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Analysis of the Effect of Severe Respiratory Failure on the HMGB1-Th17/IL-17 Inflammatory Axis in Peripheral Blood of Elderly COPD Patients

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Abstract

Abstract Objective To investigate the effect of severe respiratory failure on the HMGB1-Th17/IL-17 inflammatory axis in peripheral blood of elderly patients with chronic obstructive pulmonary disease (COPD). Methods From April 2020 to April 2023, 120 elderly COPD patients complicated with severe respiratory failure admitted to our hospital were selected as the observation group, and another 120 elderly COPD patients admitted during the same period were selected as the control group. The levels of HMGB1-Th17/IL-17 inflammatory axis-related factors HMGB1 and IL-17 were compared between the two groups, and their impact on the risk of developing severe respiratory failure in elderly COPD patients was analyzed; baseline data, HMGB1, and IL-17 levels were compared among patients with different prognoses in the observation group, the correlation between HMGB1, IL-17 and APACHE II score was analyzed, and the predictive value of HMGB1 and IL-17 for prognosis was evaluated. Results The HMGB1-Th17/IL-17 inflammatory axis-related factors HMGB1 and IL-17 in the observation group were both higher than those in the control group ($P < 0.05$); when serum HMGB1 and IL-17 levels were high in elderly COPD patients, the risk of developing severe respiratory failure was 3.286 times and 2.870 times higher than that at low levels, respectively; the APACHE II score and serum HMGB1 and IL-17 levels in deceased patients were all higher than those in surviving patients ($P < 0.05$); serum HMGB1 and IL-17 in elderly COPD patients complicated with severe respiratory failure showed an extremely significant correlation with APACHE II score ($P < 0.05$); the area under the curve (AUC) values of serum HMGB1 and IL-17 for predicting prognosis were 0.778 and 0.797, respectively, both above 0.7, indicating certain predictive efficacy; the AUC value for combined prediction of serum HMGB1 and IL-17 was 0.932,

which was significantly higher than that of each indicator alone ($P < 0.05$). Conclusion After the occurrence of severe respiratory failure in elderly COPD patients, the levels of key factors HMGB1 and IL-17 in the HMGB1-Th17/IL-17 inflammatory axis are significantly increased, and both can affect patient prognosis by regulating pulmonary inflammatory responses.

Full Text

Effect of Severe Respiratory Failure on the HMGB1-Th17/IL-17 Inflammatory Axis in Peripheral Blood of Elderly COPD Patients

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Abstract

Objective: To investigate the effects of severe respiratory failure on the HMGB1-Th17/IL-17 inflammatory axis in peripheral blood of elderly patients with chronic obstructive pulmonary disease (COPD). **Methods:** A total of 120 elderly COPD patients with severe respiratory failure admitted to our hospital from April 2020 to April 2023 were selected as the observation group, while another 120 elderly COPD patients admitted during the same period served as the control group. Levels of HMGB1-Th17/IL-17 inflammatory axis-related factors (HMGB1 and IL-17) were compared between the two groups, and their impact on the risk of severe respiratory failure in elderly COPD patients was analyzed. Baseline data and HMGB1 and IL-17 levels were compared between patients with different prognoses in the observation group.

The correlation between HMGB1, IL-17 and APACHE II scores was analyzed, and the predictive value of HMGB1 and IL-17 for prognosis was evaluated. **Results:** HMGB1 and IL-17 levels in the observation group were significantly higher than those in the control group ($P < 0.05$). Elderly COPD patients with high serum levels of HMGB1 and IL-17 had 3.286-fold and 2.870-fold higher risks of developing severe respiratory failure, respectively, compared to those with low levels. Deceased patients had significantly higher APACHE II scores and serum HMGB1 and IL-17 levels than surviving patients ($P < 0.05$). Serum HMGB1 and IL-17 levels were strongly correlated with APACHE II scores in elderly COPD patients with severe respiratory failure ($P < 0.05$). The area under the curve (AUC) values for serum HMGB1 and IL-17 in predicting prognosis were 0.778 and 0.797, respectively, both above 0.7, indicating certain predictive efficacy. The combined prediction using serum HMGB1 and IL-17 yielded an AUC value of 0.932, which was significantly higher than that of either indicator alone ($P < 0.05$). **Conclusion:** Following severe respiratory failure in elderly COPD patients, the levels of key factors HMGB1 and IL-17 in the HMGB1-Th17/IL-17 inflammatory axis increase significantly, and both can affect patient prognosis by regulating pulmonary inflammatory responses.

Keywords: Chronic obstructive pulmonary disease; Severe respiratory failure; HMGB1-Th17/IL-17 inflammatory axis; HMGB1; IL-17

Introduction

Chronic obstructive pulmonary disease (COPD) is a non-specific chronic inflammatory disease that, as it progresses, can easily evolve into ventilatory dysfunction and trigger severe respiratory failure [1-3]. According to epidemiological surveys, approximately 20% of patients with severe respiratory failure die from the condition [4], and current clinical practice still lacks effective treatment modalities. Therefore, early prediction of disease onset and outcomes is particularly critical. Research has indicated that cytokine-mediated inflammatory responses play a crucial role in the pathological evolution of severe respiratory failure in COPD patients [5-6].

High-mobility group box 1 (HMGB1) is a non-histone protein that can regulate gene transcription and translation, initiating and sustaining inflammatory cascade reactions, stimulating chemokine production, and inducing cell differentiation [7]. T helper 17 (Th17) cells, a novel subset of helper T cells, participate in immune-inflammatory responses by secreting interleukin-17 (IL-17), primarily exerting pro-inflammatory effects [8]. Currently, research on the role of the HMGB1-Th17/IL-17 inflammatory axis in elderly COPD patients with severe respiratory failure remains limited. Based on this knowledge gap, our study sought to observe changes in the HMGB1-Th17/IL-17 inflammatory axis in peripheral blood of elderly COPD patients and explore its mechanistic role in severe respiratory failure, thereby providing a reference basis for clinical diag-

nosis and treatment.

Methods

1.1 Clinical Data

We selected 120 elderly COPD patients with severe respiratory failure admitted to our hospital from April 2020 to April 2023 as the observation group, including 68 males and 52 females, aged 61-78 years (mean 67.71 $\pm$ 5.94 years), with body mass index (BMI) of 20-28 kg/m^2 (mean 23.84 $\pm$ 2.50 kg/m^2), and COPD duration of 5-13 years (mean 9.56 $\pm$ 2.37 years). Additionally, 120 elderly COPD patients admitted during the same period were selected as the control group, including 72 males and 48 females, aged 61-77 years (mean 68.45 $\pm$ 6.12 years), with BMI of 20-27 kg/m^2 (mean 23.75 $\pm$ 2.29 kg/m^2), and COPD duration of 5-14 years (mean 9.41 $\pm$ 2.34 years). The baseline data were comparable between the two groups ($P > 0.05$).

Inclusion Criteria: (1) Met diagnostic criteria for COPD and severe respiratory failure [9]; (2) Age $>$ 60 years; (3) Complete medical records; (4) Informed consent obtained from patients or their families.

Exclusion Criteria: (1) Combined dysfunction of vital organs; (2) Comorbid other pulmonary diseases such as infection, tumor, or tuberculosis; (3) History of respiratory system surgery or trauma; (4) Received antibiotic treatment before admission; (5) Comorbid chronic infectious diseases; (6) Comorbid immune system diseases.

1.2 Methods

Clinical Data Collection: We collected patient information including gender, age, COPD duration, BMI, medical history, white blood cell count (WBC), mean arterial pressure, arterial partial pressure of oxygen (PaO_2), mean oxygenation index, arterial partial pressure of carbon dioxide ($PaCO_2$), and Acute Physiology and Chronic Health Evaluation (APACHE II) scores.

Serum HMGB1 and IL-17 Level Detection: Within 24 hours of admission, 5 ml of peripheral venous blood was collected and serum was separated. Serum HMGB1 and IL-17 levels were measured using ELISA kits provided by Wuhan Chundu Biological Co., Ltd., with all operations strictly following the kit instructions. Referring to the "Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease (2013 Revised Edition)" [9], COPD patients received symptomatic treatment including oxygen therapy, expectoration, and anti-infection therapy. The 28-day mortality rate was observed.

1.3 Observation Indicators

We compared HMGB1-Th17/IL-17 inflammatory axis-related factors (HMGB1 and IL-17) between the two groups and analyzed their impact on the risk of severe respiratory failure in elderly COPD patients. Clinical data and HMGB1 and IL-17 levels were compared between patients with different prognoses in the observation group. The correlation between HMGB1, IL-17 and APACHE II scores was analyzed, and the predictive value of HMGB1 and IL-17 for prognosis was evaluated.

1.4 Statistical Methods

Data were analyzed using SPSS 21.0. Measurement data were expressed as ($\bar{x} \pm s$) and compared using t-tests. Count data were expressed as n(%) and compared using ^{2} tests. Relative risk (RR) was used to analyze the impact of serum HMGB1 and IL-17 on the risk of severe respiratory failure in elderly COPD patients. Pearson correlation analysis was used to assess the correlation between HMGB1, IL-17 and APACHE II scores. Multiple linear regression was performed with APACHE II score as the dependent variable to establish an optimal linear regression model evaluating the correlation between HMGB1, IL-17 and APACHE II scores. Receiver operating characteristic (ROC) curves were plotted to evaluate the prognostic predictive value of HMGB1 and IL-17. $P < 0.05$ was considered statistically significant.

Results

2.1 Comparison of HMGB1-Th17/IL-17 Inflammatory Axis-Related Factor Levels Between Groups

HMGB1 and IL-17 levels in the observation group were significantly higher than those in the control group ($P < 0.05$). See Table 1.

Table 1 Comparison of HMGB1-Th17/IL-17 Inflammatory Axis-Related Factor Levels Between Groups ($\bar{x} \pm s$)

Group	n	HMGB1 (g/L)	IL-17 (ng/L)
Observation group	120	5.03 ± 1.04	65.24 ± 14.83
Control group	120	3.54 ± 0.75	44.26 ± 10.25
t value		12.83	12.45
P value		< 0.001	< 0.001

2.2 Impact of HMGB1-Th17/IL-17 Inflammatory Axis-Related Factors on Risk of Severe Respiratory Failure

Serum HMGB1 and IL-17 levels were stratified using the median split method into high and low levels. Elderly COPD patients with high serum HMGB1 and IL-17 levels had 3.286-fold and 2.870-fold higher risks of developing severe respiratory failure, respectively, compared to those with low levels. See Table 2.

Table 2 Impact of HMGB1-Th17/IL-17 Inflammatory Axis-Related Factors on Risk of Severe Respiratory Failure in Elderly COPD Patients

Level	Observation Group (n=120)	Control Group (n=120)	RR (95% CI)	U value	P value
HMGB1 (g/L)			3.286 (2.341-4.612)	5.616	< 0.001
High level	92 (76.67)	31 (25.83)			
Low level	28 (23.33)	89 (74.17)			
IL-17 (ng/L)			2.870 (2.083-3.858)	5.060	< 0.001
High level	89 (74.17)	31 (25.83)			
Low level	31 (25.83)	89 (74.17)			

2.3 Comparison of Clinical Data and Inflammatory Axis-Related Factors in Patients with Different Prognoses

During the 28-day hospitalization period, 28 patients in the observation group died, yielding a mortality rate of 23.33%. No statistically significant differences were observed between deceased and surviving patients in terms of gender, age, BMI, COPD duration, medical history, WBC, mean arterial pressure, mean oxygenation index, PaO_2, or $PaCO_2$ ($P > 0.05$). However, deceased patients had significantly higher APACHE II scores and serum HMGB1 and IL-17 levels than surviving patients ($P < 0.05$). See Table 3.

Table 3 Comparison of Clinical Data and HMGB1-Th17/IL-17 Inflammatory Axis-Related Factors in Patients with Different Prognoses

Parameter	Deceased (n=28)	Survived (n=92)	t/ ^{2} value	P value
Gender (Male/Female)	16/12	52/40	0.041	0.839

Parameter	Deceased (n=28)	Survived (n=92)	t/ ^{2} value	P value
Age (years)	68.24 ± 6.12	67.55 ± 5.98	0.556	0.579
BMI (kg/m^2)	23.79 ± 2.14	23.85 ± 2.59	0.114	0.909
COPD duration (years)	9.85 ± 2.24	9.47 ± 2.31	0.795	0.428
Previous history				
Diabetes	5 (17.86)	15 (16.30)	0.053	0.818
Hypertension	7 (25.00)	21 (22.83)	0.074	0.786
Hyperlipidemia	3 (10.71)	8 (8.70)	0.128	0.720
Smoking history	9 (32.14)	28 (30.43)	0.038	0.846
Drinking history	10 (35.71)	31 (33.70)	0.045	0.832
WBC ($×10^{9}$/L)	12.37 ± 1.45	11.86 ± 1.30	1.847	0.067
Mean arterial pressure (mmHg)	80.64 ± 8.25	79.54 ± 8.41	0.632	0.529
Average oxygenation index	148.69 ± 15.49	147.95 ± 14.37	0.251	0.802
PaO_2 (mmHg)	51.24 ± 12.83	48.94 ± 10.59	0.976	0.331
$PaCO_2$ (mmHg)	59.41 ± 6.82	62.37 ± 7.14	1.932	0.056
APACHE II score (points)	31.42 ± 5.06	24.79 ± 4.83	6.430	< 0.001
HMGB1 (g/L)	6.25 ± 1.12	4.50 ± 0.94	8.256	< 0.001
IL-17 (ng/L)	80.59 ± 15.28	58.52 ± 12.31	7.894	< 0.001

2.4 Correlation Analysis

2.4.1 Pearson Correlation Analysis Correlation analysis revealed that HMGB1 and IL-17 levels were positively correlated with APACHE II scores in elderly COPD patients with severe respiratory failure ($r = 0.771$ and 0.807, respectively, $P < 0.05$). Visual inspection of scatter plots suggested a possible linear relationship between HMGB1, IL-17 levels and APACHE II scores, warranting subsequent linear correlation analysis. See Figure 1.

Figure 1 Scatter Plot with Linear Fitting of HMGB1-Th17/IL-17 Inflammatory Axis-Related Factors vs. APACHE II Score
[Figure 1: see original paper]

2.4.2 Linear Regression Analysis A multiple linear regression equation was established with APACHE II score as the dependent variable and serum HMGB1 and IL-17 levels as independent variables. The results demonstrated that serum HMGB1 and IL-17 levels were strongly correlated with APACHE II scores in elderly COPD patients with severe respiratory failure ($P < 0.05$). See Table 4.

Table 4 Results of Multiple Linear Regression Analysis

Model	Unstandardized Coefficient	Standard Error	Standardized Coefficient	t value	P value
Constant	12.354	2.145		5.759	< 0.001
HMGB1	2.867	0.456	0.412	6.287	< 0.001
IL-17	0.089	0.012	0.521	7.417	< 0.001

2.5 Predictive Value of HMGB1-Th17/IL-17 Inflammatory Axis-Related Factors for Prognosis

Serum HMGB1 and IL-17 levels were used as source data for ROC curve analysis, with deceased patients designated as positive and surviving patients as negative. The ROC curves for predicting prognosis in elderly COPD patients with severe respiratory failure showed that the AUC values for serum HMGB1 and IL-17 were 0.778 and 0.797, respectively, both above 0.7, indicating certain predictive efficacy. The combined prediction using serum HMGB1 and IL-17 yielded an AUC value of 0.932, which was significantly higher than that of either indicator alone ($P < 0.05$). See Figure 2 and Table 5.

Figure 2 ROC Curve of HMGB1-Th17/IL-17 Inflammatory Axis-Related Factors for Predicting Prognosis
[Figure 2: see original paper]

Table 5 Prognostic Predictive Value of HMGB1-Th17/IL-17 Inflammatory Axis-Related Factors

Index	AUC (95% CI)	Cut-off Value	Sensitivity	Specificity	P value	Z/P (vs. Combined)
HMGB1 (g/L)	0.778 (0.693-0.848)	5.060	71.43%	77.17%	< 0.001	2.291/0.022
IL-17 (ng/L)	0.797 (0.713-0.865)	5.616	64.29%	88.04%	< 0.001	2.313/0.021
Combined pre-diction	0.932 (0.871-0.970)		89.29%	90.22%	< 0.001	

Discussion

Respiratory failure is a common complication of COPD, characterized primarily by airway and lung parenchymal inflammation that causes continuous damage to airway and alveolar tissues, exacerbates lung function impairment, and triggers a series of physiological and metabolic disorders [10]. With the aging trend in China, the incidence of severe respiratory failure in elderly COPD patients has increased significantly, with rapid disease progression, greater treatment difficulty, and markedly elevated mortality rates [11].

In recent years, serum biochemical markers have played important roles in the early diagnosis and treatment of severe respiratory failure. Scholars both domestically and internationally have consistently agreed that the occurrence of severe respiratory failure in elderly COPD patients is closely related to exacerbated inflammatory responses [12-13]. HMGB1, as a late inflammatory mediator, can be secreted by activated immune cells and necrotic cells, participating in inflammatory responses and tissue damage [14-15]. Studies have shown that HMGB1 can induce Th17 cells to secrete large amounts of IL-17 through inflammatory cytokines and immune cell intermediaries [16]. IL-17 can induce T cell activation and stimulate epithelial cells, macrophages, and fibroblasts to secrete a series of pro-inflammatory mediators, thereby inducing inflammatory responses [17-18]. Research has indicated that the HMGB1-Th17/IL-17 inflammatory axis plays an important role in the development and progression of inflammatory diseases [19].

Therefore, this study focused on the HMGB1-Th17/IL-17 inflammatory axis and found that HMGB1 and IL-17 levels in the observation group were significantly higher than those in the control group. Moreover, elderly COPD patients with high serum HMGB1 and IL-17 levels had 3.286-fold and 2.870-fold higher risks of developing severe respiratory failure, respectively, compared to those with low levels. These findings fully demonstrate that the HMGB1-Th17/IL-17 inflammatory axis participates in the development of severe respiratory failure in elderly COPD patients, consistent with previous research showing the involvement of this inflammatory axis in inflammatory diseases. Evidently, as the disease progresses, massive proliferation and activation of immune cells lead to overexpression of serum HMGB1 and IL-17, which in turn aggravates the inflammatory response. Under inflammatory or infectious conditions, large amounts of HMGB1 are released, which can bind to Toll-like receptor 4, regulate Th17 cell secretion of IL-17, and form a positive feedback loop with IL-17. This causes massive aggregation of inflammatory mediators in the alveoli, amplifies the inflammatory response, induces airway smooth muscle hyperplasia and fibrosis, impairs respiratory function, and ultimately leads to respiratory failure [20-21].

Following the occurrence of severe respiratory failure in elderly COPD patients, pulmonary respiratory dysfunction induces acidosis or microcirculatory disturbances, resulting in poor prognosis [22]. In this study, 28 of the 120 elderly patients died within 28 days of hospitalization, with a mortality rate of 23.33%,

which is lower than that reported by Cao Tingting et al. [23]. This discrepancy may be attributed to the later case selection period in our study, with more experienced clinicians and improved medical technology. In our study, deceased patients had significantly higher serum HMGB1 and IL-17 levels than surviving patients ($P < 0.05$), suggesting that elevated serum HMGB1 and IL-17 levels may be associated with prognosis in elderly COPD patients with respiratory failure. The APACHE II score is an important indicator for assessing risk and prognosis in critically ill patients. In this study, serum HMGB1 and IL-17 levels were strongly correlated with APACHE II scores, indicating that these levels can reflect disease severity and serve as potential factors for predicting prognosis risk in this disease.

The AUC values for serum HMGB1 and IL-17 in predicting 28-day mortality were both above 0.7, with sensitivities of 71.43% and 64.29%, and specificities of 77.17% and 88.04%, respectively. Although the sensitivities were relatively low, the relatively high specificities provide good reference value for excluding mortality risk in elderly COPD patients with severe respiratory failure. Furthermore, considering that HMGB1 and IL-17 have different pro-inflammatory mechanisms in the pathogenesis of severe respiratory failure in elderly COPD patients, we combined them for prognostic prediction. The results showed that the combined prediction yielded an AUC value of 0.932, with sensitivity of 89.29% and specificity of 90.22%, which was significantly higher than that of either indicator alone. This finding provides important reference value for clinicians to predict 28-day mortality risk in patients.

In summary, following severe respiratory failure in elderly COPD patients, the levels of key factors HMGB1 and IL-17 in the HMGB1-Th17/IL-17 inflammatory axis increase significantly, and both can affect patient prognosis by regulating pulmonary inflammatory responses. Clinically, they may serve as potential therapeutic targets for treating elderly COPD patients with severe respiratory failure. However, this study included a relatively small number of cases, representing a small-sample study. Additionally, due to insufficient research funding and other factors, we did not conduct more in-depth studies on the HMGB1-Th17/IL-17 inflammatory axis. Future research should expand the sample size and include animal experiments on the HMGB1-Th17/IL-17 inflammatory axis for further investigation.

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