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## Correlation of peripheral blood ZO-1 and IL-38 levels with lung injury degree in patients with acute respiratory distress syndrome

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**Abstract: Objective** To analyze the changes of zonula occludens-1 (ZO-1) and interleukin-38 (IL-38) levels in peripheral blood of acute respiratory distress syndrome (ARDS) patients with different degrees of lung injury, and their correlations with the degree of lung injury. **Methods** A total of 105 patients with ARDS admitted to Chuiyangliu Hospital Affiliated with Tsinghua University from April 2020 to April 2023 were selected as the observation group, and 52 non-ARDS patients during the same period were included as the control group. The patients in the observation group were classified into mild, moderate and severe subgroups according to the oxygenation index. The levels of ZO-1 and IL-38 in the peripheral blood of each group were compared. The correlations of ZO-1 and IL-38 levels with the degree of lung injury and their predictive value for the survival prognosis of ARDS were analyzed. **Results** The levels of ZO-1 and IL-38 in the peripheral blood of patients in the observation group were both higher than those in the control group ( $P<0.05$ ). The levels of ZO-1 and IL-38 in peripheral blood of ARDS patients increased in the order of mild, moderate and severe, with statistically significant differences ( $P<0.05$ ). The levels of ZO-1 and IL-38 in the peripheral blood of ARDS patients were negatively correlated with the oxygenation index ( $r=-0.716, -0.740, P<0.01$ ), and were positively correlated with the degree of lung injury ( $r=0.774, 0.729, P<0.01$ ). Among 105 ARDS patients, 40 died and 65 survived within 28 days. The receiver operating characteristic (ROC) analysis results showed that the AUC of ZO-1 and IL-38 in peripheral blood for predicting the prognosis of ARDS patients were 0.769 and 0.785, respectively, with sensitivities of 85.00% and 80.00%, and specificities of 63.08% and 72.31%, respectively. **Conclusion** The elevated levels of ZO-1 and IL-38 in peripheral blood of ARDS patients are correlated with the degree of lung injury and have certain prognostic value.

**Keywords:** Acute respiratory distress syndrome; Lung injury; Zonula occludens-1; Interleukin 38; Oxygenation index; Prognosis

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Acute respiratory distress syndrome (ARDS) is a diffuse lung injury caused by multiple triggering factors such as sepsis, pneumonia, and trauma [1-2]. Data shows that 6.87% of elderly critically ill patients in the ICU in certain regions of China are diagnosed with ARDS [3], and their prognosis are poor [4]. Currently, there are few peripheral blood indicators used for the assessment of ARDS, making it of significant clinical importance to identify peripheral blood biomarkers that are related to the degree of lung injury in ARDS patients to guide diagnosis and treatment. Zonula occludens 1 (ZO-1), a protein involved in the tight junctions between epithelial and endothelial cells, is significantly reduced in an acute lung injury cell model induced by lipopolysaccharide (LPS) [4]. The expression of ZO-1 protein is also decreased in alveolar epithelial cells in rats with lung injury [5], suggesting that it is related to the function of the pulmonary endothelial barrier. Serum interleukin (IL)-38 levels are significantly elevated in patients with respiratory diseases such as lung cancer and acute pulmonary embolism [6-7]. Therefore, this study investigated the differences in peripheral blood ZO-1 and IL-38 levels in ARDS patients with varying degrees of lung injury and prognosis, and explored the correlation between ZO-1, IL-38, and the severity of lung injury in ARDS patients, as well as their predictive value for prognosis.

## 1 Subjects and Methods

### 1.1 Selection of Study Subjects

A total of 105 ARDS patients admitted to the Chuiyangliu Hospital Affiliated with Tsinghua University from April 2020 to April 2023 were selected as the observation group, and 52 non-ARDS patients during the same period were selected as the control group. The control group included 21 patients in stable chronic obstructive pulmonary disease (COPD), 13 with pulmonary nodules, 9 with bronchial asthma, 5 with cardiogenic pulmonary edema, and 4 with obstructive sleep apnea syndrome. In the observation group, there were 61 males and 44 females, with the age of ( $56.79\pm 8.31$ ) years. In the control group, there were 29 males and 23 females, with the age of ( $55.47\pm 8.19$ ) years. There was no significant difference in age and gender between the two groups ( $P>0.05$ ). This study was approved by the hospital's ethics committee (Approval number: 2022-015KY).

### 1.2 Inclusion and Exclusion Criteria

Inclusion criteria: (1) Age  $\geq 18$  years; (2) Meeting

the diagnostic criteria for ARDS [8]; (3) No anti-infection or respiratory support treatments related to ARDS in the past month; (4) The patient and their family members provided informed consent for participation in this study.

Exclusion criteria: (1) Co-existing respiratory diseases such as atelectasis and pulmonary edema; (2) Co-existing heart, liver, kidney dysfunction, malignant tumors, or immunodeficiency; (3) Pregnant or lactating women; (4) Co-existing mental illness.

### 1.3 Observation Indicators

#### 1.3.1 General Information

After the patients are enrolled, the following data will be collected: gender, age, body mass index (BMI), Acute Physiology and Chronic Health Evaluation (APACHE) II score, primary disease of ARDS, length of hospital stay, white blood cell count, neutrophil percentage, underlying diseases, smoking history, and alcohol consumption history.

#### 1.3.2 Peripheral Blood ZO-1 and IL-38 Levels

After the patients are enrolled and before treatment, fasting venous blood will be collected using EDTA anticoagulant tubes. The blood will be centrifuged within 1 hour to obtain plasma, and ZO-1 levels will be measured using an enzyme-linked immunosorbent assay (ELISA) (Shanghai Enzyme-linked Biotechnology, ml058798). Fasting venous blood will also be collected in a regular blood collection tube, allowed to clot, then centrifuged to separate the serum, and IL-38 levels will be measured using ELISA (Shanghai Enzyme-linked Biotechnology, ml038449).

#### 1.3.3 Oxygenation Index

Arterial blood gas analysis will be performed on the patients. The oxygenation index is calculated as the arterial oxygen partial pressure divided by the inspired oxygen concentration. According to the Berlin criteria [8], the degree of lung injury in the observation group will be classified into mild subgroup ( $>200$  to  $300$  mmHg), moderate subgroup ( $>100$  to  $200$  mmHg), and severe subgroup ( $\leq 100$  mmHg) based on the oxygenation index.

#### 1.3.4 Survival Prognosis

The survival status of patients will be recorded on day 28. Patients will be divided into a survival group and a death group.

### 1.4 Statistical Methods

Data was processed using SPSS 24.0 statistical software. Continuous variables was expressed as  $\bar{x} \pm s$ , and comparisons was made using  $t$ -tests or analysis of variance (ANOVA) with LSD- $t$  tests for pairwise comparisons. Categorical data was expressed as  $n(\%)$  and analyzed using the chi-square test. Correlation analysis was performed using Pearson method or Spearman method. The predictive value of the indicators for survival prognosis was analyzed using the area under the receiver

operating characteristic (ROC) curve (AUC).  $P < 0.05$  was considered statistically significant.

## 2 Results

### 2.1 Comparison of Peripheral Blood ZO-1 and IL-38

#### Levels Between the Two Groups

The peripheral blood ZO-1 levels in the observation group were significantly higher than that in the control group [ $(2.42 \pm 0.77)$  ng/mL vs  $(1.04 \pm 0.47)$  ng/mL,  $t = 11.864$ ,  $P < 0.01$ ]. And the peripheral blood IL-38 level was also higher in the observation group than that in the control group [ $(62.96 \pm 16.56)$  pg/mL vs  $(42.12 \pm 11.90)$  pg/mL,  $t = 8.093$ ,  $P < 0.01$ ].

### 2.2 Comparison of ZO-1 and IL-38 Levels in ARDS

#### Patients with Different Lung Injury Severities

In ARDS patients, the levels of peripheral blood ZO-1 and IL-38 increased sequentially with the severity of lung injury (mild, moderate, and severe), with statistically significant differences ( $P < 0.05$ ). See **Table 1**.

**Tab.1** Comparison of ZO-1, and IL-38 in ARDS patients with different degrees of lung injury ( $\bar{x} \pm s$ )

Group	Case	ZO-1 (ng/mL)	IL-38 (pg/mL)
Mild group	35	$1.68 \pm 0.38$	$49.32 \pm 10.05$
Moderate group	44	$2.58 \pm 0.47^a$	$62.60 \pm 11.43^a$
Severe group	26	$3.18 \pm 0.71^{ab}$	$81.80 \pm 11.81^{ab}$
F value		66.655	64.045
P value		$< 0.001$	$< 0.001$

### 2.3 Correlation Analysis of ZO-1 and IL-38 Levels

#### with Oxygenation Index in ARDS Patients

Pearson correlation analysis showed that the levels of peripheral blood ZO-1 ( $r = -0.716$ ,  $P < 0.01$ ) and IL-38 ( $r = -0.740$ ,  $P < 0.01$ ) were negatively correlated with the oxygenation index. Spearman correlation analysis revealed that the levels of peripheral blood ZO-1 ( $r = 0.774$ ,  $P < 0.01$ ) and IL-38 ( $r = 0.729$ ,  $P < 0.01$ ) were positively correlated with the severity of lung injury.

### 2.4 Comparison of Clinical Data in ARDS Patients

#### with Different Prognoses

Among 105 ARDS patients, 40 died and 65 survived within 28 days. The survival group had lower age, fewer comorbidities such as hypertension and diabetes, lower APACHE II score, shorter hospital stays, lower WBC, lower neutrophil percentages, lower ZO-1 and IL-38 levels, and higher oxygenation indices compared to the death group ( $P < 0.05$ ). See **Table 2**.

Tab.2 Comparison of clinical data of ARDS patients with different prognoses

Indicators	Survival Group (n=65)	Death Group (n=40)	F/ $\chi^2$ value	P value
Age $\geq$ 60 years [n(%)]	36(55.3)	31(77.50)	5.244	0.022
Male/Female [n(%)]	36/29	25/15	0.515	0.473
BMI [n(%)]	22.82 $\pm$ 1.31	23.03 $\pm$ 1.28	0.804	0.422
Hypertension [n(%)]	27(41.54)	26(65.00)	5.453	0.020
Diabetes [n(%)]	15(23.08)	17(42.50)	4.409	0.036
Smoking history [n(%)]	25(38.46)	23(57.50)	3.617	0.057
Drinking history [n(%)]	14(21.54)	7(17.50)	0.252	0.615
APACHE II score ( $\bar{x}\pm s$ )	16.04 $\pm$ 2.77	27.35 $\pm$ 5.01	14.898	0.000
ARDS primary disease				
Sepsis	18(27.69)	12(30.00)		
Disease of respiratory system	36(55.38)	20(50.00)	0.310	0.856
Others	11(16.92)	8(20.00)		
Hospital Stay (d, $\bar{x}\pm s$ )	15.22 $\pm$ 4.18	21.56 $\pm$ 4.37	7.418	<0.001
WBC ( $\times 10^9/L$ , $\bar{x}\pm s$ )	13.04 $\pm$ 3.86	15.67 $\pm$ 3.72	3.437	0.001
Percentage of neutrophils (% , $\bar{x}\pm s$ )	70.30 $\pm$ 2.36	71.88 $\pm$ 3.04	2.980	0.004
ZO-1(ng/mL, $\bar{x}\pm s$ )	2.16 $\pm$ 0.70	2.86 $\pm$ 0.68	5.030	<0.001
IL-38(pg/mL, $\bar{x}\pm s$ )	56.78 $\pm$ 14.16	72.90 $\pm$ 15.22	5.505	<0.001
Oxygenation Index (mmHg, $\bar{x}\pm s$ )	202.60 $\pm$ 60.41	110.32 $\pm$ 48.58	8.167	<0.001

2.5 Prognostic Value of Peripheral Blood ZO-1 and IL-38 Levels in ARDS Patients

ROC analysis showed that the AUC for predicting prognosis in ARDS patients using peripheral blood ZO-1 and IL-38 levels were 0.769 and 0.785, respectively. The sensitivity was 85.00% for ZO-1 and 80.00% for IL-38, while the specificity was 63.08% for ZO-1 and 72.31% for IL-38. See Table 3 and Figure 1.

Tab.3 Analysis of the predictive value of ZO-1 and IL-38 levels in peripheral blood of ARDS patients for prognosis

Indicators	Cut-off Value	Sensitivity (%)	Specificity (%)	AUC	95%CI
ZO-1	2.16 ng/mL	85.00	63.08	0.769	0.677-0.846
IL-38	64.41 pg/mL	80.00	72.31	0.785	0.694-0.859

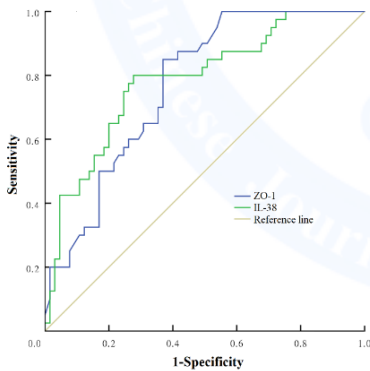


Fig.1 ROC curve of the predictive value of ZO-1 and IL-38 levels in peripheral blood for the prognosis of ARDS patients

3 Discussion

ARDS is a type of acute lung injury induced by various primary diseases that disrupt the lung vascular barrier through acute inflammatory reactions. The oxygenation index is currently the main criterion for assessing the oxygenation status of patients with ARDS [9-10], but more accurate assessment markers are still needed. Previous studies have observed alveolar capillary dilation, alveolar

structure destruction, and inflammatory infiltration in lung tissues of ARDS rat models, indicating damage to the alveolar endothelial barrier [11]. Therefore, damage to the pulmonary vascular barrier and the inflammatory response play important roles in the progression of ARDS.

The alveolar-capillary barrier prevents potential pathogens or irritants from penetrating the airway mucosa, and tight junctions are an essential component of this barrier. Among these, ZO-1 is expressed in the lung by bronchial and alveolar epithelial cells and participates in the formation of tight junctions, helping maintain the integrity of the alveolar-capillary barrier [12-13]. Previous studies have found that in COPD and acute lung injury model mice, airway epithelial barrier damage and reduced expression of ZO-1 in lung tissues were observed [14]. In this study, the peripheral blood ZO-1 levels of ARDS patients were higher than those of non-ARDS patients, and they increased with the severity of lung injury. ZO-1 levels were negatively correlated with the oxygenation index, suggesting that peripheral blood ZO-1 levels may serve as a reference for assessing the severity of lung injury in ARDS patients. However, studies have shown that in septic patients, plasma ZO-1 levels are elevated, negatively correlated with the oxygenation index, and associated with 30-day mortality, indicating a relationship with vascular barrier dysfunction [15]. We speculate that in ARDS patients, after lung injury, the capillary barrier and tight junctions are damaged, causing ZO-1 to be released from the cellular junction structures into the bloodstream. As the severity of lung injury increases, the release of ZO-1 also increases, thus indicating that peripheral blood ZO-1 levels are related to the degree of lung injury.

IL-38 has anti-inflammatory properties and is secreted by epithelial cells, monocytes, macrophages, and other cells. Its expression levels are elevated in various diseases [16]. Zhang *et al.* [17] found that the serum IL-38 levels in patients with acute exacerbations of COPD were significantly higher than those in patients during stable periods, and negatively correlated with lung function, which may have diagnostic value for acute exacerbations of COPD. Lu *et al.* [18] suggested that serum IL-38 levels are higher in COPD patients with respiratory failure, and



are correlated with lung function. Wei *et al.* [19] found that serum IL-38 levels were elevated in patients with pneumonia caused by *Pseudomonas aeruginosa*. Wang *et al.* [20] discovered that serum IL-38 levels in stroke-associated pneumonia patients were lower than those in ischemic stroke patients. The results of this study are inconsistent with theirs, but Gu *et al.* [21] found that serum IL-38 and the oxygenation index in patients with acute exacerbation of COPD combined with pulmonary embolism were both lower than those in patients without pulmonary embolism, indirectly reflecting a possible association between IL-38 levels and the degree of lung injury. The results of this study showed that peripheral blood IL-38 levels are negatively correlated with the oxygenation index in ARDS patients and increase with the severity of lung injury.

Mortality rate of ARDS is relatively high. In this study, 40 out of 105 ARDS patients (38.10%) died within 28 days, which is similar to the reported mortality rates of 36.53% and 39.44% [22]. In this study, there were significant differences between the survival and death groups of ARDS patients in terms of age, underlying disease incidence, APACHE II score, length of hospital stays, white blood cell count, neutrophil percentage, oxygenation index, peripheral blood ZO-1, and IL-38 levels. Qiao *et al.* [23] reported that in septic ARDS patients, mortality was associated with the APACHE II score, oxygenation index, smoking history, and the use of antibiotics. Zhang *et al.* [24] suggested that factors such as oxygenation index, shock, and age are risk factors for mortality in trauma patients with ARDS. The ROC analysis in this study shows that ZO-1 > 2.16 ng/mL and IL-38 > 64.41 pg/mL are predictive of the prognosis of ARDS patients.

In conclusion, elevated peripheral blood ZO-1 and IL-38 levels in ARDS patients are related to the degree of lung injury and have certain prognostic value. However, this study has a small sample size and does not explore the specific mechanisms by which ZO-1 and IL-38 contribute to lung injury. Further large-scale, multi-center in-depth studies are needed.

**Conflict of Interest** None

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· 论 著 ·

# 外周血 ZO-1 和 IL-38 水平与急性呼吸窘迫综合征患者肺损伤程度的相关性

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**摘要:** **目的** 分析急性呼吸窘迫综合征(ARDS)不同程度肺损伤患者外周血闭锁小带蛋白-1(ZO-1)、白细胞介素 38(IL-38)水平变化,及二者与肺损伤程度的相关性。**方法** 选取 2020 年 4 月至 2023 年 4 月清华大学附属垂杨柳医院收治的 ARDS 患者 105 例为观察组,纳入同期非 ARDS 患者 52 例为对照组,根据氧合指数将观察组 ARDS 患者分为轻、中、重度亚组。比较各组患者外周血 ZO-1、IL-38 水平,分析其与肺损伤程度的相关性以及对生存预后的预测价值。**结果** 观察组患者外周血 ZO-1、IL-38 水平均高于对照组( $P<0.05$ )。ARDS 患者外周血 ZO-1、IL-38 水平依轻、中和重度之序递升,差异均有统计学意义( $P<0.05$ ),ARDS 患者外周血 ZO-1、IL-38 水平与氧合指数分别呈负相关( $r=-0.716, -0.740, P<0.01$ ),与肺损伤程度分别呈正相关( $r=0.774, 0.729, P<0.01$ )。105 例 ARDS 患者 28 d 死亡 40 例,生存 65 例。受试者工作特征(ROC)曲线分析结果显示,外周血 ZO-1、IL-38 预测 ARDS 患者预后的曲线下面积(AUC)分别为 0.769 和 0.785,敏感度分别为 85.00%、80.00%,特异度分别为 63.08%、72.31%。**结论** ARDS 患者外周血 ZO-1、IL-38 水平升高与肺损伤程度相关,且具有一定的预后预测价值。

**关键词:** 急性呼吸窘迫综合征; 肺损伤; 闭锁小带蛋白-1; 白细胞介素 38; 氧合指数; 预后

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**Abstract:** **Objective** To analyze the changes of zonula occludens-1 (ZO-1) and interleukin-38 (IL-38) levels in peripheral blood of acute respiratory distress syndrome (ARDS) patients with different degrees of lung injury, and their correlations with the degree of lung injury. **Methods** A total of 105 patients with ARDS admitted to Chuiyangliu Hospital Affiliated with Tsinghua University from April 2020 to April 2023 were selected as the observation group, and 52 non-ARDS patients during the same period were included as the control group. The patients in the observation group were classified into mild, moderate and severe subgroups according to the oxygenation index. The levels of ZO-1 and IL-38 in the peripheral blood of each group were compared. The correlations of ZO-1 and IL-38 levels with the degree of lung injury and their predictive value for the survival prognosis of ARDS were analyzed. **Results** The levels of ZO-1 and IL-38 in the peripheral blood of patients in the observation group were both higher than those in the control group ( $P<0.05$ ). The levels of ZO-1 and IL-38 in peripheral blood of ARDS patients increased in the order of mild, moderate and severe, with statistically significant differences ( $P<0.05$ ). The levels of ZO-1 and IL-38 in the peripheral blood of ARDS patients were negatively correlated with the oxygenation index ( $r=-0.716, -0.740, P<0.01$ ), and were positively correlated with the degree of lung injury ( $r=0.774, 0.729, P<0.01$ ). Among 105 ARDS patients, 40 died and 65 survived within 28 days. The receiver operating characteristic (ROC) analysis results showed that the AUC of ZO-1 and IL-38 in peripheral blood for

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predicting the prognosis of ARDS patients were 0.769 and 0.785, respectively, with sensitivities of 85.00% and 80.00%, and specificities of 63.08% and 72.31%, respectively. **Conclusion** The elevated levels of ZO-1 and IL-38 in peripheral blood of ARDS patients are correlated with the degree of lung injury and have certain prognostic value.

**Keywords:** Acute respiratory distress syndrome; Lung injury; Zonula occludens-1; Interleukin 38; Oxygenation index; Prognosis

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急性呼吸窘迫综合征 (acute respiratory distress syndrome, ARDS) 是由脓毒症、肺炎、创伤等多种诱发因素导致的弥漫性肺损伤<sup>[1-2]</sup>。数据显示,我国部分地区 ICU 老年危重症患者中 6.87% 被诊断为 ARDS<sup>[3]</sup>; 且预后较差<sup>[4]</sup>。目前,用于 ARDS 病情评估的外周血指标较少,因此,寻找与 ARDS 肺损伤程度相关的外周血指标指导诊疗有重要临床意义。闭锁小带蛋白-1 (zonula occludens 1, ZO-1) 是参与上皮和内皮细胞间紧密连接组成的蛋白之一,在脂多糖诱导的急性肺损伤细胞模型中,ZO-1 水平显著降低;肺泡上皮细胞损伤大鼠 ZO-1 蛋白表达水平降低<sup>[5]</sup>,提示其与肺内皮屏障功能相关。血清白细胞介素 38 (interleukin 38, IL-38) 水平在肺癌、急性肺栓塞等呼吸系统疾病患者中升高<sup>[6-7]</sup>。因此,本文研究了不同肺损伤程度及不同预后 ARDS 患者外周血 ZO-1、IL-38 水平的差异,探讨 ZO-1、IL-38 与 ARDS 患者肺损伤程度的相关性以及对预后的预测作用。

## 1 对象与方法

**1.1 研究对象** 选取 2020 年 4 月至 2023 年 4 月清华大学附属垂杨柳医院收治的 ARDS 患者 105 例为观察组,纳入同期非 ARDS 患者 52 例为对照组。其中慢性阻塞性肺疾病 (COPD) 稳定期 21 例,肺部结节 13 例,支气管哮喘 9 例,心源性肺水肿 5 例,阻塞性睡眠呼吸暂停综合征 4 例。观察组男 61 例,女 44 例;年龄 ( $56.79 \pm 8.31$ ) 岁;对照组男 29 例,女 23 例;年龄 ( $55.47 \pm 8.19$ ) 岁。两组年龄、性别差异无统计学意义 ( $P > 0.05$ )。本研究经医院伦理委员会批准 (批准号: 2022-015KY)。

**1.2 纳入与排除标准** 纳入标准: (1) 年龄  $\geq 18$  岁; (2) 符合 ARDS 诊断标准<sup>[8]</sup>; (3) 近 1 个月未接受抗感染、呼吸支持等 ARDS 相关治疗; (4) 患者及家属对本研究知情同意。排除标准: (1) 合并肺不张、肺水肿等呼吸系统疾病; (2) 合并心、肝、肾功能不全、恶性肿瘤或免疫功能缺陷患者; (3) 妊娠或哺乳期妇女; (4) 合并精神疾病。

**1.3 观察指标** (1) 一般资料: 患者入组后,收集性别、年龄、身体质量指数 (BMI)、APACHE II 评分、ARDS 原发病、住院时长、白细胞计数、中性粒细胞百分比、基础疾病、吸烟史、饮酒史等。(2) 外周血 ZO-1、IL-38 水平: 患者入组后,在给予治疗前,采用 EDTA 抗凝管采集空腹静脉血,1 h 内离心,获得血浆,采用酶联免疫法检测血浆 ZO-1 水平 (上海酶联生物科技, ml058798); 采用普通采血管采集空腹静脉血,凝结后离心,分离血清,酶联免疫法检测血清 IL-38 水平 (上海酶联生物科技, ml038449)。(3) 氧合指数: 对患者进行动脉血气分析,氧合指数 = 动脉血氧分压 / 吸入氧浓度,根据柏林标准<sup>[8]</sup>对观察组患者按氧合指数将肺损伤程度分为轻 ( $> 200 \sim 300$  mmHg)、中 ( $> 100 \sim 200$  mmHg)、重度组 ( $\leq 100$  mmHg)。(4) 生存预后情况: 记录患者 28 d 生存情况,将患者分为生存组和死亡组。

**1.4 统计学方法** 使用 SPSS 24.0 统计软件处理数据。计量资料用  $\bar{x} \pm s$  表示,采用  $t$  检验或方差分析及两两比较的 LSD- $t$  检验; 计数资料以例 (%) 表示,采用  $\chi^2$  检验; 相关分析用 Pearson 法或 Spearman 法。采用受试者工作特征 (receiver operating characteristic, ROC) 曲线下面积 (area und the curve, AUC) 分析各指标对生存预后的预测价值。  $P < 0.05$  为差异有统计学意义。

## 2 结果

**2.1 观察组与对照组外周血 ZO-1、IL-38 水平比较** 观察组与对照组外周血 ZO-1 水平分别为 ( $2.42 \pm 0.77$ ) ng/mL、( $1.04 \pm 0.47$ ) ng/mL, 差异有统计学意义 ( $t = 11.864, P < 0.01$ ); IL-38 水平分别为 ( $62.96 \pm 16.56$ ) pg/mL、( $42.12 \pm 11.90$ ) pg/mL, 差异有统计学意义 ( $t = 8.093, P < 0.01$ )。

**2.2 不同肺损伤程度 ARDS 患者外周血 ZO-1、IL-38 水平比较** ARDS 患者外周血 ZO-1、IL-38 水平依轻、中和重度之序递升, 差异均有统计学意义 ( $P < 0.05$ ), 见表 1。

**2.3 ARDS 患者外周血 ZO-1、IL-38 水平与氧合指数**



的相关性分析 Pearson 相关分析结果显示,ARDS 患者外周血 ZO-1 水平( $r=-0.716, P<0.01$ )、IL-38 水平( $r=-0.740, P<0.01$ )与氧合指数呈负相关;Spearman 相关性分析显示,ARDS 患者外周血 ZO-1 水平( $r=0.774, P<0.01$ )、IL-38 水平( $r=0.729, P<0.01$ )与肺损伤程度呈正相关。

2.4 不同预后 ARDS 患者临床资料比较 105 例 ARDS 患者 28 d 死亡 40 例,生存 65 例。生存组年龄、合并高血压病和糖尿病、APACHE II 评分、住院时长、白细胞计数、中性粒细胞百分比、ZO-1、IL-38 水平均低于死亡组,氧合指数高于死亡组( $P<0.05$ )。见表 2。

2.5 ARDS 患者外周血 ZO-1、IL-38 水平对预后的预测价值 ROC 分析结果显示,外周血 ZO-1、IL-38 对 ARDS 患者预后预测的 AUC 分别为 0.769 和 0.785,敏感度分别为 85.00%、80.00%,特异度分别为 63.08%、72.31%。见表 3、图 1。

表 1 不同肺损伤程度 ARDS 患者外周血 ZO-1、IL-38 水平比较 ( $\bar{x}\pm s$ )

Tab.1 Comparison of peripheral blood ZO-1, and IL-38 levels among ARDS patients with different degrees of lung injury ( $\bar{x}\pm s$ )

组别	例数	ZO-1 (ng/mL)	IL-38 (pg/mL)
轻度亚组	35	1.68±0.38	49.32±10.05
中度亚组	44	2.58±0.47 <sup>a</sup>	62.60±11.43 <sup>a</sup>
重度亚组	26	3.18±0.71 <sup>ab</sup>	81.80±11.81 <sup>ab</sup>
F 值		66.655	64.045
P 值		<0.001	<0.001

注:与轻度组比较,<sup>a</sup> $P<0.05$ ;与中度组比较,<sup>b</sup> $P<0.05$ 。

表 2 不同预后 ARDS 患者临床资料比较  
Tab.2 Comparison of clinical data between ARDS patients with different prognoses

项目	生存组 (n=65)	死亡组 (n=40)	$\chi^2/t$ 值	P 值
年龄≥60 岁[例(%)]	36(55.38)	31(77.50)	5.244	0.022
男/女(例)	36/29	25/15	0.515	0.473
BMI( $\bar{x}\pm s$ )	22.82±1.31	23.03±1.28	0.804	0.422
高血压病[例(%)]	27(41.54)	26(65.00)	5.453	0.020
糖尿病[例(%)]	15(23.08)	17(42.50)	4.409	0.036
吸烟史[例(%)]	25(38.46)	23(57.50)	3.617	0.057
饮酒史[例(%)]	14(21.54)	7(17.50)	0.252	0.615
APACHE II 评分(分, $\bar{x}\pm s$ )	16.04±2.77	27.35±5.01	14.898	<0.001
ARDS 原发病[例(%)]				
脓毒症	18(27.69)	12(30.00)		
呼吸系统疾病	36(55.38)	20(50.00)	0.310	0.856
其他	11(16.92)	8(20.00)		
住院时长(d, $\bar{x}\pm s$ )	15.22±4.18	21.56±4.37	7.418	<0.001
白细胞计数( $\times 10^9/L$ , $\bar{x}\pm s$ )	13.04±3.86	15.67±3.72	3.437	0.001
中性粒细胞百分比(% , $\bar{x}\pm s$ )	70.30±2.36	71.88±3.04	2.980	0.004
ZO-1 (ng/mL, $\bar{x}\pm s$ )	2.16±0.70	2.86±0.68	5.030	<0.001
IL-38 (pg/mL, $\bar{x}\pm s$ )	56.78±14.16	72.90±15.22	5.505	<0.001
氧合指数(mmHg, $\bar{x}\pm s$ )	202.60±60.41	110.32±48.58	8.167	<0.001

表 3 外周血 ZO-1、IL-38 水平对 ARDS 患者预后的预测价值  
Tab.3 The predictive value of ZO-1 and IL-38 levels in peripheral blood for the prognosis of ARDS patients

指标	最佳截断值	敏感度 (%)	特异度 (%)	AUC	95%CI	
					下限	上限
ZO-1	2.16 ng/mL	85.00	63.08	0.769	0.677	0.846
IL-38	64.41 pg/mL	80.00	72.31	0.785	0.694	0.859

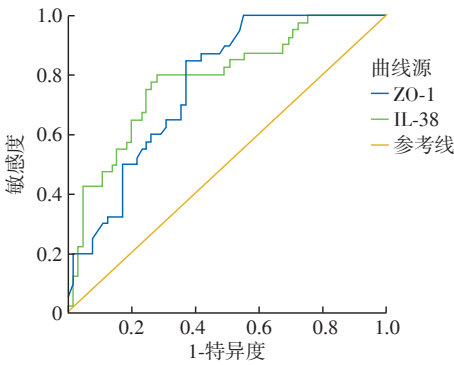


图 1 外周血 ZO-1、IL-38 水平对 ARDS 患者预后预测的 ROC 曲线

Fig.1 ROC curve of the predictive value of ZO-1 and IL-38 levels in peripheral blood for the prognosis of ARDS patients

3 讨论

ARDS 是由各种原发病诱导的急性炎症反应破坏肺血管屏障导致的肺损伤,目前主要依据氧合指数评价患者氧合状态<sup>[9-10]</sup>,但仍需更准确的评估指标。既往研究发现,在 ARDS 大鼠模型肺组织中观察到肺泡毛细血管扩张、肺泡结构破坏、炎性浸润,表明肺泡血管内皮屏障损伤<sup>[11]</sup>。因此,肺血管屏障损伤及炎症反应在 ARDS 病情进展中发挥重要作用。

肺泡毛细血管屏障可防止潜在病原体或刺激物穿透气道黏膜,紧密连接是该屏障的重要组成部分,其中 ZO-1 在肺部由支气管、肺泡上皮细胞表达,参与紧密连接的形成,具有维持肺泡毛细血管屏障完整性的作用<sup>[12-13]</sup>。既往研究发现,在 COPD 和急性肺损伤模型小鼠中,气道上皮屏障损伤,肺组织 ZO-1 表达水平降低<sup>[14]</sup>。本研究中,ARDS 患者外周血 ZO-1 水平高于非 ARDS 患者,且随肺损伤严重程度增加而升高,与氧合指数呈负相关,表明外周血 ZO-1 水平可能对 ARDS 患者肺损伤程度评估具有参考价值。但有研究显示,脓毒症患者血浆 ZO-1 水平升高,与氧合指数呈负相关,且与患者 30 d 病死率相关,认为其与机体血管屏障功能损伤相关<sup>[15]</sup>。笔者推测,ARDS 患者在肺损伤后,毛细血管屏障、紧密连接受到破坏,导致 ZO-1 从细胞连接结构中释放入血,随着肺损伤程度加重,ZO-1 的释放量也随之升高,故认为外周血 ZO-1

水平与肺损伤程度相关。

IL-38具有抗炎功能,由上皮细胞、单核细胞、巨噬细胞等分泌,其表达水平在多种疾病中均升高<sup>[16]</sup>。张巍等<sup>[17]</sup>发现,急性加重期COPD患者血清IL-38水平显著高于稳定期COPD患者,且与肺功能水平呈负相关,对急性加重期COPD具有一定诊断价值。鲁瑞涛等<sup>[18]</sup>认为COPD合并呼吸衰竭患者血清IL-38水平更高,且与患者肺功能相关。Wei等<sup>[19]</sup>发现铜绿假单胞菌感染的肺炎患者血清IL-38水平升高。王莹莹等<sup>[20]</sup>发现,卒中相关性肺炎患者的血清IL-38水平低于缺血性卒中患者,本研究结果与其不一致,但辜海涛等<sup>[21]</sup>发现急性加重期COPD合并肺栓塞患者血清IL-38和氧合指数均低于未合并肺栓塞患者,侧面反映出IL-38水平与肺损伤程度可能存在一定关联。本研究结果显示,外周血IL-38水平与ARDS患者氧合指数呈负相关,且随着肺损伤加重而升高。

ARDS致死率较高,本研究105例ARDS患者28 d死亡40例,占38.10%,与文献报道的36.53%、39.44%相近<sup>[22]</sup>。本研究生存组和死亡组ARDS患者中,年龄、基础疾病发生率、APACHE II评分、住院时长、白细胞计数、中性粒细胞百分比、氧合指数、外周血ZO-1、IL-38水平等差异有统计学意义。乔智灏等<sup>[23]</sup>报道脓毒症ARDS患者死亡与APACHE II评分、氧合指数、吸烟史、抗菌药物使用情况相关。张铭等<sup>[24]</sup>认为氧合指数、休克、年龄等因素均为创伤合并ARDS患者死亡的危险因素。本研究ROC分析结果显示,ZO-1 > 2.16 ng/mL、IL-38 > 64.41 pg/mL对ARDS患者预后具有预测价值。

综上所述,ARDS患者外周血ZO-1、IL-38水平升高与肺损伤程度相关,且具有一定预后预测价值。但本研究样本量较小,且未能就ZO-1、IL-38与肺损伤的具体作用机制进行探讨,需要进一步开展大样本、多中心的深入研究。

利益冲突 无

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