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Prognostic Value of CD14 Expression in Peripheral Blood Mononuclear Cell Membrane in Patients with Severe COPD Complicated with Pulmonary Infection

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ABSTRACT

Background: Severe chronic obstructive pulmonary disease (COPD) patients with pulmonary infections face higher morbidity and mortality.

Objective: To investigate mononuclear cell membrane CD14 as a prognostic marker for their outcome.

Methods: A total of 311 participants were included: 122 in the coinfection group, 127 in the severe COPD group, and 62 in the control group. The patients in the coinfection group were categorized into survival (n=106) and death (n=16) groups based on hospitalization prognosis. The CD14%, CD14MFI, and CD14IND values were compared between the groups. Death risk factors were assessed by COPD grading, FEV1% pred, FEV1/FVC, CD14%, CD14MFI, and CD14IND. Correlations between CD14 parameters and mortality, COPD grade, FEV1%pred, and FEV1/FVC were analyzed. The critical value for CD14IND to predict patient death was determined and survival rates were compared between the high and the low-risk groups.

Results: CD14% values were significantly lower in the COPD and co-infection groups than in the control groups ($p<0.05$). The survival group showed a steady increase in mCD14 expression, while the death group showed fluctuating low levels. Low value of CD14% was identified as a risk factor for death and correlated with mortality and COPD severity ($p<0.001$). CD14IND≤74.36 predicted death with 91.22% sensitivity and 95.51% specificity. The high-risk group had a significantly lower 30-day survival rate (68.42%) compared with the low-risk group (95.24%) (log-rank $\chi2=10.067$, $p=0.002$).

Conclusion: The CD14 parameters of mononuclear cell membranes prove to be promising markers for predicting prognosis and death in severe COPD patients with lung infection.

Keywords: Mononuclear Cell Membrane CD14, Predicted Value, Prognosis, Pulmonary Infection, Severe COPD

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) complicated with pulmonary infection could lead to acute exacerbation of COPD and seriously affect the prognosis of the disease (1). At present, COPD patients complicated with pulmonary infection were mainly treated with expectorant, oxygen inhalation and anti-infection therapy to alleviate clinical symptoms, but the in-hospital mortality rate was still as high as 15% (2). Therefore, early prediction of the prognosis of COPD patients with pulmonary infection played a key role in guiding clinical treatment and promoting disease outcome. Cluster of differentiation 14 (CD14) was a recognition receptor of bacterial cell wall fragments, which mediated the inflammatory reaction between epithelial cells and endothelial cells, played a key role in the immune response to bacterial pathogens, and was closely related to infectious diseases (3). CD14 mainly existed in the body in two forms, one of which was soluble cluster of differentiation 14 (sCD14) and the other was monocyte membrane cd14 (mCD14) (4). Leukocyte elastase could separate mCD14 from monocytes. mCD14 bounded lipopolysaccharide, and transmitted the signal to monocytes, making them secrete cytokines such as interleukin (IL)-1, tumor necrosis factor (TNF)-α, IL-6, etc. to start the immune response (5). The expression of mCD14 in patients with sepsis (6), Parkinson's disease (7) and hepatitis B-related liver cancer (8) and the influence of mCD14 on disease prognosis had been studied. Some studies had also found that (9), the serum sCD14 level of elderly COPD patients with pulmonary infection increased, and related to COPD grade and prognosis. Therefore, this study takes patients with severe COPD complicated with pulmonary infection as the research object, and explores the influence of the change of mCD14 level on the prognosis of patients with severe COPD complicated with pulmonary infection, aiming at providing theoretical basis for clinical research.

MATERIALS AND METHODS

Subjects

From January 2020 to February 2022, a total of 249 patients were recruited from xxx, including 122 patients with severe COPD complicated with pulmonary infection selected as the co-infection group and 127 patients with severe COPD selected as the severe COPD group. Another 62 healthy people were selected as the control group from xxx. After a follow-up period of 30 days, patients with severe COPD complicated with pulmonary infection were divided into survival group (n=106) and death group (n=16) according to the prognosis during hospitalization. The study was approved by the hospital's ethics committee and conducted in accordance with the Declaration of Helsinki. All patients signed the informed consent form before joining the study.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) All patients meet the criteria of diagnosis and staging in Global Initiative for Chronic Obstructive Lung Disease (GOLD) (10) revised in 2019; (2) Patients complicated with pulmonary infection were supported by imaging, blood examinations and sputum bacteria culture results; (3) not taking steroids, immunosuppressants, etc. in the near future, which will affect the blood routine.

Exclusion criteria: (1) Complicated with malignant tumors and serious diseases of heart, liver, kidney, blood, immunity and other systems, (2) other respiratory diseases affecting lung function such as pulmonary tuberculosis, acute pulmonary embolism and bronchial asthma or dilatation, (3) endocrine diseases and systemic infectious diseases.

CD14 Detection

The peripheral blood was collected on the 1st, 3rd, 5th, 7th and 14th day after the diagnosis. CD14 on the surface of peripheral blood mononuclear cells was detected by flow cytometry, and WBC content in peripheral

blood was also detected. 50μl of whole blood and 10 μ l of CD14 monoclonal antibody were incubated, 1 ml of hemolysin was added, centrifuged, supernatant was removed, PBS was added for centrifugation, and supernatant was removed. The samples were collected by FACSCalibur flow cytometry (BD Company, United States), and the data were analyzed. Each sample collected 10,000 nucleated cells. The data were analyzed by CELLQuest software, and the percentage of CD14 expression in nucleated cells and the average fluorescence intensity (CD14MFI) of CD-positive cells were counted. The membrane CD14 index (CD14IND) reflects the relative total number of membrane CD14 molecules per unit of peripheral blood, CD14IND=CD14%×CD14MFI×WBC /10000 (11).

Pulmonary Function Examination

The patient rested quietly for 10 min, and the forced expiratory volume/forced vital capacity (FEV_1/FVC) and the percentage of forced expiratory volume (FEV1% pred) in the first second were recorded by lung function detector. In addition to the pulmonary function test, history of substantial smoking, history of chronic or recurrent infections and other historical clues of symptoms in response to triggers such as exercise were reviewed to help differentiate COPD from other obstructive pulmonary disorders.

Statistical Analysis

SPSS22.0 software was used to analyze the data, the counting data was expressed by frequency, and the data comparison was done by χ^2 test. The data use (mean±standard deviation) indicating that the data of the three groups of the co-infection group, the COPD group and the control group were compared with one-way ANOVA, and the paired comparison was made via T test or SNK-q test. The correlation analysis of CD14%, CD14MFI and CD14IND with the death of patients with severe COPD complicated with pulmonary infection used Spearman correlation analysis. Cox proportional hazard regression was used to analyze the independent risk factors of death in the patients with severe COPD complicated with pulmonary infection after 30 days. The receiver operating characteristic (ROC) curve was used to analyze the predictive value of CD14%, CD14MFI and CD14IND on the prognosis and death of patients, and the area under the curve (AUC) was compared. Kaplan-Meier method was used to draw the survival curve and compare the survival of the patients with different CD14IND levels. Inspection level α=0.05.

RESULTS

MCD14 Level in Patients with Severe COPD Complicated with Infection

Compared with the control group, CD14%, CD14MFI and CD14IND in COPD group and co-infection group were significantly lower (p<0.05). Compared with COPD group, CD14%, CD14MFI and CD14IND in co-infection group were significantly lower (p<0.05).

Dynamic Changes of mCD14 Level in Patients with Severe COPD Complicated with Infection

Comparing the change trend of mCD14 expression related parameters between the survival group and the death group on the 1st, 3rd, 5th, 7th and 14th day after the diagnosis of severe COPD complicated with infection, it was found that the expression of mCD14 in the survival group increased steadily during the whole monitoring process, while that in the death group fluctuated at a low level (Fig. 1).

Comparison of General Clinical Data between the Survival Group and the Death Group in COPD Patients with Pulmonary Infection

The age, diabetes mellitus, course of disease, COPD grade, FEV1%pred, FEV1/FVC, CD14%, CD14MFI and CD14IND of the two groups were significantly different (p<0.05, Table 1).

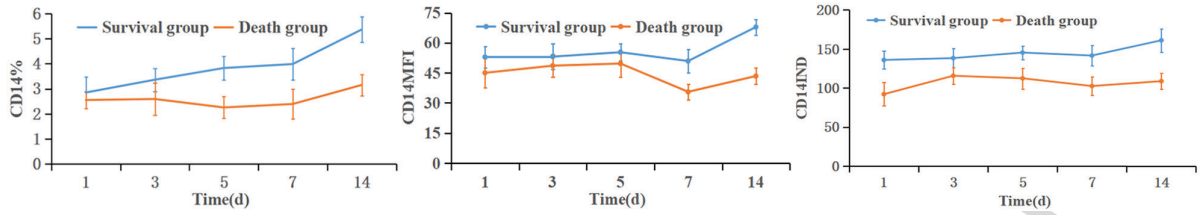

Fig. 1. Dynamic changes of mCD14 level in patients with severe COPD complicated with infection. CD14% refers to the percentage of CD14 expression in nucleated cells; CD14MFI refers to the average fluorescence intensity of CD-positive cells; CD14IND refers to the relative total number of mCD14 molecules per unit of peripheral blood.

Table 1. Comparison of general clinical data between survival group and death group in COPD patients with pulmonary infection [$\bar{x}\pm s$, n (%)]

General clinical data	Death group(n=16)	Survival group(n=106)	t/χ^2	p
Gender			0.185	0.667
Male	11	67		
Female	5	39		
Age	71.49±3.58	69.39±3.11	2.468	0.015
BMI(kg/m^2)	21.86±2.27	22.14±2.58	0.410	0.682
Drink wine/alcohol			0.129	0.720
Yes	5	38		
NO	11	68		
Smoking			1.019	0.313
Yes	6	27		
NO	10	79		
Residential area			0.246	0.620
Village	8	46		
City	8	60		
Hypertension			0.016	0.898
Yes	6	38		
NO	10	68		
Diabetes			6.136	0.013
Yes	5	10		
NO	11	96		
Coronary heart disease			0.072	0.788
Yes	3	23		
NO	13	83		
Course of a disease（year）	10.37±1.96	9.25±1.74	2.361	0.020
COPD family history			0.015	0.901
Yes	4	25		
No	12	81		
COPD classification			6.945	0.031
I	2	29		
II	5	51		
III	9	26		
FEV_1%pred	48.40±6.20	65.92±9.15	7.393	<0.001
FEV_1/FVC	60.24±3.83	65.85±4.91	4.368	<0.001
CD14%	3.05±1.22	5.92±1.47	7.425	<0.001
CD14MFI	43.48±8.06	66.74±10.37	8.578	<0.001
CD14IND	106.65±10.73	145.47±14.69	10.153	<0.001

BMI: body mass index, CD14: cluster of differentiation 14, COPD: chronic obstructive pulmonary disease, FEV1: forced expiratory volume, FVC: forced vital capacity, IND: index, MFI: average fluorescence intensity

Cox Proportional Hazard Regression Analysis of Risk Factors for Death in the Patients with Severe COPD Complicated with Pulmonary Infection

The factors with $p<0.05$ in single factor analysis were included in Cox proportional risk regression model analysis, and the results showed the likelihood ratio test of the overall model coefficient $\chi^2=130.62$, $p<0.05$; the log-likelihood ratio test $\chi^2=95.88$, $p<0.05$. It showed, too, that at least one independent variable in Cox regression model had influence on prognosis, and the model was established. Grading COPD, FEV1%pred, FEV1/FVC, CD14%, CD14MFI and CD14IND were all influencing factors for the death of the patients with severe COPD complicated with pulmonary infection ($p<0.05$, Fig. 2).

Correlation between Expression Parameters of mCD14 and Death in the Patients with Severe COPD Complicated with Pulmonary Infection

Spearman analysis of the correlation between mCD14 expression parameters and the death of the patients with severe COPD complicated with pulmonary infection showed that CD14%, CD14MFI and CD14IND negatively correlated with the mortality and COPD grade of the patients with severe COPD complicated with pulmonary infection, but positively correlated with FEV1%pred and FEV1/FVC ($p<0.001$) (Table 2).

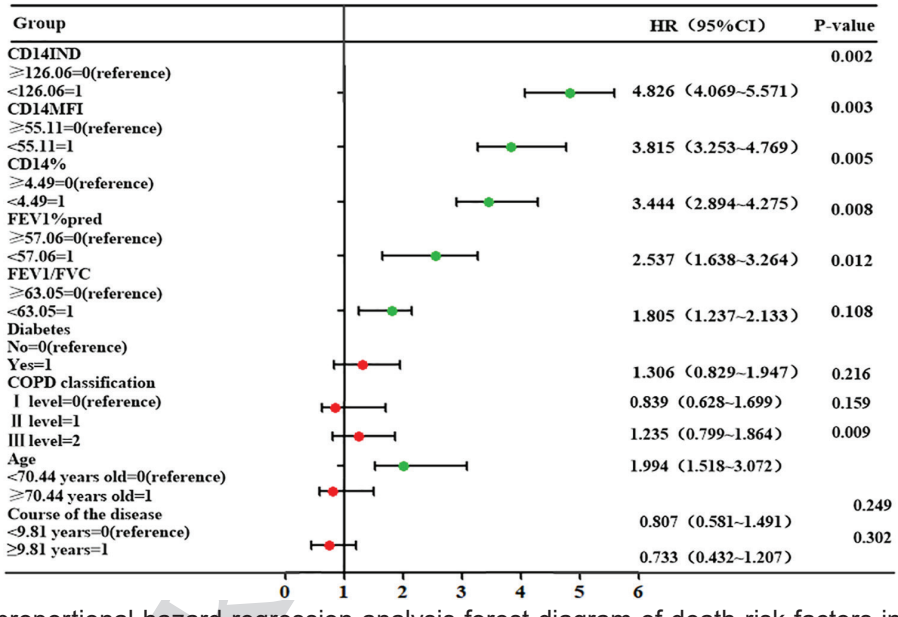

Fig. 2. Cox proportional hazard regression analysis forest diagram of death risk factors in patients with severe COPD complicated with pulmonary infection. CD14% refers to the percentage of CD14 expression in nucleated cells; CD14MFI refers to the average fluorescence intensity of CD-positive cells; CD14IND refers to the relative total number of mCD14 molecules per unit of peripheral blood; FEV1 refers to the forced expiratory volume; FEV1/FVC refers to the ratio of the forced expiratory volume to the forced vital capacity.

Table 2. Correlation analysis between MCD14 expression parameters and death of patients with severe COPD complicated with pulmonary infection

	CD14%		CD14MFI		CD14IND	
	r	*p*	*r*	*p*	*r*	*p*
Mortality rate	-0.475	<0.001	-0.429	<0.001	-0.536	<0.001
COPD classification	-0.613	<0.001	-0.450	<0.001	-0.381	<0.001
FEV_1%pred	0.578	<0.001	0.606	<0.001	0.628	<0.001
FEV_1/FVC	0.559	<0.001	0.591	<0.001	0.571	<0.001

MCD14: membrane Cluster of differentiation 14, COPD: chronic obstructive pulmonary disease, FEV1: forced expiratory volume, FVC: forced vital capacity, IND: index, MFI: average fluorescence intensity

Predictive Value of mCD14 Expression Parameters in the Death of the Patients with Severe COPD Complicated with Pulmonary Infection

The lowest values of CD14%, CD14MFI and CD14IND were analyzed by ROC curve to predict the death of patients with severe COPD complicated with pulmonary infection. The results showed that the ROC areas of the three values were 0.718 (95% CI:0.688~0.892, p=0.003) and 0.846 (95% CI: 0.651~0.996, p=0.016), 0.910 (95% CI:0.816~0.975, p<0.001), the sensitivity was 72.35%, 87.41%, 91.22%, and the specificity was 89.27%, 87.65%, 95.51%, respectively. With CD14IND≤74.36 as the critical value, the sensitivity and specificity of predicting the death of patients reached 91.22% and 95.51% respectively. It is suggested that CD14IND could predict the prognosis of patients (Table 3 and Fig. 3).

Survival Curve Analysis of Patients with Different CD14IND Levels

According to the best critical value of CD14IND obtained by ROC curve to predict the prognosis and death of the patients with severe COPD complicated with pulmonary infection, the patients with CD14IND level >74.36 were defined as low-risk group (84 cases), and the patients with CD14IND level ≤74.36 were defined as high-risk group (38 cases). Kaplan-Meier method was used to draw the survival curve and compare the survival of the two groups. The results were shown in Fig. 4. The 30-day survival rate of the high-risk group was significantly lower than that of the low-risk group (68.42% vs. 95.24%, Log-Rank χ^2=10.067, p=0.002, Fig. 4).

DISCUSSION

COPD is a respiratory disease with a high prevalence among the elderly, and its incidence

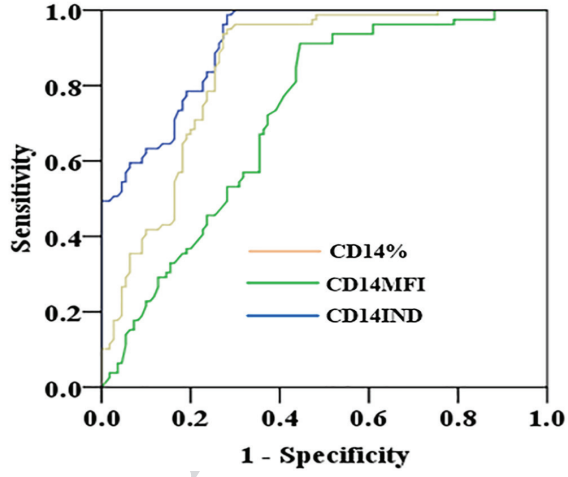

Fig. 3. Predictive value of CD14 expression parameters for death of patients with severe COPD complicated with pulmonary infection. CD14% refers to the percentage of CD14 expression in nucleated cells; CD14MFI refers to the average fluorescence intensity of CD-positive cells; CD14IND refers to the relative total number of mCD14 molecules per unit of peripheral blood.

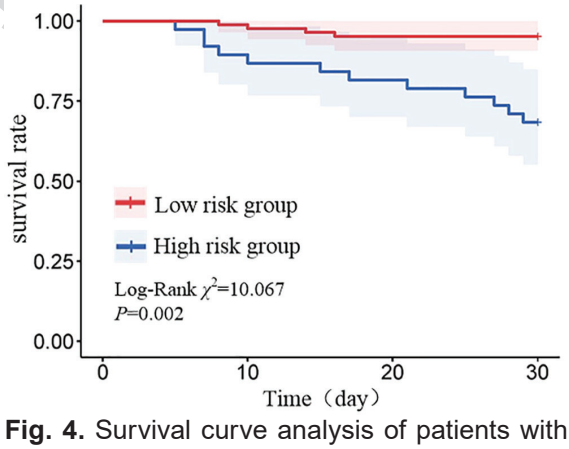

Fig. 4. Survival curve analysis of patients with different CD14IND levels. Significant difference in 30-day survival was noted when comparing low-risk to high-risk groups according to the cut-off value of CD14IND at 74.36.

Table 3. The predictive value of CD14 expression parameters for the death of patients with severe COPD complicated with pulmonary infection

	Critical value	AUC	Sensitivity (%)	Specificity (%)	95%CI	*p*
CD14%	1.20	0.718	72.35	89.27	0.688~0.892	0.003
CD14MFI	35.94	0.846	87.41	87.65	0.651~0.926	0.016
CD14IND	74.36	0.910	91.22	95.51	0.816~0.975	<0.001

CD14: cluster of differentiation 14, COPD: chronic obstructive pulmonary disease, IND: index, MFI: average fluorescence intensity

is related to smoking, dust inhalation and increased airway responsiveness (12). COPD can affect respiratory and circulatory system, cause various complications and endanger patients' lives. Pulmonary infection is one of the common complications of COPD, which will aggravate the condition of COPD, make the patient's prognosis poor, and seriously affect the patient's normal life (13). The clinical outcome of COPD complicated with pulmonary infection is influenced by many factors, with complicated mechanism and high mortality in hospital. Therefore, a crucial aspect of clinical research is to evaluate the prognosis of COPD complicated by pulmonary infection and to intervene in a timely manner. In the pathogenesis of COPD, mCD14 is the key factor of host defense, which transmits microbial antigen to T lymphocytes in immune response, produces cytokines, and initiates and regulates humoral and cellular immune responses (14). It has been reported (15) that the low expression of mCD14 will increase the risk of death in COPD patients. The present study also found that CD14%, CD14MFI and CD14IND in patients with co-infection were significantly lower than those in the COPD group and the control group, and mCD14 level in the COPD group was significantly lower than that in control group. In addition, according to the prognosis, this study divided the patients with co-infection into survival group and death group, and compared the related parameters of mCD14 between the two groups. It was found that the dynamic trends of CD14%, CD14MFI and CD14IND in the two groups were also different, in which the expression level of CD14 in the survival group gradually increased, while that in the death group fluctuated at a low level, with no obvious upward trend. It was suggested that the low expression of CD14 may contribute to poor prognosis of patients with COPD complicated with pulmonary infection.

In this study, Cox proportional hazard regression was used to screen the influence on the prognosis of COPD patients with pulmonary infection. It was found that CD14%, CD14MFI and CD14IND were independent influencing factors. In addition, the correlation analysis found that CD14%, CD14MFI and CD14IND negatively correlated with the mortality and COPD grade of the patients with severe COPD complicated with pulmonary infection, and positively correlated with pulmonary function parameters FEV1%pred and FEV1/FVC, which further confirmed that mCD14 significantly correlated with the patient's disease progress and prognosis. Therefore, mCD14 could be used to predict the prognosis of the patients with severe COPD complicated with pulmonary infection. In addition, the ROC curve of this study showed that among the three parameters, CD14%, CD14MFI and CD14IND, CD14IND had the highest sensitivity and specificity for prognosis. Therefore, our research group suggested using CD14IND as an index to predict the prognosis and death of the patients. CD14IND could reflect the total number of mCD14, indicating that the total number of CD14 should be kept above a certain level, and if it were lower than this level, the risk of death of patients will increase (16). It had also been reported (17) that the decrease of CD14% indicates that the patient was in an immunosuppressive state and the prognosis of the patient is poor, which might be the best time to adopt immunomodulatory therapy. Another study also found that patients with systemic inflammatory response syndrome, sepsis, or septic shock had a higher level of sCD14 subtype than other patients (18). However, it was a small-scale study which has limited clinical implication to acute clinical condition. Further study on the application of sCD14 and mCD14 in predicting the severity of COPD with pulmonary infection is warranted.

In this study, Kaplan-Meier method was used to draw the survival curve, and the survival situation of the patients with different CD14IND levels was compared. It was found that 12 of 16 death cases could be successfully predicted with CD14IND level ≤74.36. There

were 9 cases predicted within 3 days after diagnosis, which indicated the possibility for early intervention. Another 4 cases were predicted on the 7th and 14th days after diagnosis, and they were intervened one week before the death of these patients. Therefore, this study suggested that CD14IND could be used as a prognostic indicator of severe COPD complicated with pulmonary infection and can guide clinical treatment. However, there were some shortcomings in this study: the average fluorescence intensity was used to reflect the total amount of mCD14 in monocytes in this study, which might be affected by the experimental process, and the results might be quite different; In addition, this study was a single-center study with a small sample size. Therefore, it was necessary to increase the sample size, multi-center sampling and quantitatively measure the expression of mCD14 in monocytes to predict the prognosis of the patients with severe COPD complicated with pulmonary infection.

CONCLUSION

To sum up, the related parameters of mCD14 were expected to be a marker for predicting the prognosis and death of the severe COPD patients with pulmonary infection, among which the sensitivity and specificity of CD14IND were better than those of CD14% and CD14MFI, which was of great significance for guiding the clinical management of severe COPD patients with pulmonary infection.

AUTHOR' CONTRIBUTION

RL wrote the manuscript. WS and DM carried out the experiment and contributed to sample preparation. WS and DM conceived of the presented idea, diagnosis of patients and supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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