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Comparative Study on Soluble Urokinase-Type Plasminogen Activator Receptor (SuPAR) and C-Reactive Protein (CRP) Levels in Stable Chronic Obstructive Pulmonary Disease

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Chronic obstructive pulmonary disease (COPD) is characterized by a progressive and irreversible airflow limitation. In COPD, the initial low-grade pulmonary inflammation slowly progress to systemic inflammation which is usually confirmed by non-specific inflammatory biomarker like C-reactive protein (CRP). However, the disease progress can be diagnosed at the early stage of pulmonary inflammation by using a novel biomarker, like Soluble urokinase-type plasminogen activator receptor (suPAR) released from the respiratory epithelium in COPD. The objective of this study was to compare the serum levels of suPAR and CRP in stable COPD and to assess the progress of low-grade pulmonary inflammation in COPD. Stable COPD [SCOPD] study participants (male-35; female-15) and healthy controls (male-38; female-12) were recruited for the study after obtaining informed consent. Based on post-bronchodilator FEV1% predicted values as specified by GOLD criteria, SCOPD study participants were graded into grades I-IV. Serum suPAR and CRP assays were done for all the study participants. The level of suPAR among SCOPD grades I-IV (4.03±0.40 ng/ml; 5.16 ±0.26 ng/ml; 5.82±0.17ng/ml; 6.39±0.07ng/ml respectively) were high compared to healthy control (1.84±0.90ng/ml) and was statistically significant. The level of CRP among SCOPD grade I-IV (3.30±0.13 ng/ml; 3.60 ±0.09 ng/ml; 3.91±0.12ng/ml; 4.41±0.10 ng/ml respectively) were high compared to healthy control (1.63±0.77ng/ml) and was statistically significant. Our study indicated that serum suPAR and CRP may play an important role in the inflammatory process of COPD particularly in grades III and IV SCOPD. Hence, serum suPAR and CRP measurements may be useful for the evaluation and prognosis of stable COPD.

Keywords: Biomarker; COPD; Inflammation; Pulmonary; suPAR.

Chronic Obstructive Pulmonary Disease (COPD) occurs due to inflammatory lung response characterised by progressive airflow obstruction.[1,2] Lung parenchymal destruction with decrease in mucociliary clearance (MCC) and phagocytic activity of alveolar macrophages occurs leading to an increased risk of exacerbation. This alteration in the lung defence mechanism and oxidative stress can lead to mortality among exposed due to COPD[3-7].

Conventionally, the diagnosis for SCOPD was by clinical symptoms and pulmonary function test (PFT). However, there is a need for a better tool to monitor prognosis of COPD. In the ECLIPSE cohort studies for COPD, previous exacerbation, older age, increased WBC count and poor health status were associated with increased risk of future hospitalization. Various biomarkers like C-reactive protein (CRP) and fibrinogen have been assessed to know the association of disease severity and mortality risk among COPD patients. Recent systematic review has showed that CRP was consistently elevated in COPD patients compared with control groups. However, these routine non-specific markers are not reliable for assessing disease mortality and prognosis.

Recent studies have shown that suPAR is a more stable biomarker for low-grade pulmonary inflammation. The cleavage of urokinase plasminogen activator receptor (uPAR) from the inflamed respiratory epithelium into suPAR, reflects the pathogenesis (both small airway fibrosis and emphysema) of COPD through complex molecular pathways and gene expression patterns. Assessment of serum suPAR reflects lung function impairment during acute exacerbation and for monitoring treatment response..[5,8,9]

Hence, this study was conducted to compare the serum levels of suPAR and CRP in stable COPD study participants in order to assess the progress of low-grade pulmonary inflammation in COPD.

Aim

To assess and compare the serum soluble urokinase-type plasminogen activator receptor (suPAR) and C-reactive protein (CRP) levels in stable COPD.

METHODOLOGY

After obtaining IEC clearance Institutional Ethics Committee [IEC-NI/17/JUN/60/59], this cross- sectional study was carried out in a private medical college hospital in Puducherry, South India among stable COPD study participants. SCOPD study participants (n=50) with history of dyspnoea, chronic cough and sputum production for a period of 3 months for 2 consecutive years and apparently healthy controls (n=50) aged between 35-65 years inclusive of both sexes were included in the study based on the selection criteria after getting informed consent. Subjects with history of bronchial asthma, bronchiectasis, cystic fibrosis, collagen tissue disease, cirrhosis of liver and renal failure with conditions that could affect serum suPAR and CRP levels were excluded from the study. General information such as age, gender, occupation, literacy status, smoking status and socio-economic status were collected using a standard questionnaire. Study participants were subjected to spirometry and post-bronchodilator testing and were then grouped into grades I - IV as per Global Initiative for Obstructive Lung Disease (GOLD) criteria[10]. Blood samples were collected from the study participants and serum suPAR and CRP levels were measured using Abcam's Human

Table 1. Descriptive characteristics of the study population

Descriptive characterisitics		Control N(%)	SCOPD N(%)
Age (years)	35-55	29(58%)	34(68%)
	55-65	21(42%)	16(32%)
Gender	Male	38(76%)	35(70%)
	Female	12(24%)	15(30%)
BMI (Kg/m^2)	Underweight/Healthy	39(78%)	37(74%)
	Overweight	5(10%)	8(16%)
	Obese	6(12%)	5(10%)
Occupation	Unemployed/ Semi-skilled	45(90%)	44(88%)
	Skilled	5(10%)	6(12%)
Education status	Illiterate	44 88%	45(90%)
	Literate	6(12%)	5(10%)
Smoking status	Smoker/Ex-smokers	40(80%)	5(10%
	Non-smoker	10(20%)	45(90%)

ELISA (Enzyme- Linked Immunosorbent Assay) kit.[11]

Statistical Analysis

Results were tabulated in EXCEL and data analysis was done by using SPSS software version 20.0. The difference between control group and different grades of SCOPD were analysed using ANOVA.

RESULTS

The present cross-sectional study was conducted among 50 SCOPD study participants and 50 apparently healthy controls with age group 35 to 65 years. The distribution of study participants based on age, gender, occupation, literacy status, socio-economic and smoking status is shown in Table 1.

Table 2 shows Mean ± SD for Pulmonary function parameters like Forced expiratory volume in the 1st second (FEV1% predicted), Forced Vital Capacity (FVC), FEV1/FCV ratio, peak expiratory flow rate (PEFR) for control group and mean ± SD for post-bronchodilator parameters like FEV1% predicted, FVC, FEV1/FVC ratio and for SCOPD participants.

Table 3 represents Mean ± SD values for serum suPAR and CRP level among different SCOPD grades and controls. It was observed that levels of suPAR and CRP among SCOPD were high compared to healthy control. In addition, Serum suPAR and CRP levels were high among GOLD IV and III compared to GOLD II and I ,which was statistically significant (p=0.000)

Table 2. Pulmonary function test parameters of the study participants

PFT parameters (% prediced values)	Controls (n=50) (mean±SD)	SCOPD (N=50) (mean±SD)
FEV1	85.56±1.82	49.3±17.81
FVC	107.16±3.44	86±19.82
FEV1/FVC	79.54±2.27	57.64±10.64
PEFR	85.72±1.77	43.78±15.7

DISCUSSION

This cross-sectional study which involved SCOPD participants (grade I to IV) and healthy controls showed that the plasma suPAR level was higher among SCOPD grade III and IV compared to grade I and II. This indicates the role of urokinase plasminogen activator system in lung parenchymal destruction and small airway fibrosis. Similar finding has been reported by Can U et al., who observed that serum suPAR was high among grade III and IV than grade I,II and control groups [12]

Moreover, the raised suPAR level in SCOPD participants in our study could be due to increased expression of suPAR in the small airway epithelia and pulmonary epithelial-mesenchymal transition process among SCOPD patients which lead to disease progression and it could also be due to increased expression of urokinase plasminogen activator receptor in the small airway epithelia of SCOPD patients which contributes for the airflow limitation due to activation of inflammatory immune response. Similar finding is reported by a study done by Wang et al.,and Godtfredsen et al., which shows suPAR level was higher among grade IV SCOPD when compared to grade I-III and normal subjects[13,14]. Besides, studies done by Prins HJ and AboEl-Magd GH have also shown that serum suPAR was high among SCOPD than normal individuals due to activation of pulmonary inflammation.[15,16]

Table 3. Comparison of Serum suPAR level and CRP among different grades of SCOPD and control participants

Serum biomarker	Control (mean±SD)	GOLD stage classification of COPD (mean±SD) I (n=4)	II(n=15)	III(n=26)	IV(n=5)	p value
suPAR (ng/ml)	1.84 ± 0.90	4.03 ± 0.40	5.16 ± 0.26	5.82 ± 0.17	6.39 ± 0.07	0.000*
CRP (ng/ml)	1.63 ± 0.77	3.30 ± 0.13	3.60 ± 0.09	3.91 ± 0.12	4.41 ± 0.10	0.000*

* $p<0.05$

- Statistically significant

In this study, it was observed that CRP levels were also elevated in SCOPD study participants when compared to the controls. Similar observation was reported in a study which indicated CRP as a promising diagnostic marker among SCOPD.[17] Study done by Al-Aarag et al.,and and Zhang et al.,also found a significant difference between the COPD and the control group in relation to the CRP level which was similar to our study results. [18,19]

Systematic review done by few researchers confirmed that CRP levels increases in patients with stable COPD among different grades with decline in lung function.[20,21] Yende S et al., and Broekhuizen R et al., also observed that the CRP level was high among SCOPD than normal individuals and the difference was statistically significant.[22,23] In a study done by Sever ZK et al., it was reported that serum CRP and suPAR levels were high among COPD patients which suggested that they have significant roles in systemic inflammation associated with worse prognosis and severity.[24]

Similarly, meta-analysis has shown that serum suPAR was high among grade IV compared to grade I and the level of suPAR correlated with diseases severity hence suPAR was suggested to be used clinically to monitor COPD patients on treatment and their prognosis.[25] In addition suPAR is a very stable biomarker when compared to CRP, less affected by the exacerbation and directly related to disease severity which favours its high prognostic value for COPD.[26]

Limitation of the Study

Drug intervention with novel anti-inflammatory therapy and follow up for lung function decline was not done to rule out ongoing pulmonary inflammation among stable COPD patients.

CONCLUSION

The study results support that suPAR and CRP can be used as surrogative biomarker to predict the inflammatory changes among COPD patients. suPAR seems to be independent, stable biomarker when compared to CRP, less affected by the exacerbation and is better than CRP in discriminating adverse outcome and severity progression. Further, prospective studies need to be conducted to explore whether suPAR can be used as a novel biomarker in predicting the severity of SCOPD in the early stages of disease

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Conflict of Interest

None.

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REFERENCES

1. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med.*; **195**(5):557-82 (2017).
2. Wedzicha JA, Mackay AJ, Singh R. COPD exacerbations: impact and prevention. *Breathe*.; **9**(6):434-40 (2013).
3. Soriano JB. An Epidemiological overview of chronic obstructive pulmonary disease: What can real-life data tell us about disease management? *COPD J Chronic Obstr Pulm Dis*.;**14**(S1):S3-S7 (2017).
4. Dicker AJ, Crichton ML, Pumphrey EG, et al. Neutrophil extracellular traps are associated with disease severity and microbiota diversity in patients with chronic obstructive pulmonary disease. *J Allergy Clin Immunol.*; **141**(1):117-27 (2018).
5. Suberviola B, Castellanos A, Ruiz Ruiz A. Hospital mortality prognostication in sepsis using the new biomarkers suPAR and proADM in a single determination on ICU admission. *Intensive Care Med*.; **39**(11):1945-52 (2013).
6. Pavord ID, Jones PW, Burgel PR, Rabe KF. Exacerbations of COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:21–30.Rasmussen LJH, Ladelund S, Haupt TH, Ellekilde G, Poulsen JH, Iversen K, et al. Soluble urokinase plasminogen activator receptor (suPAR) in acute care: a strong marker of disease presence and severity, readmission and mortality. A retrospective cohort study. *Emerg Med J*.; **33**:769–75 (2016).
7. Koller L, Stojkovic S, Richter B, Sulzgruber P, Potolidis C, Liebhart F, et al., Soluble urokinase-

type plasminogen activator receptor improves risk prediction in patients with chronic heart failure. *JACC Heart Fail.;* **5**:268–77 (2017).

8. Reilly JJ, Silverman EK, Shapiron SD. Chronic Obstructive Pulmonary disease. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editors. Harrison's principles of internal medicine. 19th edition. Newyork: The McGraw-Hill Companies.; (2):1700-7 (2015).
9. Mirza S, Clay RD, Koslow MA, Scanlon PD. COPD Guidelines: A Review of the 2018 GOLD Report. *Mayo Clin Proc.*; **93**(10):1488-1502 (2018)
10. Bocskei RM, Benczúr B, Losonczy G, Illyés M, Cziráki A, Müller V et al., Soluble Urokinase-Type Plasminogen Activator Receptor and Arterial Stiffness in Patients with COPD. *Lung.;* **197**(2):189-197 (2019).
11. Eugen-Olsen J. suPAR—a future risk marker in bacteremia. *J Intern Med.*; **270**(1):29–31 (2011).
12. Can U, Guzelant A, Yerlikaya FH, et al. The role of serum soluble urokinase-type plasminogen activator receptor in stable chronic obstructive pulmonary disease. *J Investig Med.;* **62**(7):938-43 (2014).
13. Wang Q, Wang Y, Zhang Y, Zhang Y, Xiao W. The role of uPAR in epithelial-mesenchymal transition in small airway epithelium of patients with chronic obstructive pulmonary disease. *Respir Res*.; **14**:67 (2013).
14. Godtfredsen NS, Jørgensen DV, Marsaa K, Ulrik CS, Andersen O, Eugen-Olsen J, Rasmussen LJH. Soluble urokinase plasminogen activator receptor predicts mortality in exacerbated COPD. *Respir Res.*; **19**(1):97 (2018).
15. Prins HJ, Duijkers R, van der Valk P, Schoorl M, Daniels JMA, van der Werf TS, Boersma WG. CRP-guided antibiotic treatment in acute exacerbations of COPD in hospital admissions. *Eur Respir J.;* **53**(5):1802014 (2019).
16. AboEl-Magd GH, Mabrouk MM. Soluble urokinase-type plasminogen activator receptor as a measure of treatment response in acute exacerbation of COPD. *J Bras Pneumol.;* **44**(1):36-41 (2018).
17. Huang Q, Xiong H, Shuai T, Wang Y, Zhang C, Zhang M et el.,. The clinical value of suPAR in diagnosis and prediction for patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Ther Adv Respir Dis.*; **14**:1-13 (2020).
18. Al-Aarag AH, Ismaeil Y, Mohammad AA. Study of Serum C-Reactive Protein Level in Patients with COPD. *Med. J. Cairo Univ.*; **80**(2):163-8 (2012).
19. Zhang M, LI Y, Zhang J, Zhang Q, Yang X, Shan H, Xie Y et al., Mean platelet volume is elevated in exacerbated and convalescent COPD patients. *Clinica Chimica Acta.*; **451**:227-31 (2015).
20. Mannino DM, Buist AS, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function?. *Thorax.;* **62**(3):237-41 (2007).
21. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax.*; **59**(7):574-80 (2004).
22. Hu Z, Wang J, Zhen J. Serum suPAR level in patients with AECOPD and its clinical diagnostic value. *J Modern Medicine;* **45**:33–37 (2017).
23. Stolz D, Meyer A, Rakic J, Boeck L, Scherr A, Tamm M. Mortality risk prediction in COPD by a prognostic biomarker panel. *Eur Respir J.* ; **44**:1557-70 (2014).
24. Yende S, Waterer GW, Tolley EA, Newman AB, Bauer DC, Taaffe DR, et al. Inflammatory markers are associated with ventilatory limitation and muscle dysfunction in obstructive lung disease in well functioning elderly subjects. *Thorax.*; **61**(1):10- 6 (2006).
25. Broekhuizen R, Wouters EF, Creutzberg EC, Schols AM. Raised CRP levels mark metabolic and functional impairment in advanced COPD. *Thorax.*; **61**(1):17-22 (2006).
26. Sever ZK, Bircan HA, Sirin FB, Evrimler S, Celik S, Merd N. Serum biomarkers in patients with stable and exacerbated COPD-bronchiectasis overlap syndrome. *Clin Respir J.*; **14**(11):1032-39 (2020).
27. Hu Z, Wang J, Zhen J. Serum suPAR level in patients with AECOPD and its clinical diagnostic value. *J Modern Medicine;* **45**:33–37 (2017).
28. Stolz D, Meyer A, Rakic J, Boeck L, Scherr A, Tamm M. Mortality risk prediction in COPD by a prognostic biomarker panel. *Eur Respir J.*; **44**: 1557-70 (2014).