Cite as: Du D. Wei G, Wang LX, Liu HB. The relationship between serum IL-33, vWF, G-CSF and prognosis of acute massive hemorrhage patients with transfusion-related acute lung injury [J]. Chin J Clin Res, 2025, 38(8): 1202-1206.
DOI: 10.13429/j.cnki.cjcr.2025.08.013

The relationship between serum IL-33, vWF, G-CSF and prognosis of acute massive hemorrhage patients with transfusion-related acute lung injury

DU Dan, WEI Ge, WANG Lingxue, LIU Hongbin*

**Department of Laboratory, Weinan Central Blood Station, Weinan, Shaanxi 714000, China*

Corresponding author: WANG Lingxue, E-mail：m13772001005@163.com

Abstract: Objective To explore the predictive value of serum interleukin-33 (IL-33), von Willebrand factor (vWF), and granulocyte colony-stimulating factor (G-CSF) for the prognosis of acute massive hemorrhage patients with transfusion-related acute lung injury (TRALI). **Methods** From June 2022 to December 2024, 270 patients with acute massive bleeding admitted to Chang'an Hospital were selected. Among them, 98 patients with TRALI were labeled as the TRALI group, and 172 patients with simple acute massive bleeding were labeled as the non TRALI group. ELISA kits were used to detect serum IL-33, vWF, and G-CSF. According to the survival and death status of TRALI patients after 10 days of blood transfusion, they were classified into the poor prognosis group (death, 31 cases) and the good prognosis group (survival, 67 cases). Multiple logistic regression model was used to explore the factors affecting the prognosis of TRALI patients. ROC was used to explore the predictive value of serum IL-33, vWF, and G-CSF for the prognosis of TRALI. **Results** The proportions of transfusion history, allergy history, blood to transfusion interval ⩾ 0.5 h, transfusion frequency >2 times, and serum IL-33, vWF, and G-CSF in the TRALI group and poor prognosis group were higher than those in the non TRALI group and good prognosis group, respectively (P<0.05). The transfusion history[OR=2.356,95%CI:1.329-4.176], allergy history[OR=2.154, 95%CI:1.383-3.354], blood to transfusion interval, transfusion frequency, and serum IL-33, vWF, and G-CSF were factors affecting poor prognosis in TRALI patients (P<0.05). The area under the curve (AUC) of serum IL-33, vWF, and G-CSF alone (0.694, 0.789, 0.808) in predicting TRALI prognosis were smaller than the combined prediction of the three (0.919). **Conclusion**: This study found that elevated levels of serum IL-33, vWF, and G-CSF in TRALI patients are risk factors affecting their prognosis. The combination of the three has high prognostic value and can assist in the clinical treatment and evaluation of TRALI.

Keywords: Acute massive hemorrhage; Transfusion-related acute lung injury; Interleukin-33; von Willebrand factor; Granulocyte colony-stimulating factor; Prognosis
Fund program: Weinan Science and Technology Planning Project (2022ZDYFJH-163)

Transfusion-related acute lung injury (TRALI) is one of the acute respiratory distress syndromes that occur within 6 hours after blood transfusion. It causes acute pulmonary edema and rapid deterioration of respiratory function, and is a major cause of transfusion-related morbidity and mortality [1]. Patients with TRALI often present with dyspnea, cough, and fever, and may even develop respiratory failure and severe hypoxemia, posing a threat to their life and health [2]. Unfortunately, the pathogenesis of TRALI remains incompletely understood, and current clinical management is limited to supportive therapy and acute respiratory distress syndrome-derived treatments, which are not specific to the mechanism of TRALI and have significant limitations in improving long-term prognosis [3]. Therefore, identifying biomarkers associated with the prognosis of TRALI patients is of great significance for early identification of high-risk patients, formulating individualized intervention measures, and improving outcomes. Studies have found that TRALI is associated with neutrophil activation and damage caused by endothelial cell and platelet abnormalities [4]. Interleukin-33 (IL-33) is an inflammatory factor involved in various pathological processes. Lei *et al.* [5] reported that upregulated IL-33 expression promotes the development of uncontrolled pulmonary inflammation in mice with acute lung injury. Von Willebrand factor (vWF) is a key hemostatic factor for vascular endothelial function, and its level changes are closely related to the levels of inflammatory factors in septic acute lung injury [6]. Thus, it is hypothesized that vWF is a biomarker for evaluating the severity of such diseases and may be associated with the condition of TRALI patients. In addition, Li *et al.* [7] found that granulocyte colony-stimulating factor (G-CSF) affects the prognosis of patients with acute lung injury and is a

biomarker for predicting the occurrence of acute lung injury. Therefore, this study will comprehensively analyze the impact of these three indicators on the prognosis of TRALI patients.

1 Subjects and methods

1.1 Study subjects

A total of 270 patients with acute massive hemorrhage admitted to Chang An Hospital from June 2022 to December 2024 were prospectively selected. Among them, 98 patients complicated with TRALI were included in the TRALI group, and 172 patients with simple acute massive hemorrhage were included in the non-TRALI group.

Inclusion criteria: (1) All patients met the diagnostic criteria for acute massive hemorrhage as defined by Guo *et al.* [8], and TRALI patients conformed to the Chinese Expert Consensus on the Diagnosis and Treatment of Transfusion-Related Acute Lung Injury (2023 Edition) [9]; (2) Transfused patients met the blood transfusion indications of the Ministry of Health [10]; (3) Complete baseline data were available, and written informed consent was obtained from all patients or their families.

Exclusion criteria: (1) Pre-transfusion lung injury or infection; (2) Abnormal liver function; (3) Pulmonary hypertension; (4) Hematological diseases. This study was approved by the Medical Ethics Committee of Chang An Hospital (approval number: CA2022-017).

1.2 Methods

1.2.1 Collection of general data

Age and gender of patients were collected from admission records. Smoking, alcohol consumption, and staying up in the past three months were recorded. Previous transfusion history and allergies to drugs, food, or other substances were documented. The primary bleeding site was confirmed based on clinical diagnosis and auxiliary examination results. Shock status before transfusion was evaluated. Two times when the blood bank releases blood and the start time of transfusion were accurately recorded. The number of red blood cell product transfusions from the start of transfusion to the study endpoint (e.g., TRALI diagnosis, discharge, or death) during hospitalization was counted.

1.2.2 Detection of serum indicators

For the non-TRALI group, 2 mL of elbow venous blood was collected within 6 hours after transfusion completion. For the TRALI group, 2 mL of elbow venous blood was collected at the time of diagnosis. The blood samples were tilted and left to stand at room temperature for 30 minutes to coagulate, then centrifuged under laboratory conditions (4°C, 2 500×*g* , 15 minutes). The supernatant (serum) was aspirated, aliquoted into EP tubes, and stored at -80°C. Serum samples were thawed on ice, and precipitates were removed by centrifugation (10 000×*g*, 4°C, 5 minutes). Dilution was performed according to the instructions of each ELISA kit. All kit components were removed 30 minutes in advance from -20°C, equilibrated to room temperature, and deionized water was added in specified volumes as per the instructions. After standing for 10 minutes, the mixture was vortexed to homogeneity. Serial dilutions were prepared using dilution buffer to generate standard curves, and serum concentrations of IL-33 [Abcam (Shanghai) Trading Co., Ltd., batch number: ab223865], vWF (Shanghai Jining Biotechnology Co., Ltd., batch number: JN22440), and G-CSF (Hangzhou Lianke Biotechnology Co., Ltd., batch number: EK169HS) were calculated from sample OD values using the standard curves. All detections were performed by the same team of medical personnel.

1.2.3 Prognosis assessment

The status of TRALI patients was evaluated 10 days after transfusion. Thirty-one patients who died were classified into the poor prognosis group, and the remaining 67 surviving patients were classified into the favorable prognosis group.

1.3 Statistical methods

Data were analyzed using SPSS 25.0 and MedCalc software. Categorical data were expressed as cases (%), and comparisons were performed using the chi-square test. Measurement data were expressed as $\bar{x}\pm s$, and comparisons were performed using the t-test. Multivariate logistic regression models were used to analyze factors influencing the prognosis of TRALI patients. ROC curves were used to evaluate the prognostic value of serum IL-33, vWF, and G-CSF levels in TRALI patients. A P-value <0.05 was considered statistically significant.

2 Results

2.1 Baseline data and levels of serum IL-33, vWF, G-CSFin non-TRALI and TRALI groups

The proportions of patients with transfusion history, allergy history, blood dispatch-to-transfusion interval ≥0.5 h, and transfusion frequency >2, as well as serum IL-33, vWF, and G-CSF levels in the TRALI group were significantly higher than those in the non-TRALI group (P<0.05). There were no statistically significant differences between the two groups in terms of age, gender, lifestyle habits, bleeding site, or blood transfusion volume (P>0.05). **[Table 1]**

2.2 Levels of serum IL-33, vWF, and G-CSF in patients with different prognoses

Serum IL-33, vWF, and G-CSF levels in the poor prognosis group of TRALI patients were higher than those in the favorable prognosis group (P<0.05). **[Table 2]**

2.3 Univariate analysis of factors affecting TRALI prognosis

The proportions of patients with transfusion history, allergy history, blood dispatch-to-transfusion interval ≥0.5 h, and transfusion frequency >2 in the poor prognosis group were higher than those in the favorable prognosis group (P<0.05). There were no statistically significant differences between the two groups in age, gender, lifestyle habits, bleeding site, or blood transfusion volume (*P*>0.05). **[Table 3]**

Tab.1 Comparison of baseline data and serum levels of IL-33, vWF, and G-CSF between two groups [case (%)]

Item	Non-TRALI group (*n*=172)	TRALI group (*n*=98)	χ^2/t value	*P* value
Age (years)	54.06±5.82	54.32±5.94	0.350	0.726
Gender (Male/Female)	102/70	50/48	1.740	0.187
Lifestyle				
Smoking	87（50.58）	46（46.94）	0.331	0.565
Alcohol consumption	74（43.02）	31（31.63）	3.408	0.065
Staying up late	65（37.79）	28（28.57）	2.350	0.125
Transfusion history	49（28.49）	43（43.88）	6.582	0.010
Allergy history	25（14.53）	57（58.16）	56.193	<0.001
Bleeding site			0.466	0.792
Gastrointestinal tract	61（35.47）	36（36.73）		
Cerebral trauma	48（27.91）	30（30.61）		
Traumatic splenic rupture	63（36.63）	32（32.65）		
Shock before transfusion	57（33.14）	31（31.63）	0.065	0.799
Blood issuance-to-transfusion interval			40.255	<0.001
<0.5 h	136（79.07）	40（40.82）		
≥0.5 h	36（20.93）	58（59.18）		
Transfusion frequency			5.104	0.024
>2 times	18（10.47）	20（20.41）		
≤2 times	154（89.53）	78（79.59）		
Blood transfusion volume (mL, ±s)	1726.85±325.42	1731.93±320.26	0.124	0.901
IL-33 (pg/mL, ±s)	78.36±15.54	92.52±15.65	7.181	<0.001
vWF (ug/mL, ±s)	1521.83±230.76	1785.47±232.19	9.007	<0.001
G-CSF (pg/mL, ±s)	39.08±10.13	48.61±10.25	7.401	<0.001

2.4 Multivariate analysis of factors influencing TRALI prognosis

Using poor prognosis of TRALI patients as the dependent variable (survival = 0, death = 1), and transfusion history, allergy history, time interval from blood issuance to transfusion, transfusion frequency, and serum levels of IL-33, vWF, and G-CSF as independent variables, logistic regression analysis was performed. The results revealed that transfusion history, allergy history, blood issuance-to-transfusion interval, transfusion frequency, and serum IL-33, vWF, and G-CSF levels were significant influencing factors for poor prognosis in TRALI patients (*P* < 0.05). **[Table 4]**

2.5 Predictive value of serum IL-33, vWF, and G-CSF levels for TRALI prognosis

The combined detection of serum IL-33, vWF, and G-CSF levels yielded the largest AUC for predicting TRALI prognosis. **[Figure 1 & Table 5]**

Tab.2 Comparison of serum levels of IL-33, vWF and G-CSF in patients with different prognoses （$\bar{x}\pm s$）

Group	IL-33（pg/mL）	vWF（ug/mL）	G-CSF（pg/mL）
Favorable prognosis (*n*=67)	88.48±17.70	1702.03±245.83	44.68±10.13
Poor prognosis (*n*=31)	101.24±11.46	1965.81±215.98	57.11±1.30
t value	3.668	5.126	6.788
P value	<0.001	<0.001	<0.001

Tab.3 Univariate analysis of factors affecting TRALI prognosis [case (%)]

Item	Favorable prognosis (n=67)	Poor prognosis (n=31)	χ^2/t value	P value
Age (years, ±s)	54.21±5.46	54.55±5.42	0.287	0.774
Gender (Male/Female)	31/36	19/12	1.914	0.167
Lifestyle				
Smoking	35（52.24）	11（35.48）	2.389	0.122
Alcohol consumption	18（26.87）	13（41.94）	2.226	0.136
Staying up late	16（23.88）	12（38.71）	2.284	0.131
Transfusion history	24（35.82）	19（61.29）	5583	0.018
Allergy history	34（50.75）	23（74.19）	4.788	0.029
Bleeding site			3.684	0.159
Gastrointestinal tract	22（32.84）	14（45.16）		
Cerebral trauma	19（28.36）	11（35.48）		
Traumatic splenic rupture	26（38.81）	6（19.35）		
Shock before transfusion	20（29.85）	11（35.48）	0.311	0.577
Blood issuance-to-transfusion interval			6.242	0.012
<0.5 h	33（49.25）	7（22.58）		
≥0.5 h	34（50.75）	24（77.42）		
Transfusion frequency			6.344	0.012
>2 times	9（13.43）	11（35.48）		
≤2 times	58（86.57）	20（64.52）		
Blood transfusion volume (mL, ±s)	1729.84±319.32	1736.45±320.21	0.095	0.924

Tab.4 Multivariate analysis of factors affecting TRALI prognosis

Indicator	*β*	*SE*	*Wald*χ^2	*P* value	*OR* value	*95%CI*
Transfusion history	0.857	0.292	8.613	0.003	2.356	1.329-4.176
Allergy history	0.767	0.226	11.528	0.001	2.154	1.383-3.354
Blood issuance-to-transfusion interval ≥0.5 h	1.031	0.359	8.248	0.004	2.804	1.387-5667
Transfusion frequency >2 times	0.763	0.357	4.564	0.033	2.144	1.065-4.316
IL-33	1.067	0.314	11.550	0.001	2.907	1.571-5.379
vWF	1.079	0.267	16.334	0.000	2.942	1.743-4.965
G-CSF	1.052	0.311	11.432	0.001	2.862	1.556-5.265

Tab.5 Predictive value of serum IL-33, vWF and G-CSF levels for prognosis of patients

Indicator	Cut-off Value	AUC	95%CI	Sensitivity (%)	Specificity (%)	Youden's Index
IL-33	89.00 pg/mL	0.694	0.593-0.783	80.65	62.69	0.433
vWF	1871.47 ug/mL	0.789	0.695-0.865	80.65	76.12	0.568
G-CSF	48.29 pg/mL	0.808	0.716-0.880	87.10	62.69	0.498
Combination		0.919	0.846-0.965	90.32	85.07	0.754

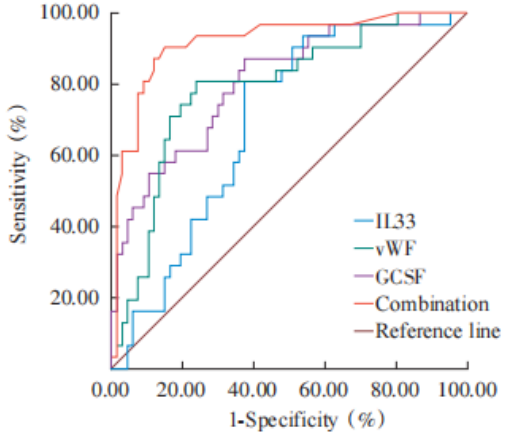

Fig.1 ROC curve analysis of serum IL-33, vWF, and G-CSF levels for predicting TRALI prognosis

3 Discussion

The interleukin family is a crucial group of cytokines. Akgun *et al.* [11] found that IL-6 can inhibit the progression of TRALI, while Kapur *et al.* [12] reported abnormal IL-10 levels in TRALI patients, suggesting a close association between the IL family and the development of TRALI. In the present study, serum IL-33 levels were elevated in both the TRALI group and the poor prognosis group. Previous research has indicated that increased IL-33 promotes eosinophil proliferation, inhibits the progression of acute lung injury, and enhances patient survival [13]. Zheng *et al.* [14] identified IL-33 as a biomarker of lung function impairment. Given its role in immune regulation, we hypothesize that IL-33 may influence TRALI pathogenesis and prognosis through immune-related pathways, a finding supported by the multivariate analysis results of this study. Gong *et al.* [15] demonstrated that stimulating IL-33 levels in mice with sepsis-induced lung injury modulates type 2 immune responses and reduces disease damage. Zou *et al.* [16] further revealed that IL-33 binds to the ST2 receptor during cellular or tissue injury, activating the IL-33/ST2 axis and recruiting iNKT cells to promote early inflammatory responses in acute respiratory distress syndrome, which predicts poor patient prognosis. These findings suggest that early elevation of IL-33 may exacerbate TRALI inflammation and disease progression, while sustained high levels in later stages may alleviate prognostic damage.

The current study observed increased serum vWF levels in both the TRALI group and the poor prognosis group, consistent with the trend reported in a rat model of lung injury [17]. A 2024 meta-analysis highlighted that elevated vWF levels are closely associated with disease severity and prognosis in patients with acute lung injury complicated by acute respiratory distress syndrome, aligning with the multivariate analysis results of this study [18]. As a multimeric protein, vWF primarily participates in primary and secondary hemostasis by mediating platelet adhesion and aggregation, with well-established roles in thrombosis [19]. Emerging evidence indicates that vWF also regulates neutrophil function to modulate inflammatory responses [20]. Ling *et al.* [21] noted that endothelial cells and neutrophils, through interactions with platelets, collectively drive TRALI pathogenesis. vWF may influence TRALI progression by regulating neutrophil activity and platelet aggregation during inflammatory responses.

In this study, serum G-CSF levels were elevated in the TRALI group and poor prognosis group, consistent with findings in a mouse model of diabetes-associated lung injury [22]. G-CSF is produced by bone marrow stromal cells, monocytes/macrophages, endothelial cells, and epithelial cells, and plays a central role in regulating neutrophil activity by promoting the proliferation and differentiation of granulocyte precursors into mature cells [23]. Secreto *et al.* [24] found that elevated G-CSF levels exacerbate respiratory parameters in patients with respiratory failure and lung injury, suggesting that increased G-CSF may aggravate lung damage and promote TRALI progression. Conversely, Luo *et al.* [25] demonstrated that G-CSF alleviates cardiopulmonary bypass-induced lung dysfunction by suppressing inflammatory responses in lung tissue and circulation, as well as pre-mobilization of CD133+ progenitor cells. These findings indicate that G-CSF may influence TRALI development and prognosis by modulating inflammatory processes.

Additionally, this study identified transfusion history, allergy history, blood issuance-to-transfusion interval, and transfusion frequency as prognostic factors for TRALI. These results emphasize the importance of monitoring patients' transfusion history—particularly prior allergies and transfusion reactions—during clinical practice to identify high-risk populations. Proactive measures, such as selecting low-risk blood products, optimizing transfusion strategies, or adopting alternative therapies, may reduce TRALI incidence and improve prognosis. Timely monitoring and intervention during and after transfusion are also critical for mitigating adverse outcomes.

ROC curve analysis revealed that the combined detection of serum IL-33, vWF, and G-CSF exhibited the highest AUC and sensitivity for predicting TRALI prognosis, highlighting significant clinical value. Given its high sensitivity, further exploration of incorporating these

three indicators into routine clinical testing is warranted. Routine monitoring could enable early identification of TRALI patients at risk of severe disease, facilitating timely adjustments to transfusion strategies and treatment optimization. Moreover, these indicators may serve as auxiliary tools for evaluating the efficacy of TRALI interventions, providing precise guidance for clinical decision-making and improving patient outcomes.

In conclusion, this study demonstrated elevated IL-33, vWF, and G-CSF levels in TRALI patients, with higher levels observed in non-survivors. These three factors independently influence TRALI prognosis and may serve as potential prognostic markers. A limitation of this study is the relatively small sample size due to practical constraints, which may restrict the generalizability of the findings. Future studies will expand data collection to validate these results.

Conflict of interest None

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Submission Received: 2025-06-18/**Revised:**2025-07-14

·论　著·

血清IL-33、vWF、G-CSF水平与急性大出血输血相关性急性肺损伤患者预后的关系

杜丹[1]，　魏鸽[2]，　王凌雪[2]，　刘宏斌[3]

1. 渭南市中心血站检验科，陕西 渭南 714000；2. 长安医院输血科，陕西 西安 710016；
3. 长安医院呼吸内科，陕西 西安 710016

摘要：目的　探究急性大出血输血相关急性肺损伤(TRALI)患者血清白细胞介素-33(IL-33)、血管性血友病因子(vWF)、粒细胞集落刺激因子(G-CSF)水平对其预后的预测价值。**方法**　选择2022年6月至2024年12月长安医院收治的急性大出血患者270例，将合并TRALI患者98例纳入TRALI组，将单纯急性大出血患者172例纳入非TRALI组。通过ELISA试剂盒检测血清IL-33、vWF、G-CSF水平；根据TRALI患者输血10 d后生存死亡情况分为预后不良组(死亡，31例)、预后良好组(存活，67例)。采用多因素logistic回归分析影响TRALI患者预后的因素。采用受试者工作特征曲线(ROC)分析血清IL-33、vWF、G-CSF水平对TRALI患者预后的预测价值。**结果**　TRALI组与预后不良组患者输血史、过敏史、发血至输血间隔≥0.5 h、输血次数>2次占比，以及血清IL-33、vWF、G-CSF水平分别高于非TRALI组与预后良好组(P<0.05)。输血史[OR=2.356，95%CI：1.329~4.176]、过敏史[OR=2.154，95%CI：1.383~3.354]、发血至输血间隔≥0.5 h[OR=2.804，95%CI：1.387~5.667]、输血次数>2次[OR=2.144，95%CI：1.065~4.316]、血清IL-33[OR=2.907，95%CI：1.571~5.379]、vWF[OR=2.942，95%CI：1.743~4.965]和G-CSF[OR=2.862，95%CI：1.556~5.265]水平是TRALI患者预后不良的独立影响因素(P<0.05)。血清IL-33、vWF、G-CSF水平单独预测TRALI预后的曲线下面积(AUC)(0.694，0.789，0.808)均小于三者联合预测(0.919)。**结论**　TRALI患者血清IL-33、vWF、G-CSF水平升高是影响其预后的风险因素，三者联合预测预后价值较高，可辅助TRALI的临床治疗与评估。

关键词：急性大出血；输血相关性急性肺损伤；白细胞介素-33；血管性血友病因子；粒细胞集落刺激因子；预后
中图分类号：R457.1+3　**文献标识码：**A　**文章编号：**1674-8182(2025)08-1202-05

The relationship between serum IL-33, vWF, G-CSF and prognosis of acute massive hemorrhage patients with transfusion-related acute lung injury

DU Dan*, WEI Ge, WANG Lingxue, LIU Hongbin

*Department of Laboratory, Weinan Central Blood Station, Weinan, Shaanxi 714000, China

Corresponding author: WANG Lingxue, E-mail: m13772001005@163.com

Abstract: Objective　To explore the predictive value of serum interleukin-33 (IL-33), von Willebrand factor (vWF), and granulocyte colony-stimulating factor (G-CSF) for the prognosis of acute massive hemorrhage patients with transfusion-related acute lung injury (TRALI). **Methods**　From June 2022 to December 2024, 270 patients with acute massive bleeding admitted to Chang'an Hospital were selected. Among them, 98 patients with TRALI were labeled as the TRALI group, and 172 patients with simple acute massive bleeding were labeled as the non-TRALI group. ELISA kits were used to detect serum IL-33, vWF, and G-CSF. According to the survival and death status of TRALI patients after 10 days of blood transfusion, they were classified into the poor prognosis group (death, 31 cases) and the good prognosis group (survival, 67 cases). Multivariate logistic regression model was used to explore the factors affecting the prognosis of TRALI patients. Receiver operating characteristic (ROC) was used to explore the predictive value of serum IL-33,

DOI：10.13429/j.cnki.cjcr.2025.08.013
基金项目：渭南市科技计划项目(2022ZDYFJH-163)
通信作者：王凌雪，E-mail：m13772001005@163.com
出版日期：2025-08-20

QR code for English version

vWF, and G-CSF for the prognosis of TRALI. **Results** The proportions of transfusion history, allergy history, interval of blood sending to transfusion ≥ 0.5 h, transfusion frequency >2 times, and the levels of serum IL-33, vWF, and G-CSF in the TRALI group and poor prognosis group were higher than those in the non-TRALI group and good prognosis group, respectively (P<0.05). The transfusion history [OR=2.356, 95%CI: 1.329-4.176], allergy history [OR=2.154, 95%CI: 1.383-3.354], interral of blood sending to transfusion ≥0.5 hours [OR=2.804, 95%CI: 1.387-5.667], number of transfusions >2 [OR=2.144, 95%CI: 1.065-4.316], serum IL-33 levels [OR=2.907, 95%CI: 1.571-5.379], vWF levels [OR=2.942, 95%CI: 1.743-4.965], and G-CSF levels [OR=2.862, 95%CI: 1.556-5.265] were the factors affecting prognosis in TRALI patients (P<0.05). The area under the ROC curve of serum IL-33, vWF, and G-CSF alone (0.694, 0.789, 0.808) in predicting TRALI prognosis were smaller than the combined prediction of the three indicators (0.919). **Conclusion** Elevated levels of serum IL-33, vWF, and G-CSF in TRALI patients are risk factors affecting their prognosis. The combination of the three has high prognostic value and can assist in the clinical treatment and evaluation of TRALI.

Keywords: Acute massive hemorrhage; Transfusion-related acute lung injury; Interleukin-33; von Willebrand factor; Granulocyte colony-stimulating factor; Prognosis

Fund program: Weinan Science and Technology Planning Project (2022ZDYFJH-163)

输血相关急性肺损伤(transfusion-related acute lung injury,TRALI)是在输血后6 h内发生的急性呼吸窘迫综合征之一,会引发急性肺水肿与呼吸功能急剧减退,是造成输血相关疾病和死亡的主要原因[1]。TRALI患者多表现为呼吸困难、咳嗽和发热,甚至出现呼吸衰竭和严重的低氧血症,对患者的生命健康构成威胁[2]。遗憾的是,迄今为止,TRALI的发病机制尚不完全清楚,目前临床仅限于支持性治疗和急性呼吸窘迫综合征衍生疗法,这些疗法对TRALI并无特异性,在改善患者长期预后方面存在明显的局限性[3]。因此,寻找与TRALI患者预后相关的生物标志物,对于早期识别高风险患者并针对患者制定个体干预措施以改善转归等方面意义重大。研究发现,TRALI发生与中粒细胞的激活以及内皮细胞、血小板异常引发的损伤有关[4]。白细胞介素-33(interleukin-33,IL-33)是一种炎性因子,与多种病理过程相关。雷铭等[5]研究报道,IL-33表达上调可促进急性肺损伤小鼠肺部失控性炎症的发展。血管性血友病因子(von Willebrand factor,vWF)是血管内皮功能的关键性止血因子,其水平变化与脓毒症急性肺损伤的炎性因子水平密切相关[6]。笔者推测,vWF可能是评估此类疾病病情的生物标志物,与TRALI患者病情存在关联。此外,李宏等[7]研究发现,粒细胞集落刺激因子(granulocyte colony-stimulating factor,G-CSF)影响急性肺损伤患者的预后,是预测急性肺损伤发生的生物标志物。因此,本研究综合分析这三个指标对TRALI患者预后的影响。

1 对象与方法

1.1 *研究对象* 前瞻性选择2022年6月至2024年12月长安医院收治的急性大出血患者270例,将合并TRALI患者98例纳入TRALI组,将单纯急性大出血患者172例纳入非TRALI组。纳入标准:(1)符合郭维等[8]研究关于急性大出血的诊断标准,且TRALI患者符合《输血相关急性肺损伤诊治中国专家共识(2023版)》[9];(2)输血患者符合卫生部输血指征[10];(3)患者基础资料完整,且其家属均知情同意。排除标准:(1)输血前存在肺损伤或感染;(2)肝功能异常;(3)肺动脉高压;(4)血液系统疾病。本研究通过长安医院医学伦理委员会批准同意(批号:CA2022-017)。

1.2 *方法*

1.2.1 一般资料的收集 通过入院记录统计患者年龄、性别;询问患者入院前抽烟、饮酒以及近三个月熬夜情况;详细询问并记录患者既往是否有输血经历;详细记录患者是否有药物、食物或其他物质过敏史;根据临床诊断和辅助检查结果明确主要出血部位;评估患者在开始输血治疗前是否处于休克状态;精确记录发血时间、开始输血时间;统计患者在本次住院期间,从开始输血到研究观察终点(如TRALI诊断、出院或死亡)所接受的红细胞制品输注次数。

1.2.2 血清指标的检测 非TRALI组患者在输血结束后6 h内抽取肘部静脉血2 mL,TRALI组患者则在确诊时抽取肘部静脉血2 mL,室温下倾斜静置30 min凝固,在实验室条件(4 ℃,2 500×g,离心15 min)下离心,吸取上清(血清),分装至EP管储存于-80 ℃冰箱中。血清置于冰上解冻,离心去除沉淀(10 000×g,4 ℃,5 min),稀释要求参照各ELISA试剂盒说明书调整,所有试剂盒组分提前30 min从-20 ℃取出,室温平衡,并按说明书加入指定体积去离子水,静置10 min后涡旋混匀。使用稀释液进行梯度稀释绘制标准曲

线，根据样本OD值从标准曲线反推血清浓度，包括以下指标：IL-33[艾博抗（上海）贸易有限公司，批号：ab223865]、vWF（上海纪宁生物科技有限公司，批号：JN22440）、G-CSF（杭州联科生物技术股份有限公司，批号：EK169HS）。检测均由同一批医护人员操作。

1.2.3　预后情况　统计TRALI患者输血10 d后的情况，将死亡的31例患者纳入预后不良组，其余67例存活患者纳入预后良好组。

1.3　统计学方法　采用SPSS 25.0软件以及MedCalc软件分析数据。计数资料以例（%）表示，比较采用χ^2检验；计量资料以$\bar{x}\pm s$表示，比较采用t检验。多因素logistic回归模型分析影响TRALI患者预后的因素。受试者工作特征曲线（ROC）分析血清IL-33、vWF、G-CSF水平对TRALI患者预后的预测价值。P<0.05为差异有统计学意义。

2　结　果

2.1　非TRALI组与TRALI组患者基础资料以及血清IL-33、vWF、G-CSF水平　TRALI组输血史、过敏史、发血至输血间隔≥0.5 h、输血次数>2的患者占比，以及血清IL-33、vWF、G-CSF水平显著高于非TRALI组（P<0.05）；两组在年龄、性别、生活习惯、出血部位、输血前休克、输血量等方面差异无统计学意义（P>0.05）。见表1。

表1　两组患者基础资料以及血清IL-33、vWF、G-CSF水平比较　[例（%）]

Tab.1　Comparison of baseline data and serum levels of IL-33, vWF, and G-CSF between two groups　[case（%）]

项目	非TRALI组（n=172）	TRALI组（n=98）	t/χ^2值	P值
年龄（岁，$\bar{x}\pm s$）	54.06±5.82	54.32±5.94	0.350	0.726
男/女（例）	102/70	50/48	1.740	0.187
生活习惯				
抽烟	87(50.58)	46(46.94)	0.331	0.565
饮酒	74(43.02)	31(31.63)	3.408	0.065
熬夜	65(37.79)	28(28.57)	2.350	0.125
输血史	49(28.49)	43(43.88)	6.582	0.010
过敏史	25(14.53)	57(58.16)	56.193	<0.001
出血部位				
消化道	61(35.47)	36(36.73)		
脑外伤	48(27.91)	30(30.61)	0.466	0.792
外伤性脾破裂	63(36.63)	32(32.65)		
输血前休克	57(33.14)	31(31.63)	0.065	0.799
发血至输血间隔				
<0.5 h	136(79.07)	40(40.82)	40.255	<0.001
≥0.5 h	36(20.93)	58(59.18)		
输血次数				
>2次	18(10.47)	20(20.41)	5.104	0.024
≤2次	154(89.53)	78(79.59)		
输血量（mL，$\bar{x}\pm s$）	1 726.85±325.42	1 731.93±320.26	0.124	0.901
IL-33（pg/mL，$\bar{x}\pm s$）	78.36±15.54	92.52±15.65	7.181	<0.001
vWF（μg/mL，$\bar{x}\pm s$）	1 521.83±230.76	1 785.47±232.19	9.007	<0.001
G-CSF（pg/mL，$\bar{x}\pm s$）	39.08±10.13	48.61±10.25	7.401	<0.001

2.2　不同预后患者血清IL-33、vWF、G-CSF水平比较　RALI患者预后不良组血清IL-33、vWF、G-CSF水平高于预后良好组（P<0.05）。见表2。

2.3　影响TRALI预后的单因素分析　TRALI患者预后不良组输血史、过敏史、发血至输血间隔≥0.5 h、输血次数>2患者占比高于预后良好组（P<0.05）；而两组在年龄、性别、生活习惯、出血部位、输血前休克、输血量等方面差异无统计学意义（P>0.05）。见表3。

2.4　影响TRALI预后的多因素分析　以TRALI患者预后不良为因变量（生存=0，死亡=1），TRALI患者输血史、过敏史、发血至输血间隔、输血次数、血清IL-33、vWF、G-CSF水平为自变量进行logistic回归分析，结果显示，输血史、过敏史、发血至输血间隔、输血次数以及血清IL-33、vWF、G-CSF水平是TRALI患者预后不良的影响因素（P<0.05）。见表4。

2.5　血清IL-33、vWF、G-CSF水平预测TRALI预后的

表2　不同预后患者血清IL-33、vWF、G-CSF水平比较　（$\bar{x}\pm s$）

Tab.2　Comparison of serum levels of IL-33, vWF and G-CSF in patients with different prognoses　（$\bar{x}\pm s$）

组别	例数	IL-33（pg/mL）	vWF（ug/mL）	G-CSF（pg/mL）
预后良好组	67	88.48±17.70	1 702.03±245.83	44.68±10.13
预后不良组	31	101.24±11.46	1 965.81±215.98	57.11±1.30
t值		3.668	5.126	6.788
P值		<0.001	<0.001	<0.001

表3　影响TRALI预后的单因素分析　[例（%）]

Tab.3　Univariate analysis of factors affecting TRALI prognosis　[case（%）]

项目	预后良好组（n=67）	预后不良组（n=31）	χ^2/t值	P值
年龄（岁，$\bar{x}\pm s$）	54.21±5.46	54.55±5.42	0.287	0.774
男/女（例）	31/36	19/12	1.914	0.167
生活习惯				
抽烟	35(52.24)	11(35.48)	2.389	0.122
饮酒	18(26.87)	13(41.94)	2.226	0.136
熬夜	16(23.88)	12(38.71)	2.284	0.131
输血史	24(35.82)	19(61.29)	5583	0.018
过敏史	34(50.75)	23(74.19)	4.788	0.029
出血部位				
消化道	22(32.84)	14(45.16)		
脑外伤	19(28.36)	11(35.48)	3.684	0.159
外伤性脾破裂	26(38.81)	6(19.35)		
输血前休克	20(29.85)	11(35.48)	0.311	0.577
发血至输血间隔				
<0.5 h	33(49.25)	7(22.58)	6.242	0.012
≥0.5 h	34(50.75)	24(77.42)		
输血次数				
>2次	9(13.43)	11(35.48)	6.344	0.012
≤2次	58(86.57)	20(64.52)		
输血量（mL，$\bar{x}\pm s$）	1 729.84±319.32	1 736.45±320.21	0.095	0.924

价值　血清 IL-33、vWF、G-CSF 水平三者联合预测 TRALI 预后的 AUC 最大。如图 1、表 5 所示。

表 4　影响 TRALI 预后的多因素分析

Tab.4　Multivariate analysis of factors affecting TRALI prognosis

指标	*β*	*SE*	Wald χ^2	*P* 值	*OR* 值	95%*CI*
输血史	0.857	0.292	8.613	0.003	2.356	1.329~4.176
过敏史	0.767	0.226	11.528	0.001	2.154	1.383~3.354
发血至输血间隔≥0.5 h	1.031	0.359	8.248	0.004	2.804	1.387~5.667
输血次数>2次	0.763	0.357	4.564	0.033	2.144	1.065~4.316
IL-33	1.067	0.314	11.550	0.001	2.907	1.571~5.379
vWF	1.079	0.267	16.334	0.000	2.942	1.743~4.965
G-CSF	1.052	0.311	11.432	0.001	2.862	1.556~5.265

表 5　血清 IL-33、vWF、G-CSF 水平对患者预后的预测价值

Tab.5　Predictive value of serum IL-33，vWF and G-CSF levels for prognosis of patients

指标	截断值	AUC	95%*CI*	灵敏度（%）	特异度（%）	约登指数
IL-33	89.00 pg/mL	0.694	0.593~0.783	80.65	62.69	0.433
vWF	1 871.47 ug/mL	0.789	0.695~0.865	80.65	76.12	0.568
G-CSF	48.29 pg/mL	0.808	0.716~0.880	87.10	62.69	0.498
三者联合		0.919	0.846~0.965	90.32	85.07	0.754

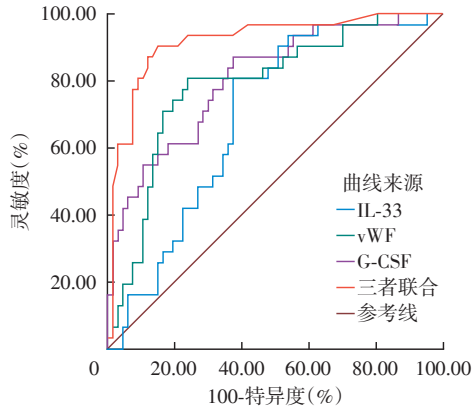

图 1　血清 IL-33、vWF、G-CSF 水平预测 TRALI 预后的 ROC 曲线分析

Fig.1　ROC curve analysis of serum IL-33，vWF，and G-CSF levels for predicting TRALI prognosis

3　讨　论

IL 家族是非常重要的细胞因子家族，Akgun 等[11]研究发现 IL-6 可以抑制 TRALI 的病情发展，Kapur 等[12]研究发现 TRALI 患者 IL-10 水平异常，这提示 IL 家族与 TRALI 的发生发展密切相关。本研究结果发现，血清中 IL-33 水平在 TRALI 组以及预后不良组患者中升高。研究发现，IL-33 升高可以促进嗜酸性粒细胞增多，抑制急性肺损伤进展，改善患者生存预后[13]。Zheng 等[14]研究指出，IL-33 水平是肺功能损伤的生物标志物。考虑到 IL-33 在免疫调节中的作用，猜测其可能通过免疫相关途径参与影响 TRALI 病情与预后，本研究多因素分析结果证实了该观点。Gong 等[15]研究发现，鞘氨醇-1-磷酸受体 2 基因缺失的脓毒症肺损伤小鼠，可通过上调 IL-33 来调节 2 型免疫反应，并减轻疾病损伤。Zou 等[16]研究发现 IL-33 在细胞损伤或组织损伤时会与生长刺激表达基因 2（ST2）受体结合，形成 IL-33/ST2 轴激活并募集恒定自然杀伤 T 细胞（iNKT）促进急性呼吸窘迫综合征中早期的炎症反应，可预测该患者不良预后。这提示早期 IL-33 水平升高可能加剧 TRALI 炎症反应，促进病情发展，后期高水平的 IL-33 可能会缓解患者相关组织损伤。

本研究结果发现，vWF 水平在 TRALI 组以及预后不良组患者血清中升高。与 vWF 在肺损伤大鼠血清中的变化趋势一致[17]。2024 年一项综合分析研究指出，vWF 水平升高与急性肺损伤合并急性呼吸窘迫综合征患者病情关联密切，且与其预后显著相关[18]。本研究多因素分析结果与其一致。vWF 是一种多聚体蛋白，主要参与原发性和继发性止血，可介导血小板黏附和聚集，与血栓形成密切相关[19]。随着研究的深入，发现其可通过调节中性粒细胞功能参与炎症反应[20]。Ling 等[21]研究也指出，内皮细胞和嗜中性粒细胞参与 TRALI 发生，且二者与血小板相互作用，共同参与 TRALI 炎症反应。猜测 vWF 可通过调节中性粒细胞以及血小板聚集参与 TRALI 炎症反应，进而影响 TRALI 病情发展。

本研究结果发现，G-CSF 水平在 TRALI 组以及预后不良组患者血清中升高，与其在糖尿病合并肺损伤小鼠体内水平变化一致[22]。G-CSF 源自骨髓基质细胞、单核/巨噬细胞、内皮细胞以及上皮细胞，它在调节中性粒细胞活性方面发挥着核心作用，可推动粒细胞前体向成熟阶段的增殖与分化过程[23]。Secreto 等[24]研究发现，G-CSF 水平升高会使呼吸衰竭肺损伤患者呼吸参数恶化。提示 G-CSF 水平升高可能会加剧肺部损伤，进而促进 TRALI 发展。Luo 等[25]研究指出，G-CSF 可通过抑制肺组织和循环中的炎症反应以及相关的 $CD133^+$ 祖细胞的预动员来减轻体外循环诱导的肺功能障碍。表明 G-CSF 可能通过调整炎症影响 TRALI 发展与预后。除此之外，本研究还发现，输血史、过敏史、发血至输血间隔、输血次数也是影响 TRALI 预后的因素。提示在临床输血过程中，要注意患者既往输血情况，特别是先前是否发生过过敏史以及其他输血情况，帮助医生识别高风险群体，尽早采取预防措施，如选择低风险的血液制品、优化输血策略或采用替代疗法，以降低 TRALI 发生

的风险并改善患者的预后。此外,及时的监测和干预也是减少TRALI预后不良的关键,确保在输血过程中及输血后能迅速识别并处理任何潜在的不良反应。本研究通过ROC曲线分析发现,血清IL-33、vWF、G-CSF水平联合预测TRALI预后的AUC与灵敏度均表现最优。这一结果具有显著的临床价值,鉴于其较高的灵敏度,有必要进一步探讨将这三项指标纳入临床常规检测的可行性。若能实现常规检测,将有助于临床医生提前识别可能发展为重症的TRALI患者,从而及时调整输血策略,优化治疗方案。此外,在评估针对TRALI的干预措施效果时,这三项指标也可作为重要的辅助评估工具,为临床决策提供更为精准的依据,进而切实改善患者的预后情况。

综上所述,本研究发现IL-33、vWF、G-CSF水平在TRALI患者体内均表现为升高趋势,且死亡患者水平更高;三者是影响TRALI患者预后的因素,可用于评估TRALI患者预后。本研究在收集样本的过程中,由于各种实际条件的限制,所获取的样本量相对较少,可能会使研究结果存在一定局限性。后续研究会继续收集数据用于本研究结果的验证。

利益冲突 无

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收稿日期:2025-06-18 **修回日期**:2025-07-14 **编辑**:李方