Intensive Care Research (2022) 2:26–33
https://doi.org/10.1007/s44231-022-00004-5

RESEARCH ARTICLE

Evaluating the Roles of sCD14 and sCD14-ST in Diagnosing COPD and Predicting an Acute Exacerbation of COPD

Rui Zhang[1] · Guangxin Sun[2] · Zhengwei Xing[3] · Yuling Bai[4] · Hui Pei[4] · Yulei Gu[4] · Yahui Huang[4] · Xiaofan Zhang[4] · Luanluan Zhang[4]

Received: 1 November 2021 / Accepted: 28 April 2022 / Published online: 15 June 2022

Abstract

Aim To evaluate the roles of plasma soluble cluster of differentiation 14 (sCD14) and sCD14 subtype (sCD14-ST) in the diagnosis of chronic obstructive pulmonary disease (COPD) and in the prediction of an acute exacerbation of COPD (AECOPD).

Methods We quantified the levels of white blood cell count (WBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin (IL)-6, IL-8, sCD14, and sCD14-ST in patients with COPD and healthy controls. The relationships between sCD14 or sCD14-ST and inflammatory markers were analyzed in each group. We used receiver operating characteristics (ROC) curves to evaluate the potential roles of sCD14 and sCD14-ST in the diagnosis of COPD and in predicting AECOPD.

Results A total of 62 subjects were recruited, including 15 controls and 47 COPD patients, with the latter including 32 stable COPD and 15 AECOPD. WBC, IL-8, sCD14, and sCD14-ST were significantly higher in COPD than in the controls (all $P < 0.05$). WBC, CRP, ESR, IL-6, IL-8, sCD14, and sCD14-ST were higher in AECOPD than in the controls (all $P < 0.05$). In the COPD group, sCD14 levels were positively correlated with WBC, IL-8, and sCD14-ST ($P < 0.05$), and sCD14-ST levels were positively correlated with WBC and IL-8 ($P < 0.05$). In the AECOPD group, sCD14 was positively correlated with WBC, CRP, IL-8, and sCD14-ST ($P < 0.05$); sCD14-ST was positively correlated with WBC, IL-6, and IL-8 ($P < 0.05$). Discrimination between COPD and controls was tested by calculating areas under the ROC curve (AUCs) for sCD14 and sCD14-ST showing scores of 0.765 (95% CI 0.648–0.883) and 0.735 (95% CI 0.537–0.933) respectively. Similarly, discrimination between AECOPD and controls using sCD14 and sCD14-ST showed scores of 0.862 (95% CI 0.714–1.000) and 0.773 (95% CI 0.587–0.960), respectively.

Conclusion Our study suggests that the inflammatory markers sCD14 and sCD14-ST might play an important diagnostic role in COPD and help predict AECOPD.

Keywords COPD · sCD14 · sCD14-ST · Areas under the ROC curve

✉ Rui Zhang
zrhndoc@aliyun.com

✉ Guangxin Sun
sunguangxin2006@163.com

[1] Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China

[2] Department of Respiratory and Critical Care Medicine, The First People's Hospital of Zhengzhou, Zhengzhou 450052, China

[3] Department of Medical Affair, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China

[4] Department of Emergency Intensive Care Unit, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, China

Abbreviations

AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AUCs	Areas under the receiver operating characteristics curve
COPD	Chronic obstructive pulmonary disease
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
FEV1	Forced expiratory volume in the first second
FEV1%pred	Forced expiratory volume in the first second as a percentage of the predicted value
FVC	Forced vital capacity
IL	Interleukin
PCT	Procalcitonin
ROC	Receiver operating characteristics

sCD14	Cluster of differentiation 14
sCD14-ST	Cluster of differentiation 14 subtype
WBC	White blood cell count

1 Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic lower respiratory diseases. COPD is a preventable and treatable disease characterized by persistent airflow restriction [1]. The incidence and mortality rate of COPD have been increasing in recent years, largely due to rapid industrialization and environmental pollution. Zhong N et al. surveyed 20,000 adults from 7 different regions in China and reported a COPD incidence of 8.2% among females and males aged 40 and older [2]. This, in addition to an annual COPD-related mortality of 1 million results in significant economic and healthcare burdens in China [3].

Acute exacerbation of COPD (AECOPD) is characterized by a sudden worsening of symptoms, such as dyspnea, cough, and expectoration, requiring prompt changes in treatment strategy [1]. AECOPD often leads to frequent intensive care unit admissions and increases the risk of death [4]. Therefore, an early accurate diagnosis of AECOPD and timely intervention are critical for proper patient management and recovery.

During a microbial infection of the lungs, many inflammatory cells such as neutrophils, macrophages, and lymphocytes, secrete inflammatory mediators that contribute to the emergence of COPD [1]. Cluster of differentiation 14 (CD14), a gram-negative bacterial endotoxin lipopolysaccharide (LPS)-binding protein and pattern recognition receptor, is mainly expressed by granulocytes and monocytes/macrophages. CD14 plays a key role in the response to gram-negative bacterial infection and leads to an inflammatory cascade response [5]. CD14 has two isoforms, a membrane-bound CD14 (mCD14) and a soluble CD14 (sCD14). Whether sCD14 is associated with COPD remains unclear. Hollander C et al. [6] found that in patients with COPD or asthma, the concentration of sCD14 was higher in serum than in alveolar lavage fluid and that there was no difference in sCD14 levels between the two diseases. Soluble CD14 subtype (sCD14-ST) is composed of an N-terminal fragment of sCD14 hydrolyzed by cathepsin-D, namely presepsin [7]. Several studies have shown that sCD14-ST is an effective inflammatory marker that may signal the severity and prognosis of sepsis with greater sensitivity and specificity than other inflammatory markers, such as procalcitonin (PCT), C-reactive protein (CRP), or interleukin (IL)-6 [8–13]. However, the role of plasma sCD14-ST in COPD has not been addressed. Therefore, we designed this study to test the utility of plasma sCD14 and sCD14-ST in diagnosing COPD and predicting AECOPD.

2 Methods

2.1 Subjects

For this study, COPD patients admitted into the First Affiliated Hospital of Zhengzhou University and the First People's Hospital of Zhengzhou from June 2018 to January 2021 were recruited. Inclusion criteria were as follows: the diagnosis of COPD (stable COPD and AECOPD) met the diagnostic criteria of the global strategy for diagnosis, treatment and prevention of COPD [1]. Regardless of gender, patients were 18–75 years of age with forced expiratory volume in the first second (FEV1)/forced vital capacity (FVC) < 70% after inhalation of bronchodilator and negative bronchial dilation test. Exclusion criteria were as follows: patients with bronchiectasis, bronchial asthma, pulmonary tuberculosis, diffuse pulmonary interstitial fibrosis, lung cancer, and other diseases were excluded. Pregnant women and patients with mental disorder were also excluded. Healthy 18–75 years old subjects, without a history of respiratory or systemic diseases, with normal chest X-ray image and normal spirometry values were included.

The study was approved by the Ethics Committees of the First Affiliated Hospital of Zhengzhou University and the First People's Hospital of Zhengzhou (2018–21). Informed consent was obtained from each individual. All participants underwent spirometry and bronchodilation tests. Venous blood samples were obtained at 24 h following admission and used to quantify plasma inflammatory markers including white blood cell count (WBC), CRP, and erythrocyte sedimentation rate (ESR), IL-6, IL-8, sCD14, and sCD14-ST.

2.2 Spirometry Test

Spirometry test was performed before bronchodilation and 15 min after inhalation of salbutamol 400 μg through a metered-dose inhaler with a spacer using Masterscreen spirometers (Jaeger Co. Ltd, Hochberg, Germany) following the American Thoracic Society recommendations [14]. A positive test of reversibility was defined as an increase in FEV1 of > 12% and > 0.2 L. Lung function parameters including FEV1, FVC, forced expiratory volume in the first second as a percentage of the predicted value (FEV1%pred), and post-bronchodilator FEV1 were recorded.

2.3 Inflammatory Marker Assay

We used fasting venous blood to quantify the WBC and erythrocyte sedimentation rate (ESR) using routine clinical laboratory tests. The plasma PCT was detected on a Cobas 8000 system (Roche Diagnostics, Germany) and the CRP by immunoturbidimetry. Additional markers were

quantified in plasma using enzyme-linked immunoassays according to the manufacturer's instructions as follows: IL-6 (cloud clone Corp Kit, China), IL-8 (cloud clone Corp Kit, China), sCD14 (cloud clone Corp Kit, China), and sCD14-ST (Shanghai enzyme linked Biotechnology Co., Ltd Kit, China).

2.4 Statistical Analyses

Statistical analyses were performed using SPSS 23.0 software (SPSS, Inc., Chicago, IL, USA). The values were presented as mean ± SD or median (interquartile range) for continuous variables, and as numbers for categorical variables. Categorical variables were tested using the Chi-square or Fisher exact tests. Group comparisons for normally distributed continuous variables were conducted by using *t* tests. Non-normally distributed continuous variables were compared between the two groups using the Mann–Whitney U test. The correlation between sCD14 or sCD14-ST and other inflammatory markers was done by using Pearson rank correlation test for normally distributed data or the Spearman rank correlation test for abnormally distributed data. Whether sCD14 and sCD14-ST could be used to diagnose COPD and predict AECOPD was tested using receiver operating characteristics (ROC) curves. Two-tailed *P* values of < 0.05 were considered to indicate statistical significance.

3 Results

3.1 Clinical Characteristics

The clinical characteristics of the study cohort are shown in Table 1. A total of 62 individuals were recruited, including 15 controls and 47 COPD, the latter including 32 stable COPD and 15 AECOPD. There were no significant differences in age, sex, BMI, and smoking status between COPD, stable COPD, or AECOPD and control groups, and between stable COPD and AECOPD groups (all $P > 0.05$). The COPD group had lower FEV1, FVC, FEV1%pred, and post-bronchodilator FEV1 than controls ($P < 0.05$). The stable COPD group had lower FEV1, FEV1%pred, and post-bronchodilator FEV1 than controls ($P < 0.05$). The AECOPD group had lower FEV1, FVC, FEV1%pred, and post-bronchodilator FEV1 than the controls ($P < 0.05$). The AECOPD group also had lower FEV1 than the stable COPD group ($P < 0.05$).

3.2 Inflammatory Markers

There was no difference between COPD and control groups in CRP, ESR, PCT, or IL-6 levels ($P > 0.05$). The COPD group showed higher levels of WBC, IL-8, sCD14, and sCD14-ST than controls ($P < 0.05$). The stable COPD group had higher IL-8, sCD14, and sCD14-ST than controls

Table 1 Clinical characteristics of the study cohort

Clinical characteristics	Control group	COPD group	*P**	COPD	
				Stable COPD	AECOPD
Number	15	47	–	32	15
Age (years)	58.40 ± 11.20	62.77 ± 8.90	0.126	62.91 ± 9.83	62.47 ± 6.80
Females/males	7/8	25/22	0.660	16/16	9/6
BMI (kg/m^2)	23.64 ± 2.43	24.50 ± 4.20	0.454	24.68 ± 4.60	24.11 ± 3.31
Current smoking/previous smoking /no smoking (No.)	6/2/7	26/6/15	0.485	9/5/8	7/1/17
Duration (years)	–	8.90 ± 6.60	–	8.4 ± 7.00	10.37 ± 5.58
FEV1 (L)	2.75 ± 0.72	1.37 ± 0.60	**0.000**	1.41 ± 0.58[a]	0.83 (0.73–2.09)[a/b]
FVC (L)	3.36 ± 0.91	2.73 ± 0.93	**0.025**	2.81 ± 0.93	2.57 ± 0.93[a]
FEV1%pred	115.47 ± 12.96	52.24 ± 19.74	**0.000**	56.16 ± 18.94[a]	43.88 ± 19.39[a]
Post-bronchodilator FEV1 (L)	2.77 ± 0.73	1.45 ± 0.65	**0.000**	1.51 ± 0.61[a]	0.92 (0.82–2.09)[a]

All data are presented as mean ± SD or median (range) for continuous variables, or as numbers for categorical variables. All significance values are derived by using independent t tests, Mann–Whitney U tests, or Chi-square tests as indicated. $P < 0.05$ is considered statistically significant. Significant values are indicated in bold

AECOPD acute exacerbation of chronic obstructive pulmonary disease, *COPD* chronic obstructive pulmonary disease, *FEV1* forced expiratory volume in the first second, *FEV1%pred* first second forced expiratory volume as a percentage of the predicted value, *FVC* forced vital capacity

[a] $P < 0.05$ compared with control group

[b] $P < 0.05$ compared with stable COPD

*Comparison between the COPD versus control groups

($P < 0.05$). The AECOPD group had higher WBC, CRP, ESR, IL-6, IL-8, sCD14, and sCD14-ST than the stable COPD and control groups ($P < 0.05$). The levels of pre-treatment inflammatory markers in the study cohort are shown in Table 2.

3.3 Correlation Between sCD14 or sCD14-ST and Inflammatory Markers

In COPD, sCD14 was positively correlated with WBC (r = 0.557, $P = 0.000$), IL-8 (r = 0.666, $P = 0.000$), and sCD14-ST (r = 0.594, $P = 0.000$); sCD14-ST was positively correlated with WBC (r = 0.552, $P = 0.000$) and IL-8 (r = 0.619, $P = 0.000$). In stable COPD, sCD14 was positively correlated with IL-8 (r = 0.662, $P = 0.000$) and sCD14-ST (r = 0.513, $P = 0.003$); sCD14-ST was also positively correlated with IL-8 (r = 0.519, $P = 0.002$). In AECOPD, plasma sCD14 was positively correlated with WBC (r = 0.589, $P = 0.021$), CRP (r = 0.631, $P = 0.012$), IL-8 (r = 0.671, $P = 0.006$), and sCD14-ST (r = 0.718, $P = 0.003$); plasma sCD14-ST was positively correlated with WBC (r = 0.726, $P = 0.002$), IL-6 (r = 0.611, $P = 0.015$), and IL-8 (r = 0.754, $P = 0.001$). The results of correlation tests are shown in Table 3.

3.4 sCD14 and sCD14-ST in Diagnosing COPD and Predicting AECOPD

sCD14 and sCD14-ST discriminated COPD from controls, with respective sensitivities of 78.72% and 89.36%, and specificities of 60.00% and 66.67%. The associated

Table 3 Correlation between inflammatory markers and sCD14 or sCD14-ST in each group

Group	sCD14		sCD14-ST	
	r	*P*	r	*P*
COPD				
WBC ($\times 10^9$/L)	0.557	**0.000**	0.552	**0.000**
IL-8 (pg/ml)	0.666	**0.000**	0.619	**0.000**
sCD14-ST (ng/ml)	0.594	**0.000**	–	–
sCD14 (ng/ml)	–	–	0.594	**0.000**
Stable COPD				
IL-8 (pg/ml)	0.662	**0.000**	0.519	**0.002**
sCD14-ST (ng/ml)	0.513	**0.003**	–	–
sCD14 (ng/ml)	–	–	0.513	**0.003**
AECOPD				
WBC($\times 10^9$/L)	0.589	**0.021**	0.726	**0.002**
CRP (mg/L)	0.631	**0.012**	0.477	0.072
ESR (mm/h)	0.345	0.208	0.204	0.466
IL-6 (pg/ml)	0.359	0.188	0.611	**0.015**
IL-8 (pg/ml)	0.671	**0.006**	0.754	**0.001**
sCD14-ST (ng/ml)	0.718	**0.003**	–	–
sCD14 (ng/ml)	–	–	0.718	**0.003**

To determine the relationship between inflammatory markers and sCD14 or sCD14-ST in COPD, stable COPD, and AECOPD groups, data are subjected to Pearson or Spearman rank correlation test. $P < 0.05$ is considered statistically significant. Significant values are indicated in bold

AECOPD acute exacerbation of chronic obstructive pulmonary disease, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *IL* interleukin, *sCD14* cluster of differentiation 14, *sCD14-ST* cluster of differentiation 14 subtype, *WBC* white blood cell count

Table 2 The levels of pre-treatment inflammatory markers in the study cohort

Inflammatory index	Control group	COPD group	*P**	COPD	
				Stable COPD	AECOPD
Number	15	47	–	32	15
WBC ($\times 10^9$/L)	5.80 ± 1.45	7.50 (6.00–9.80)	**0.001**	6.78 ± 1.89	10.02 (8.70–13.43)[a/b]
CRP (mg/L)	2.66 ± 1.84	3.43 (1.04–21.74)	0.155	2.29 (0.77–4.10)	87.71 ± 81.38[a/b]
ESR (mm/h)	8.60 ± 2.97	12.00 (6.00–39.00)	0.090	8.50 (4.25–12.00)	47.47 ± 26.20[a/b]
PCT (ng/ml)	0.03 (0.02–0.05)	0.04(0.03–0.06)	0.105	0.04(0.02–0.06)	0.05 (0.04–0.08)
IL-6 (pg/ml)	16.24 ± 2.09	16.52 (14.42–23.76)	0.243	17.54 ± 4.50	26.97 (16.05–32.11)[a/b]
IL-8 (pg/ml)	25.64 (20.70–30.58)	41.38 (30.89–60.53)	**0.000**	39.58 ± 13.66[a]	78.43 (34.28–162.72)[a/b]
sCD14 (ng/ml)	2.44 ± 1.17	4.58 ± 2.36	**0.000**	4.01 ± 2.09[a]	5.80 ± 2.51[a/b]
sCD14-ST (ng/ml)	5.98 (2.34–19.64)	18.57 (15.27–20.17)	**0.007**	16.89 ± 3.94[a]	19.57 (18.14–21.57)[a/b]

All data are presented as mean ± SD or median (range) for continuous variables. All significance values are derived by using independent t tests or Mann–Whitney U tests. $P < 0.05$ is considered statistically significant. Significant values are indicated in bold

AECOPD acute exacerbation of chronic obstructive pulmonary disease, *COPD* chronic obstructive pulmonary disease, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *IL* interleukin, *PCT* procalcitonin, sCD14 = cluster of differentiation 14, sCD14-ST = cluster of differentiation 14 subtype, WBC = white blood cell count

[a] $P < 0.05$ compared with control group

[b] $P < 0.05$ compared with stable COPD

*Comparison between the COPD versus control groups

areas under the ROC curve (AUCs) were 0.765 (95% CI 0.648–0.883) and 0.735 (95% CI 0.537–0.933), respectively. sCD14 and sCD14-ST discriminated stable COPD from controls with respective sensitivities of 75.00% and 87.50%, specificities of 60.04% and 66.68%, AUCs of 0.720 (95% CI 0.575–0.864) and 0.717 (95% CI 0.509–0.925). sCD14 and sCD14-ST discriminated AECOPD from controls with respective sensitivities of 80.00% and 86.67%, specificities of 73.33% and 67.00%, AUCs of 0.862 (95% CI 0.714–1.000) and 0.773 (95% CI 0.587–0.960). sCD14 and sCD14-ST discriminated AECOPD from stable COPD with respective sensitivities of 73.33% and 73.00%, specificities of 62.50% and 65.63%, and AUCs of 0.705 (95% CI 0.535–0.876) and 0.714 (95% CI 0.552–0.875). Meanwhile, there was no significant difference in AUCs between sCD14 and sCD14-ST in discriminating between COPD, or stable COPD, AECOPD and healthy controls ($P > 0.05$). The results of the ROC curve analyses are shown in Fig. 1.

4 Discussion

sCD14 is an acute-phase reactive protein that is released into the blood directly by monocytes/macrophages and neutrophils. Upon binding to the Toll-like receptor 4, sCD14 mediates the endotoxin-induced signal, sequentially activating a series of downstream kinases, thereby inducing the production of a variety of pro-inflammatory cytokines. These include tumor necrosis factor (TNF)-α, interferon-γ, IL-1, IL-6, and IL-8 and can stimulate an inflammatory cascade reaction [15, 16]. Previous studies have shown that sCD14 is associated with lupus erythematosus [17], sepsis [18, 19], acute respiratory distress syndrome [20], sarcoidosis [21], and asthma [22]. In the circulation, sCD14-ST is produced by proteolytic cleavage of sCD14, beginning to increase around two hours after the inflammatory stimulus and peaking at around three hours. In patients with infectious diseases, serum sCD14-ST levels might be higher than PCT and CRP, and its increase can persist for around one week [9]. sCD14-ST, combined with other inflammatory indicators such as WBC, CRP, and PCT, might provide a better predictor for 30-day sepsis mortality [23]. Therefore, sCD14 and sCD14-ST are important biomarkers for predicting the severity of sepsis and infectious diseases.

COPD is classified into stable and acute exacerbation stages. Respiratory tract infections are important risk factors for COPD, and their severity closely correlates with COPD prognosis [24]. Previous studies have shown that WBC, CRP, and fibrinogen can predict the risk of AECOPD development, and are correlated with decreased pulmonary function [25, 26]. In our study, we showed that COPD had higher WBC, IL-8, sCD14 and sCD14-ST than controls. This suggests that inflammatory markers, such as those identified in our study, could be an important component of COPD pathophysiology, and that sCD14 and sCD14-ST might serve as new therapeutic targets. Previous studies have demonstrated plasma inflammatory markers IL-6 and IL-8 were increased in patients with COPD [27–29]. Contrary to previous study [27], the stable COPD group did not show higher plasma IL-6 levels than controls. This may be related to the mild clinical status of the stable COPD patients. We also showed that sCD14 and sCD14-ST levels were significantly higher in stable COPD than in controls and that levels of sCD14 and sCD14-ST were positively correlated with IL-8. sCD14 and sCD14-ST levels were significantly higher in AECOPD than in stable COPD and controls; sCD14 was positively correlated with WBC, CRP, IL-8, and sCD14-ST, and sCD14-ST positively correlated with WBC, IL-6, and IL-8. We also showed that in stable COPD and AECOPD groups, plasma sCD14 was related to sCD14-ST level; this is likely because sCD14-ST is a metabolite of sCD14. Finally we showed that plasma sCD14 and sCD14-ST could discriminate stable COPD and AECOPD from controls, and strongly discriminated AECOPD from the stable COPD group with higher sensitivity but lower specificity. Together, our results suggest that plasma sCD14 and sCD14-ST levels might be used as surrogate markers for the diagnosis of COPD or AECOPD.

Pulmonary function tests are important in the diagnosis of COPD. Levan TD et al. [30] reported that decreased pulmonary function in agricultural workers with COPD was associated with sCD14. However, we found no correlation between pulmonary function in patients with COPD and sCD14 or sCD14-ST levels. It remains unknown whether sCD14 and sCD14-ST can be used to measure the extent of pulmonary impairment in COPD patients.

There were some limitations of this study. First, our modeling utilized simple approaches that included inflammatory biomarkers but we did not attempt more complex modeling that included clinical parameters such as symptoms and lung function. Second, we believe that given the study sample size this would have resulted in model overfitting and such results might not have been generalizable. In addition, although our results have provided potentially important biomarkers of COPD, the relatively small sample sizes require additional clinical verification. Finally, we did not attempt to longitudinally profile these inflammatory markers, especially before and after therapy. Therefore, future studies should test whether sCD14 and sCD14-ST levels are responsive to the usage of antibiotics, bronchodilator, and glucocorticoid drugs.

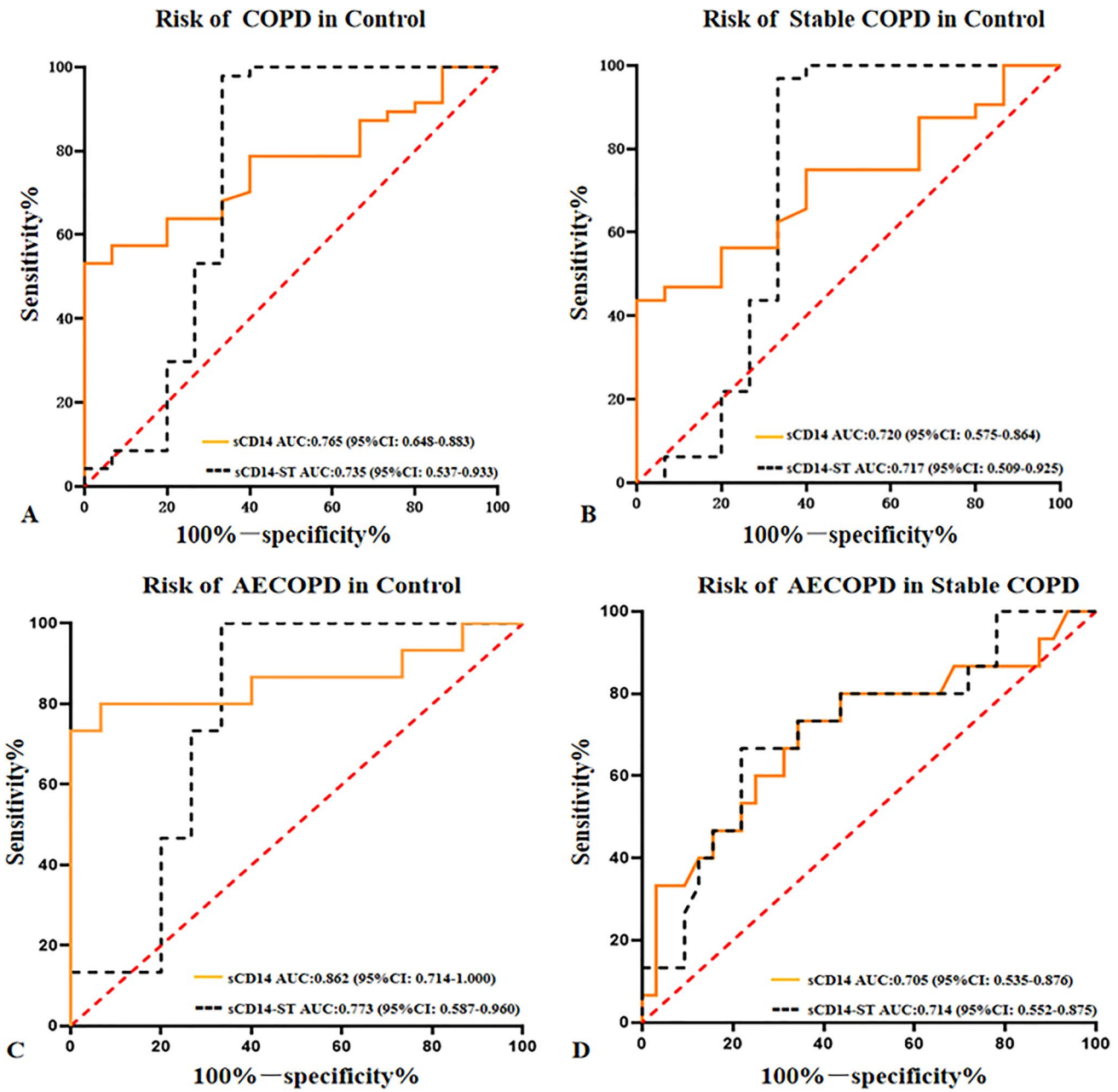

Fig. 1 ROC curves of sCD14 and sCD14-ST predicting COPD, stable COPD and AECOPD. **A** The sCD14 and sCD14-ST predicted COPD from the control group, with areas under the receiver operating characteristics curve (AUCs) of 0.765 (95% CI 0.648–0.883) and 0.735 (95% CI 0.537–0.933) respectively. **B** The sCD14 and sCD14-ST predicted stable COPD from the control group with AUCs of 0.720 (95% CI 0.575–0.864) and 0.717 (95% CI 0.509–0.925) respectively. **C** The sCD14 and sCD14-ST predicted AECOPD from the control group with AUCs of 0.862 (95% CI 0.714–1.000) and 0.773 (95% CI 0.587–0.960) respectively. **D** The sCD14 and sCD14-ST predicted AECOPD from stable COPD with AUCs of 0.705 (95% CI 0.535–0.876) and 0.714 (95% CI 0.552–0.875), respectively

5 Conclusion

In summary, plasma inflammatory markers sCD14 and sCD14-ST might play an important role in the diagnosis of COPD and prediction of AECOPD.

Acknowledgements We thank EditSprings (https://www.editsprings.com) for its linguistic assistance during the preparation of this manuscript.

Author Contributions RZ and GS conceived and designed the study. RZ, GS, ZX, YB, and HP gathered and analyzed the data, and wrote the

paper. RZ, GS, ZX, YB, HP, YG, YH, XZ, and LZ critically reviewed and validated the final version of the manuscript.

Funding This work was supported by the Medical Science and Technology Research Program of Henan Province (No. 2018020726 and LHGJ20190226).

Data Availability All data are fully available without restriction.

Declarations

Conflict of Interest The authors declare that they have no competing interests.

Ethical Approval This study was approved by the Ethics Committees of the First Affiliated Hospital of Zhengzhou University and the First People's Hospital of Zhengzhou.

Trial ChiCTR1900022900 (April 30, 2019) registered.

References

1. Singh D, Agusti A, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease: the GOLD science committee report 2019. Eur Respir J. 2019;53(5):1900164.
2. Zhong N, Wang C, Yao W, Chen P, Kang J, Huang S. Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. Am J Respir Crit Care Med. 2007;176(8):753–60.
3. Chinese center for disease control and prevention. Report on chronic disease in China. 2006. 5[EB/OL]. http://www.gov.cn/gzdt/2006-05/12/content_279061.htm. Accessed 12 May 2006.
4. Morantes-Caballero JA, Fajardo Rodriguez HA. Effects of air pollution on acute exacerbation of chronic obstructive pulmonary disease: a descriptive retrospective study (pol-AECOPD). Int J Chron Obstruct Pulmon Dis. 2019;14:1549–57.
5. Litvack ML, Palaniyar N. Soluble innate immune pattern-recognition proteins for clearing dying cells and cellular components:implications on exacerbating or resolving inflamm ation. Innate Immun. 2010;16(3):191–200.
6. Hollander C, Sitkauskiene B, Sakalauskas R, Westin U, Janciauskiene SM. Serum and bronchial lavage fluid concentrations of IL-8, SLPI, sCD14 and sICAM-1 in patients with COPD and asthma. Respir Med. 2007;101(9):1947–53.
7. Mussap M, Noto A, Fravega M, Fanos V. Soluble CD14 subtype presepsin (sCD14-ST) and lipopolysaccharide binding protein (LBP) in neonatal sepsis: new clinical and analytical perspectives for two old biomarkers. J Matern Fetal Neonatal Med. 2011;24:12–4.
8. Ali FT, Ali MA, Elnakeeb MM, Bendary HN. Presepsin is an early monitoring biomarker for predicting clinical outcome in patients with sepsis. Clin Chim Acta. 2016;460:93–101.
9. Chenevier-Gobeaux C, Borderie D, Weiss N, Mallet-Coste T, Claessens YE. Presepsin (sCD14-ST), an innate immune response marker in sepsis. Clin Chim Acta. 2015;450:97–103.
10. Li ZY, Zhao HJ, Zhao J, Chen B. The early diagnostic value and prognostic significance of serum presepsin(sCD14-ST) in patients with sepsis. Chin J Emerg Med. 2016;25(7):896–902.
11. Masson S, Caironi P, Fanizza C, Thomae R, Bernasconi R, Noto A, et al. Circulating presepsin (soluble CD14 subtype) as a marker of host response in patients with severe sepsis or septic shock: data from the multicenter, randomized ALBIOS trial. Intensive Care Med. 2015;41(1):12–20.
12. Káňová M, Dobiáš R, Liszková K, Frelich M, Ječmínková R, Kula R. Presepsin in the diagnostics of sepsis. Vnitr Lek. 2019;65(7–8):497–505.
13. Behnes M, Bertsch T, Lepiorz D, Lang S, Trinkmann F, Brueckmann M, et al. Diagnostic and prognostic utility of soluble CD 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment. Crit Care. 2014;18(5):507.
14. Miller MR, Hankinson J, Brusasco V, Burgos F, Wanger J. Standardisation of spirometry. Eur Respir J. 2005;26(2):319–38.
15. Jiang Y, Liu AH, Huang QB. p38 MAPK signal is necessary for TNF-alpha gene expression in RAW Cells. Acta Biochim Biophys Sin. 1999;31(1):9–15.
16. Schumann RR, Pfeil D, Lamping N, Kirschning C, Scherzinger G, Schlag P. Lipopolysaccharide induces the rapid tyrosine phosphorylation of the mitogen- activ ated protein kinases erk-1 and p38 in cultured human vascular endothelial cells requiring the presence of soluble CD14. Blood. 1996;87(7):2805–14.
17. Egerer K, Feist E, Rohr U, Pruss A, Burmester GR, Dörner T. Increased serum soluble CD14, ICAM-1 and E-selectin correlate with disease activity and prognosis in systemic lupus erythematosus. Lupus. 2000;9(8):614–21.
18. Burgmann H, Winkler S, Locker GJ, Presterl E, Laczika K, Staudinger T. Increased serum concentration of soluble CD14 is a prognostic marker in gram-positive sepsis. Clin Immunol Immunopathol. 1996;80(3):307–10.
19. Berner R, Fürll B, Stelter F, Dröse J, Müller HP, Schütt C. Elevated levels of lipopolysaccharide-binding protein and soluble CD14 in plasma in neonatal early-onset sepsis. Clin Diagn Lab Immunol. 2002;9(2):440–5.
20. Martin TR, Rubenfeld GD, Ruzinski JT, Goodman RB, Steinberg KP, Leturcq DJ, et al. Relationship between soluble CD14, lipopolysaccharide binding protein, and the alveolar inflammatory response in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 1997;155(3):937–44.
21. Striz I, Zheng L, Wang YM, Pokorná H, Bauer PC, Costabel U. Soluble CD14 is increased in bronchoalveolar lavage of active sarcoidosis and correlates with alveolar macrophage membrane-bound CD14. Am J Respir Crit Care Med. 1995;151(2):544–7.
22. Dubin W, Martin TR, Swoveland P, Leturcq DJ, Moriarty AM, Tobias PS, et al. Asthma and endotoxin: lipopolysaccharide-binding protein and soluble CD14 in bronchoalveolar compartment. Am J Physiol. 1996;270(5):L736–44.
23. Kim H, Hur M, Moon HW, Yun YM, Di Somma S, Great Network. Multi-marker approach using procalcitonin, presepsin, galectin-3, and soluble suppression of tumorigenicity 2 for the prediction of mortality in sepsis. Ann Intensive Care. 2017;7(1):27.
24. Chang C, Zhu H, Shen N, Chen Y, He B, Zhao J, et al. Bacterial infection, airway and systemic inflammation and clinical outcomes before and after treatment of AECOPD, a longitudinal and cross-sectional study. COPD. 2015;12(1):19–30.

25. Thomsen M, Ingebrigtsen TS, Marott JL, Dahl M, Lange P, Vestbo J, et al. Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. JAMA. 2013;309(22):2353–61.
26. Gammal AIE, Farrell RO, Mahony LO, Shanahan F, Killian K, Connor TO. Systemic inflammatory markers and disease severity in chronic obstructive pulmonary disease—the effect of acute exercise and pulmonary rehabilitation. Open J Respir Dis. 2015;5(1):19–31.
27. Yanbaeva DG, Dentener MA, Spruit MA, Houwing-Duistermaat JJ, Kotz D, Passos VL, et al. IL6 and CRP haplotypes are associated with COPD risk and systemic inflammation: a case-control study. BMC Med Genet. 2009;10:23.
28. Vernooy JH, Küçükaycan M, Jacobs JA, Chavannes NH, Buurman WA, Dentener MA, et al. Local and systemic inflammation in patients with chronic obstructive pulmonary disease: soluble tumor necrosis factor receptors are increased in sputum. Am J Respir Crit Care Med. 2002;166(9):1218–24.
29. Shaker SB, Von Wachenfeldt KA, Larsson S, Mile I, Persdotter S, Dahlbäck M, et al. Identification of patients with chronic obstructive pulmonary disease (COPD) by measurement of plasma biomarkers. Clin Respir J. 2008;2(1):17–25.
30. Levan TD, Smith LM, Heires AJ, Mikuls TR, Meza JL, Weissenburger-Moser LA, et al. Interaction of CD14 haplotypes and soluble CD14 on pulmonary function in agricultural workers. Respir Res. 2017;18(1):49.