0.793	4.151
Height	0.144	0.430	0.112	1	0.738	1.154	0.497	2.680
HLA antibody I	-0.791	0.620	1.628	1	0.202	0.453	0.134	1.529
HLA antibody II	1.198	0.467	6.594	1	0.010	3.314	1.328	8.270
WBC count	0.003	0.053	0.004	1	0.950	1.003	0.904	1.113
CRP	0.004	0.013	0.112	1	0.738	1.004	0.980	1.029
Neutrophil proportion	-0.025	0.029	0.761	1	0.383	0.975	0.922	1.032
Mean arterial pressure	-0.007	0.028	0.068	1	0.795	0.993	0.940	1.049
Amount of blood transfusion	0.001	0.000	7.161	1	0.007	1.001	1.000	1.001
Total amount of blood transfusion	0.000	0.000	6.225	1	0.013	1.000	1.000	1.001
Mechanical ventilation	1.281	0.553	5.374	1	0.020	3.600	1.219	10.632
Smoking history	0.970	0.429	5.102	1	0.024	2.638	1.137	6.121
TNF-α	0.027	0.011	6.284	1	0.012	1.028	1.006	1.050
IL-10	0.141	0.043	10.625	1	0.001	1.151	1.058	1.253

Table 5. Multi-factor risk analysis for prognosis

	B	SE	Wald	df	Sig.	Exp (B)	95.0% CI	
							Lower limit	Upper limit
HLA antibody II	-0.114	0.577	0.039	1	0.844	0.893	0.288	2.764
Amount of blood transfusion	0.001	0.000	5.61	1	0.018	1.001	1.000	1.001
Total amount of blood transfusion	0.000	0.000	1.158	1	0.282	1.000	1.000	1.001
Mechanical ventilation	0.678	0.637	1.134	1	0.287	1.971	0.565	6.868
Smoking history	-0.008	0.542	0.000	1	0.989	0.992	0.343	2.872
TNF-α	0.006	0.017	0.125	1	0.724	1.006	0.973	1.040
IL-10	0.107	0.055	3.763	1	0.052	0.112	0.099	0.239

between TNF-α and IL-10 expression and prognosis in terms of non-immune factors. Our results provide a reference for the clinical diagnosis of TRALI and evaluation of prognosis in patients.

We performed prospective analysis in this study. The expression of TNF-α and IL-10 in patients TRALI and those with non-TRALI was found to be significantly higher than that in healthy subjects. Further, the expression in TRALI patients was much higher than that in non-TRALI patients. The theories of "two hit model" and "threshold model" are generally recognized for the pathogenesis of TRALI. The "two hit model" theory suggests that the first inflammatory reaction is activated by trauma, infection, and other factors. Release of relevant inflammatory factors is subsequently promoted. It is also an important process in ALI caused by other reasons. The two hit model is the transfusion of blood product by which sensitized leukocytes are further activated and the second injury is caused, thus triggering TRALI [17, 18]. This may be one of the reasons why the expression of TNF-α and IL-10 in patients with TRALI is higher than that in patients with non-TRALI. This study provides a theoretical basis for the differential diagnosis of TRALI and non-TRALI using TNF-α and IL-10.

We also used ROC to analyze the efficacy of TNF-α and IL-10 in the differential diagnosis of TRALI and non-TRALI. The analysis results showed that the efficacy of IL-10 was higher than that of TNF-α. However, the efficacy of diagnosis with TNF-α and IL-10 in combination was not greater than the efficacy of either of

them alone. In the report by Fremont et al. [19], RAGE, PCPIII, BNP, Ang2, IL-10, TNF-α, and IL-8 were considered as biomarkers to diagnose traumatic ALI, with an AUC up to 0.86. Roubinian et al. [20] used IL-6, IL-8, IL-10, GM-CSF, and TNF-α for the differential diagnosis of TRALI and transfusion-related circulation overload, with an AUC of 0.88. Roubinian et al. also used pre-transfusion cytokine levels for the diagnostic analysis. However, the relationship between these cytokines and the diagnosis of patients was not analyzed. In this study, we used post-transfusion cytokine levels to analyze the diagnostic efficacy. However, only two markers were considered. In future studies, additional biomarkers can be included in the analysis to improve the diagnostic efficacy.

We next analyzed the relationship between TNF-α, IL-10, and the prognosis of patients with TRALI. The analysis results showed that high expression of TNF-α and low expression of IL-10 were related to prognosis (death). Transplantation of mesenchymal stem cells can also treat the endotoxin-induced ALI in mice by reducing the expression of TNF-α and MIP-2, resulting in inhibition of the inflammatory reaction and increased expression of IL-10 [21]. All the above-mentioned studies have shown that TNF-α and IL-10 are closely associated with survival after lung injury. However, our Cox regression analysis showed that although TNF-α and IL-10 were the risk factors of prognosis, they were not independent risk factors. This also indicated that multiple cytokines should be considered in the treatment of TRALI. However, studies have reported that IL-10 has no difference in expression between TRALI and patients with acute lung injury caused by sepsis [22]. This reason requires further analysis. We speculate that it may be because sepsis is an inflammatory response syndrome of whole body, which has a high level of inflammatory response itself, masks the second inflammatory response caused by acute lung injury.

This study also has some limitations. The number of included subjects was small and the scope of the study was narrow. Multi-center clinical trials conducted in the future will further validate our results. The components of blood transfusion products also need to be further subdivided. Different blood transfusion products may have different degrees of stimulation to the body's inflammatory response. It is necessary to further determine the expression of TNF-α and IL-10 in TRALI caused by different blood transfusion products. In summary, TNF-α and IL-10 levels in the peripheral blood of patients with TRALI were elevated compared to those in patients with ALI caused by other reasons. IL-10 showed good efficacy in the differential diagnosis of TRALI and non-TRALI with a critical value of 24.41 pg/ml. The survival rate of TRALI patients with high expression of TNF-α or low expression of IL-10 is lower. Finally, TNF-α and IL-10 are risk factors of prognosis, but are not independent risk factors.

Disclosure of conflict of interest

None.

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