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ABOUT COVER

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Case Control Study

Correlation between circulating endothelial cell level and acute respiratory distress syndrome in postoperative patients

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Abstract

BACKGROUND

Acute respiratory distress syndrome (ARDS) is injury of alveolar epithelial cells and capillary endothelial cells caused by various factors, including endogenous and exogenous lung factors, leading to diffuse pulmonary interstitial and alveolar edema, and acute respiratory failure. ARDS involves alveolar epithelial cells and pulmonary interstitial capillary endothelial cells. Circulating endothelial cells (CECs) are the only marker that directly reflects vascular endothelial injury *in vivo*. There have been few studies on the correlation between peripheral blood CECs and ARDS at home and abroad. The lungs are the organs with the highest capillary density and the most endothelial cells, thus, it is speculated that when ARDS occurs, CECs are stimulated and damaged, and released into the circulatory system.

AIM

To explore the correlation between CEC level and severity of ARDS in patients postoperatively.

METHODS

Blood samples were collected from all patients on day 2 (d2) and day 5 (d5) after surgery. The control group comprised 32 healthy volunteers. Number of CECs was measured by flow cytometry, and operation time was recorded. Changes in various indexes of patients were monitored, and diagnosis of ARDS was determined based on ARDS Berlin definition. We comprised d2 CECs in different groups, correlation between operation time and d2 CECs, ARDS of different severity by d2 CECs, and predictive value of d2 CECs for ARDS in postoperative patients.

RESULTS

The number of d2 CECs in the ARDS group was significantly higher than that in

competing interests.

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the healthy control group ($P < 0.001$). The number of d2 CECs in the ARDS group was significantly higher than that in the non-ARDS group ($P < 0.001$). The number of d2 CECs in the non-ARDS group was significantly higher than that in the healthy control group ($P < 0.001$). Operation time was positively correlated with number of CECs on d2 ($rs = 0.302$, $P = 0.001$). The number of d2 CECs in the deceased group was significantly higher than that in the improved group ($P < 0.001$). There was no significant difference in number of d2 CECs between patients with mild and moderate ARDS. The number of d2 CECs in patients with severe ARDS was significantly higher than that in patients with mild and moderate ARDS ($P = 0.041$, $P = 0.037$). There was no significant difference in number of d5 and d2 CECs in the non-ARDS group after admission to intensive care. The number of d5 CECs was higher than the number of d2 CECs in the ARDS improved group ($P < 0.001$). The number of d5 CECs was higher than the number of d2 CECs in the ARDS deceased group ($P = 0.002$). If the number of CECs was $> 1351/\text{mL}$, sensitivity and specificity of predicting ARDS were 80.8% and 78.1%, respectively.

CONCLUSION

Changes in number of CECs might predict occurrence and adverse outcome of ARDS after surgery, and higher numbers of CECs indicate worse prognosis of ARDS.

Key Words: Circulating endothelial cells; Acute respiratory distress syndrome; Intensive care unit; Postoperative period; Outcome; Flow cytometry

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Core Tip: This manuscript evaluated the changes in number of circulating endothelial cells (CECs) might predict occurrence and adverse outcome of acute respiratory distress syndrome (ARDS) postoperatively, and higher numbers of CECs are associated with a worse prognosis of ARDS.

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INTRODUCTION

Acute respiratory distress syndrome (ARDS) is injury of alveolar epithelial cells and capillary endothelial cells caused by various factors, including endogenous and exogenous lung factors, leading to diffuse pulmonary interstitial and alveolar edema, and acute respiratory failure[1-3]. The clinical manifestations are progressive respiratory distress and refractory hypoxemia, and the imaging manifestations are heterogeneous exudative changes[4]. The incidence rate of ARDS is 25%-50% when caused by severe infection, 11%-25% when caused by multiple trauma, and the incidence rate can reach 40% when caused by massive blood transfusion. The incidence rate of ARDS may increase further when two or more risk factors are present [5]. The longer the exposure to risk factors, the higher the incidence rate of ARDS. Studies have shown that when exposure to risk factors persisted for 24, 48 and 72 h, the incidence of ARDS was 76%, 85% and 93%, respectively. The incidence rate of ARDS is high, treatment is difficult, and ARDS has a long course and poor prognosis. Many studies have tried to identify the best marker to predict development and prognosis of ARDS at an early stage[6,7]. However, predictive ARDS markers are still in the research stage[3].

ARDS involves alveolar epithelial cells and pulmonary interstitial capillary endothelial cells. Current research on the markers related to capillary endothelial cells is mainly focused on angiotensin-2, selectin, von Willebrand factor antigen,

intercellular adhesion molecule-1, vascular endothelial growth factor, insulin-like growth factor binding protein-3, apolipoprotein A1, S-100, *PPFIA1* gene and other aspects[8], although the sensitivity and specificity of these markers are low. Compared with above indicators, Eizawa *et al*[9] have considered that circulating endothelial cells (CECs) are the only marker that directly reflects vascular endothelial injury *in vivo*. There have been few studies on the correlation between peripheral blood CECs and ARDS at home and abroad. The lungs are the organs with the highest capillary density and the most endothelial cells, thus, it is speculated that when ARDS occurs, CECs are stimulated and damaged, and released into the circulatory system.

The present study aimed to investigate the correlation between number of CECs and incidence of ARDS, and to explore whether CECs can be used as a predictive biomarker for incidence and adverse clinical outcomes of ARDS.

MATERIALS AND METHODS

Research objective

During 2012–2014, 125 surgical patients were admitted postoperatively to Tianjin Medical University General Hospital. Blood samples were collected on day 2 (d2) and day 5 (d5) after surgery.

Inclusion criteria were: (1) patients after general anesthesia; and (2) operation time \geq 4 h. Exclusion criteria were: (1) thoracic surgery, including thoracotomy, thoracoscopic surgery and chest wall mass operation; (2) vascular diseases, such as arteriosclerosis (including hypertensive arteriosclerosis and atherosclerosis), systemic vasculitis, and arteriovenous thrombosis; (3) patients with malignant tumors; (4) patients with chronic organ dysfunction, such as chronic obstructive pulmonary disease, chronic liver failure, or chronic renal insufficiency; (5) head trauma; and (6) non-ARDS related death.

The clinical data of the enrolled patients are shown in Table 1. There were 32 healthy people in the control group, including 19 men and 13 women, with an average age of 53 ± 11 years (range: 33–67 years).

Research methods

We selected CD146⁺ CD45-labeled CECs, FITC Mouse anti-Human CD146 (Cat No: 560846; BD Biosciences, Franklin Lakes, NJ, United States), FITC Mouse IgG1, κ Isotype Control (Cat No: 554679; BD Biosciences), PE Mouse anti-Human CD45 (Cat No: 555483; BD Biosciences), PE Mouse IgG1, κ Isotype Control (Cat No: 555489; BD Biosciences). We counted 500000 nucleated cells in each blood sample. The samples were detected by flow cytometry with 488 nm excitation wavelength. The results were analyzed by Flow Cytometry CellQuest software. The percentage of CECs among nuclear cells was calculated.

We collected 5 mL peripheral blood from the median cubital vein of enrolled patients. Two EDTA anticoagulant tubes were used to collect blood samples, with 3 mL for the first tube and 2 mL for the second tube, and placed in ice. The blood (200 mL) was taken from the second tube for detection. We added 4 mL red blood cell lysate; incubated at room temperature for 20 min; centrifuged at 1500 rpm at room temperature for 5 min; discarded supernatant and washed with once or twice with PBS; resuspended the blood cells in PBS to 100 mL; and added antibodies in the following sequence: 10 mL IgG1, κ PE; 5 mL IgG1, κ FITC; 10 mL CD45 PE; 5 mL CD146 FITC; 10 mL CD45 PE; 5 mL IgG1, κ FITC; 10 mL CD45 PE; and 5 mL CD146 FITC. The samples were then incubated in the dark for 20 min, resuspended in 300 mL PBS and subjected to flow cytometry. At the same time, blood samples were removed and analyzed by automatic blood cell analyzer to obtain the white blood cell count.

Statistical analysis

SPSS version 20.0 software was used for data processing (IBM Corp., Armonk, NY, United States). The measurement data were expressed as mean \pm SD. We compared by independent sample *t* test the numbers of CECs between the ARDS and healthy control groups, and ARDS and non-ARDS groups, the number of CECs between groups with different severity of ARDS, and the number of CECs between the improved and dead groups. The change in number of CECs after surgery was analyzed by paired *t* test. Spearman's correlation was used to analyze the relationship between d2 CECs and operation time. Receiver operating characteristic (ROC) curve was used to detect the number of d2 CECs as best cut-off value to predict ARDS occurrence (obtained by calculating the maximum sensitivity and specificity), and

Table 1 Clinical data of patients enrolled

Clinical data	n (%)
Gender	
Male	75 (60)
Female	50 (40)
Age	
Age distribution	33-67
Average	53 ± 11
Mechanical ventilation	105 (84)
ARDS occurrence	52 (42)
Improvement	39 (31)
Death	13 (10)
Average APACHE II score	11 ± 5
Department type	
General surgery	77 (62)
Orthopedics	25 (20)
Other	23 (18)

ARDS: Acute respiratory distress syndrome.

defined the number of d2 CECs higher than cut-off value as Hd2. A binary regression model was used to detect the predictive value on the occurrence of ARDS. All tests were bilateral, and $P < 0.05$ was considered to be statistically significant.

RESULTS

General clinical results

Among the 125 patients enrolled, 105 patients received ventilator support. If their condition progressed to ARDS, a protective lung ventilation strategy was implemented[10,11]. Comprehensive parameters were monitored including vital signs, blood gas analysis, central venous pressure, and pulse contour cardiac output monitoring was carried out if necessary, and all patients were given bundle treatment in the intensive care unit. We enrolled 52 patients with ARDS; 13 died and the others showed eventual improvement; 73 patients did not develop ARDS and improved (Table 1). CECs were measured by flow cytometry (Figure 1). A1, B1 and C1 were isotype control groups, and A2, B2 and C2 were experimental groups.

Comparison of d2 CECs in ARDS, healthy control and non-ARDS groups

D2 CECs were significantly higher in patients with ARDS compared with the healthy control group ($P < 0.001$) (Table 2). D2 CECs of the ARDS group were significantly higher in the ARDS group than in the non-ARDS group ($P < 0.001$). D2 CECs in the non-ARDS group were significantly higher than in the healthy control group ($P < 0.001$).

Correlation between operation time and d2 CECs

Spearman's correlation analysis showed a significantly positive correlation between operation time and d2 CECs ($r_s = 0.302$, $P = 0.001$) (Figure 2).

Comparison of d2 CECs between the deceased and improved groups of ARDS patients

The number of d2 CECs in the dead group was significantly higher than in the improved group ($P < 0.001$) (Table 3).

Table 2 Comparison of the levels of circulating endothelial cells in three groups, mean \pm SD

Group	Number	Count of CECs, in mL
ARDS Group	52	2064 \pm 892
Non-ARDS Group	73	1038 \pm 1371
Healthy control group	32	167 \pm 148

ARDS: Acute respiratory distress syndrome; CECs: Circulating endothelial cells.

Table 3 Comparison of day 2 circulating endothelial cells levels between death group and improvement group in acute respiratory distress syndrome patients, mean \pm SD

Group	Number	Count of CECs, mL	P value
Deceased group	13	2863 \pm 651	< 0.001
Improvement group	39	1799 \pm 801	

CECs: Circulating endothelial cells.

Comparison of d2 CECs in patients with ARDS of different severity

There was no significant difference in number of CECs in patients with mild compared with moderate ARDS ($P = 0.924$). The number of CECs in patients with severe ARDS was significantly greater than in patients with moderate ARDS ($P = 0.037$). The number of CECs in patients with severe ARDS was significantly greater than in patients with mild ARDS ($P = 0.041$) (Table 4).

Changes in CECs over time in the non-ARDS, improved and deceased groups

There was no significant difference between the number of d5 and d2 CECs in the non-ARDS group after admission ($P = 0.273$). The number of d5 CECs was significantly higher than the number of d2 CECs in the improved group ($P < 0.001$). The number of d5 CECs was significantly higher than the number of d2 in the deceased group ($P = 0.002$) (Table 5).

Predictive value of d2 CECs for ARDS in postoperative patients

The Youden index of the ROC curve was used to calculate the best cut-off value of d2 CECs at 1351/mL (area under the curve = 0.85, 95%CI: 0.781–0.919, $P < 0.001$), sensitivity to predict occurrence of ARDS was 80.8%, and specificity was 78.1%. Hd2 was an independent predictor of ARDS (odds ratio = 14.96, 95%CI: 6.18–36.25, $P < 0.002$) (Figure 3).

DISCUSSION

CECs refer to vascular endothelial cells (VECs) obtained from circulating blood under physiological or pathological conditions[12]. VECs are large cells that are present in large numbers throughout the pulmonary circulation, and have active metabolism and complex function. Pulmonary VECs are important target and effector cells in ARDS, and are damaged earliest in the disease course[13]. Under pathological conditions, the number of CECs often increases significantly. At present, although research on CECs is common, most of it is limited to studies of infection, cardiovascular disease and oxidative stress. There are few clinical studies on the changes in CECs and their predictive potency in patients with ARDS. Recently, a relationship between endothelial damage, CECs and ARDS has been seen in the study of ARDS induced by coronavirus disease 2019[14].

The cellular immunophenotype of CECs is currently not clear[15], and most endothelial progenitor cells and partially activated T lymphocytes also express part of the same phenotype as CECs. Therefore, it is necessary to label multiple phenotypic antibodies at the same time to identify CECs more accurately by flow cytometry. In this study, we defined CECs as CD146⁺ CD45⁻ cells.

Table 4 Comparison of number of day 2 circulating endothelial cells in patients with acute respiratory distress syndrome under different severity, mean \pm SD

Severity of ARDS	Number	Count of CECs, mL
Mild	19	1924 \pm 872
Moderate	20	1897 \pm 890
Severe	13	2580 \pm 791

ARDS: Acute respiratory distress syndrome; CECs: Circulating endothelial cells.

Table 5 Changes of circulating endothelial cells levels in three groups as acute respiratory distress syndrome development, mean \pm SD

Group	Number	Count of CECs, mL		P value
		Count of d2 CECs	Count of d5 CECs	
Non-ARDS group	73	1038 \pm 1371	854 \pm 648	0.273
Improvement group	39	1799 \pm 801	2274 \pm 1017	< 0.001
Death group	13	2863 \pm 652	3548 \pm 1035	0.002

ARDS: Acute respiratory distress syndrome; CECs: Circulating endothelial cells.

This is believed to be the first study to compare numbers of CECs in patients with ARDS. In patients with ARDS postoperatively, the number of d2 CECs in the deceased group was higher than in the improved group, so increased number of CECs might predict increased mortality at an early stage. Number of CECs on d2 was correlated with whether patients developed ARDS, severity of ARDS and clinical outcome of ARDS, which indicated that degree of endothelial injury represented by CECs had a predictive and warning effect on the clinical outcome of ARDS. Most ARDS patients have respiratory dysfunction, but not all of them die of respiratory failure. A large number of etiological studies have shown that multiple organ dysfunction is an independent risk factor for poor prognosis of ARDS[16]. Therefore, extensive endothelial injury and massive platelet thrombosis lead to tissue hypoxia and multiple organ dysfunction. Therefore, changes in CECs, which are a marker of endothelial cell injury, might predict mortality of ARDS patients. Moussa *et al*[17] have suggested that activation and dysfunction of endothelial cells are involved in the pathophysiological process of ARDS. CECs might be a useful biomarker of endothelial dysfunction and injury. Therefore, they conducted a study on sepsis-related ARDS. The median CECs count in moderate and severe ARDS on d1 was significantly higher than that in patients with sepsis and mild ARDS and sepsis control patients, and all sepsis patients (with or without ARDS) had higher CECs counts on d1 than patients without ARDS. Therefore, CECs count on d1 of ARDS could be used as a useful indicator of severity of ARDS.

In our study, the number of CECs in patients with ARDS on d2, postoperatively, was significantly higher than that in the control group. Moreover, ROC curve analysis showed that the best cut-off value of d2 CECs was 1351 cells/mL. Therefore, number of CECs was an effective marker to predict development and outcome of ARDS. The cut-off value showed that when CECs were > 1351 cells/mL, patients were more likely to have ARDS, and sensitivity and specificity were 80.8% and 78.1%, respectively. For patients with ARDS, there was no significant difference in number of d2 CECs between mild and moderate disease, while the number of d2 CECs in severe ARDS was significantly higher than that in mild and moderate ARDS. Therefore, it could be inferred that number of CECs in peripheral blood is significantly increased in patients with severe ARDS, which reflected severity of ARDS. We need to expand sample size and investigate specific changes in CECs in peripheral blood of patients with ARDS of different severity.

According to the current consensus, the time course of ARDS is: corresponding respiratory symptoms appear, or respiratory symptoms are aggravated, or new respiratory symptoms appear after an external stress within 1 wk[18,19]. Therefore, in our study, the number of CECs was detected on d5 for patients enrolled postoperatively. We found that there was no significant change in CECs during recovery of

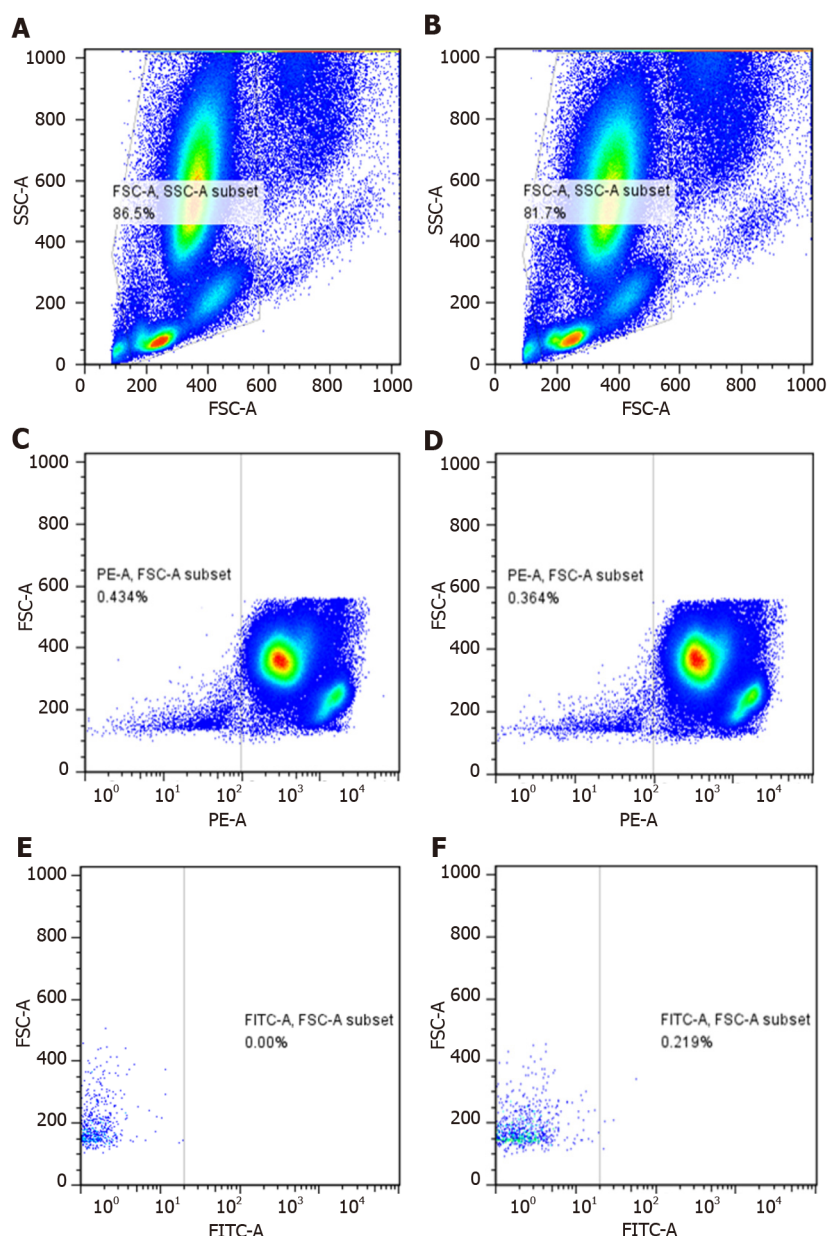


Figure 1 Circulating endothelial cells were measured by flow cytometry. A, C, E: Isotype control group; B, D, F: Experimental groups.

non-ARDS patients, suggesting that there was no further damage to the vascular endothelial system; however, the number of CECs increased in the improved and deceased groups of ARDS patients, which was thought to be related to the combined effects of many factors such as shock and infection postoperatively. We found that there was a positive correlation between operation time and number of CECs, suggesting that longer operation time resulted in greater trauma. The effects of the operation itself and postoperative inflammatory reaction could both lead to damage of the vascular endothelial system. This mechanism is consistent with pathogenesis of extrapulmonary ARDS[20].

CONCLUSION

Changes in number of CECs might predict occurrence and adverse outcome of ARDS postoperatively, and higher numbers of CECs are associated with worse prognosis of ARDS.

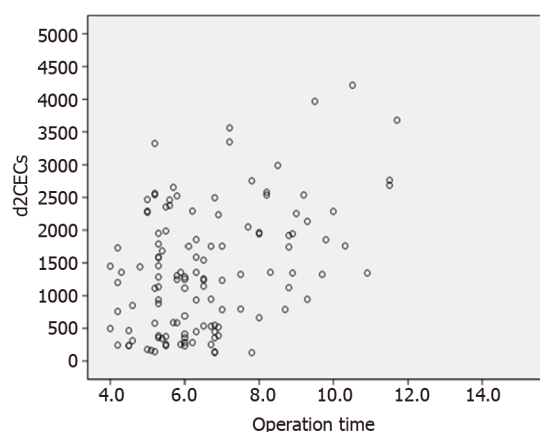


Figure 2 Spearman's correlation analysis was utilized, and there was significantly positively correlated between two groups. d2 CECs: Day 2 circulating endothelial cells.

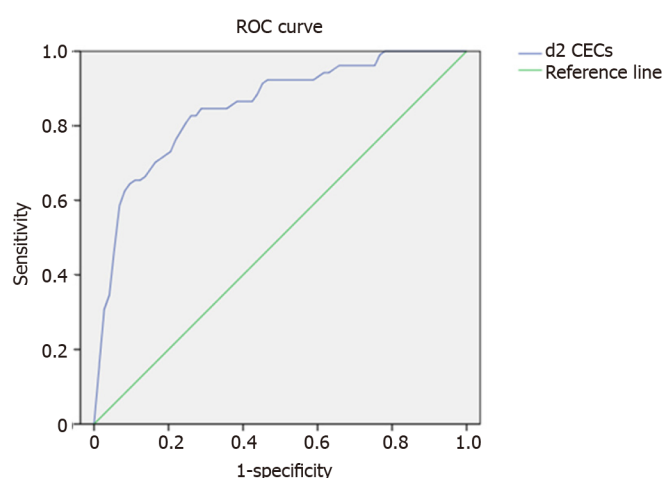


Figure 3 Youden index in receiver operating characteristic curve. ROC: Receiver operating characteristic; d2 CECs: Day 2 circulating endothelial cells.

ARTICLE HIGHLIGHTS

Research background

Acute respiratory distress syndrome (ARDS) involves alveolar epithelial cells and pulmonary interstitial capillary endothelial cells. Circulating endothelial cells (CECs) are the only marker that directly reflects vascular endothelial injury *in vivo*. There have been few studies on the correlation between peripheral blood CECs and ARDS at home and abroad.

Research motivation

This research studied correlation between level of CECs and severity of ARDS, and preliminarily observed change trend of CECs at different time points. This is believed to be initiated research to compare CECs levels changes in patients with ARDS, and it had value of guiding treatment and evaluating prognosis for ARDS patients.

Research objectives

This study aimed to explore the correlation between CEC level and severity of ARDS in patients postoperatively.

Research methods

Blood samples were collected from all patients on day 2 (d2) and day 5 (d5) after surgery. Number of CECs was measured by flow cytometry, and operation time was recorded. Changes in various indexes of patients were monitored, and diagnosis of ARDS was determined based on ARDS Berlin definition.

Research results

The number of d2 CECs in the ARDS group was significantly higher than that in the healthy control group. The number of d2 CECs in the ARDS group was significantly higher than that in the non-ARDS group. The number of d2 CECs in the non-ARDS group was significantly higher than that in the healthy control group. There was no significant difference in number of d2 CECs between patients with mild and moderate ARDS. The number of d2 CECs in patients with severe ARDS was significantly higher than that in patients with mild and moderate ARDS. The number of d5 CECs was higher than the number of d2 CECs in the ARDS deceased group.

Research conclusions

Changes in number of CECs might predict occurrence and adverse outcome of ARDS postoperatively, and higher numbers of CECs are associated with worse prognosis of ARDS.

Research perspectives

In future experiments, we need to further expand sample size by collecting more enrolled patients, refining grouping, and conducting hierarchical analysis. If one special group of patients was dynamically tracked for detection, this would increase the refinement of CECs detection time points for better observation of dynamic changes of CECs.

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