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Original Research Article

Levels of Biomarkers PCT,CRP and Neopterin in COPD patients with exacerbations

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ABSTRACT

Background: The motive of this study was to establish the role of various circulating biomarkers in identification of etiology of exacerbation in COPD and assessment of prognosis of COPD on the basis of these biomarkers i.e PCT, CRP and neopterin.

Materials and Methods: In this study 200 patients of COPD were enrolled 36 in the stable state, 116 in the exacerbation phase and 48 with pneumonia. Serum sample was collected in all the groups at the time of inclusion in the study and after one month 20 samples were collected from the exacerbation group. Sputum culture, microbiological findings, biomarkers levels and clinical characteristics were compared in each group. PCT and CRP levels were measured by immunofluorescence assay and neopterin by competitive assay.

Results: Significant differences were observed in the three groups with regard to PCT and CRP being increased in pneumonic and exacerbation groups as compared to stable group. (P = 0.0001). For paired samples of 20 patients in the exacerbation group PCT and CRP levels were found to be decreased after a period of one month whereas neopterin was found to be increased. All the three biomarkers were increased in patients who died within a month as compared to patients who died later on.

Conclusions: Our results showed that biomarker levels vary with the clinical status of the patients and this helps in identification of the aetiology of exacerbation which therefore helps in better assessment of prognosis and management of COPD patients.

1. Introduction

COPD is the leading cause of death in the world. It is characterised by progressive and nearly irreversible blockage of the airway passage of the lungs. This pathological condition is due to systemic inflammatory response to outside pathogens like viral, bacterial, smoke and noxious gases.[1] Risk factors of COPD includes generalised inflammation, oxidative stress, sedentary lifestyle and many others.[2–5] Earlier smoking was considered as the major cause of this disorder but many studies have also suggested the importance of various inflammatory biomarkers in the pathology of this disease. Some of them linked with the progression of this disease are tumor necrosis factor-α (TNF-α), interleukin (IL-6), and C-reactive protein (CRP), neopterin and procalcitonin (PCT). However some of the studies done in the past had refuted the role of CRP linked with increased risk of development and progression of COPD. Hartley et al[6] showed the link of lower level of interleukin-6 with increased risk of COPD whereas other five studies showed lower or negligible level of TNF-α in cases of COPD. In 2004 Gan et al.,[7] analysed 14 studies done on the association of COPD with inflammatory markers and suggested that indeed these systemic inflammatory markers were associated with poor lung function. Tobacco smoking, etiology for acute

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exacerbation cannot be attributed to any factors. Prognosis of COPD can be assessed with FEV and BODE index, severity and frequency of exacerbations and level of various inflammatory markers in the serum routinely pulmonary biomarkers are measured in bronsputum and exhaled breath condensate, but these are invasive procedures subjected to high variability so nowadays global interest has been on to study the systemic inflammatory markers associated with COPD to assess severity and the prognosis.[8] In this study three systemic inflammatory markers were being studied in association with COPD i.e., procalcitoninneopterin and CRP.[8–10] PCT is a systemic and specific marker of bacterial infection, so measuring PCT helps to reduce unnecessary antibiotic prescriptions and it also correlates very well with the severity aetiology of pneumonia.[11–13] CRP is an acute phase reactant also associated with systemic chronic inflammatory conditions.[14] Neopterin is a marker for cellular immunity and used against intracellular pathogens and also predicts the lower respiratory tract infections very well, prognosis of COPD.[15–18] In this study these three biomarkers were used in COPD patients at three different stages, one in stable period, aetiology of exacerbations and also to assess the short-term and long term prognosis after exacerbations.

2. Materials and Methods

A total of 2 of January 2017 to December 2017 in K.D medical college and hospital and research center patients dignosedi espirometric (80%,FEV1,60%),,FEV,,4019].36 COPD patients who were clinically stable included, Acute symptoms defined as worsening dyspnea and color and patients requiring change in medication. Pneumonia defined by clinical presentation like fever, dysnoea chest[19,20] Sputum samples and blood culture for microscopic examination were collected and transported in cold medium to preserve the samples. Bacteriological culture were also done to identify the etiology.[21] 164 sputum samples from patients a with exacerbation and with pneumonia were taken and sent to micro lab Opolymorphonuclears.[22] Diagnosis was based on culture report.[23–25] All relevant data from the patients like age, gender, clinical., ts. After one year all the data exacerbationsand number Out of 116 exacerbation patients, 20 samples were collected after a month and stored–20°Ctill the biomarkers were measured.

3. Results

Statistical analysis was done using Mann-Whitney U test and kruskal-Wallis test, used to compare biomarker levels during exacerbation, stable period and pneumonia. For comparing results of 20 with second samples Wilcoxon matched paired test was done. Pearson's chi-square test was done to compare baseline characteristics between patient's groups and exacerbations patients according to sputum culture results.

Figure 1 shows the comparison of biomarkers in stable, exacerbation and during pneumonia groups. Levels of circulating biomarkers i.e., PCT and CRP showed significant differences in the three groups lower in clinically stable patients and higher in pneumonic patients (p=0.0001) but neopterin does not show any significant difference between the groups. When paired samples were compared within the subgroups after a period of one month both PCT (p= 0.0678) and CRP (p= 0.0171) were found while neoptrin levels were increased (p=0.0435) depicted in Figure 2.

Most frequently isolated pathogenic bacterias were gram negative accounting for 70% of all microorganism like (Haemo- philus influenzae, Pseudomonas aeruginosa, and Moraxella catarrhalis) whereas gram positives accounts for only 27.3% and fungal infections accounts for 2.7 % only being most common was aspergillus fumigates as shown in Table 1. However levels of three biomarkers shown no significant differences in gram results, PCT (P = 0.191), CRP (P = 0.080) and neopterin (P = 0.109).

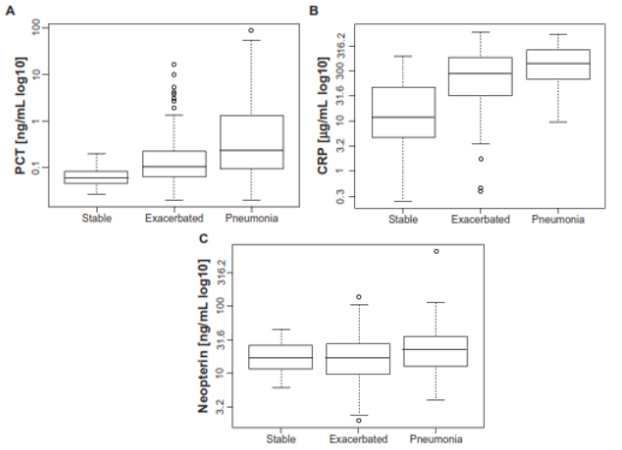

Fig. 1: Distribution of procalcitonin (PCT) (ng/mL) (A), C-reactive protein (CrP) (μg/mL) (B), and neopterin (ng/mL) (C) levels according to patient group. PCT levels during stable state, exacerbation, and pneumonia are as follows: 0.06 ng/mL (0.04–0.08), 0.10 ng/mL (0.06–0.22), and 0.24 ng/mL (0.1–1.32). CrP levels during stable state, exacerbation and pneumonia were as follows: 11.83 μg/mL (5.07–44.90), 88.66 μg/mL (31.69–184.5), and 140.4 μg/mL (67.1–252.5). neopterin levels during stable state, exacerbation, and pneumonia are as follows: 17.09 ng/mL (12.53–25.36), 17.43 ng/mL (9.85–27.84), and 22.26 ng/mL (13.31–35.34). Values of PCT and CRP showed significant differences among the 3 groups of patients (p , 0.0001), being lower during clinical stability. Neopterin did not show any significant differences.

Table 1: umber of isolates and levels of PCT, CRP, and neopterin according to the microorganism isolated

Microorganism isolated	Number Isolates (%)	PCT (ng/mL) median (IQR)	CRP (ng/mL) Median (IQR)	Neopterin (ng/mL) median (IQR)
Haemophilus influenzae	27 (35.6)	0.09 (0.08–0.14)	69.8 (23.89–160.9)	15.7 (8.34–23.19)
pseudomonas aeruginosa	14 (18.4)	0.11 (0.05–0.23)	78.75 (19.42–181.5)	15.02 (11.39–17.89)
Moraxella catarrhalis	9 (11.8)	0.07 (0.04–0.09)	77.63 (46.8–157.9)	9.87 (6.32–15.64)
enterobacteria	6 (7.9)	0.20 (0.07–0.44)	101.6 (27.83–364.92)	18.02 (12.89–30.17)
Streptococcus pneumoniae	15 (19.8)	0.14 (0.07–0.42)	133.4 (74.77285.97)	12.42 (6.8–20)
Staphylococcus aureus	2 (2.6)	0.44	307.95	10.83
Aspergillus fumigatus	2 (2.6)	0.15	172.73	16.81
Co-infection S. pneumoniae and H. influenzae	1 (1.3)	0.34	310.7	21.07

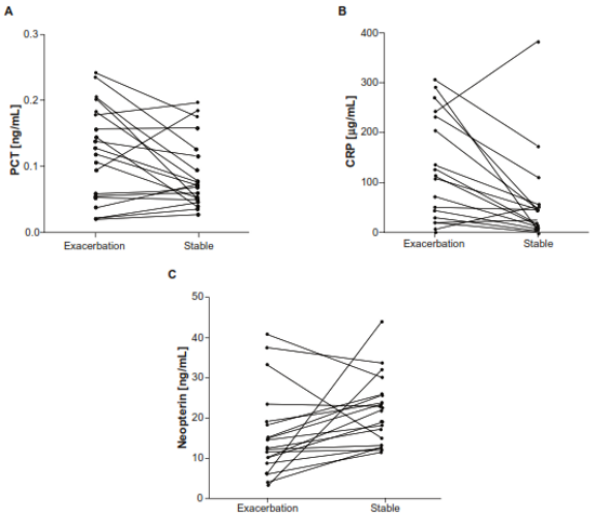

Fig. 2: Levels of procalcitonin (PCT) (ng/mL) (A), C-reactive protein (CrP) (μg/mL) (B) and neopterin (ng/mL) (C) for the 23 patients with 2 samples, the first collected during an exacerbation and the second collected 1 month later. each patient is represented individually. Levels of PCT (p =0.0678) and CrP (p=0.0171) decreased in one month. Neopterin levels increased significantly (p=0.0435).

4. Discussion

COPD is defined as a chronic inflammatory disorder which has systemic manifestations also. COPD patients constitutes a heterogeneous groups with various clinical manifestation. Several factors influence the prognosis of COPD patients. Circulating biomarkers specific for inflammation has been studied in this research work these biomarkers levels can be influenced by various factors like any co morbid condition,[26] smoking status, previous treatment, severity of COPD and influence of other medications. Our study focussed on these factors which can influence the levels of these biomarkers, interestingly smoking in our study does not influence the biomarkers levels statistically. But it was seen in other studies that PCT, Neopterin and CRP levels were low in ex-smokers and current smokers compared to non-smokers which emphasizes the fact that smoking does generates a low grade level of inflammatory response.[27,28] In some studies it was found that corticosteroids decreases the levels of these biomarkers.[26,29] We found the similar results in our study with PCT and neopterin. Both PCT and CRP showed significant differences in the three groups. PCT and CRP found to be increased during exacerbation as compared to stable condition.[30–32] But this increase was different in different individual patients owing to differences in the basal level of these biomarkers in stable condition. Moreover during exacerbation some parenchyma damage of the lungs happened which can go undetected by X-ray but increase of biomarkers levels can be detected without evidence of any parenchyma damage. Several factors influence the prognosis of COPD. Various biomarkers have been suggested to play an important role in assessing the prognosis of COPD.[30] In our study Neopterin and PCT shows significant relationship with the severity of COPD. Patients who died within the first month showed higher levels of both of these biomarkers. So it is reasonable to hypothesize the use of these biomarkers levels in routine measurement during exacerbation to identify the high risk patients in short duration to improve the prognosis and prevent the death.[33,34] Though the study has some limitation i.e the number of patients were small and duration of study was for only one year further studies are needed with with inclusion of some more novel markers copeptin, pro-adrenomedullin, and pro-atrial natriuretic peptide in combination with the classical ones.

5. Conclusion

This study provides relevant data on the significance and use of biomarkers in assessing the COPD patients. The results shows that these biomarkers can be used to identify the exacerbations and short term prognosis. The combination of clinical examination and standard investigations (X-ray) along with the use of circulating levels of these biomarkers will be useful to manage the patients with COPD and help in improving the prognosis in these patients.

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8. Conflict of Interest

Authors has no conflict of interest whatsoever.

References

1. Sapey E. COPD exacerbations {middle dot} 2: Aetiology. *Thorax*. 2006;61(3):250–8. doi:10.1136/thx.2005.041822.
2. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax*. 2002;57(10):847–52.
3. Celli BR, Cote CG, Marin JM, Casanova C, de Oca MM, Mendez RA, et al. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2004;350(10):1005–12. doi:10.1056/nejmoa021322.
4. Agustí AGN, Noguera A, Sauleda J, Sala E, Pons J, Busquets X, et al. Systemic effects of chronic obstructive pulmonary disease. *Eur Respir J*. 2003;21(2):347–60. doi:10.1183/09031936.03.00405703.
5. Seemungal TA, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD - a review of potential interventions. *Int J Chron Obstruct Pulmon Dis*. 2009;4:203–23.
6. Harting JR, Gleason A, Romberger DJ, Essen SGV, Qiu F, Alexis N, et al. Chronic Obstructive Pulmonary Disease Patients Have Greater Systemic Responsiveness to Ex Vivo Stimulation with Swine Dust Extract and its Components Versus Healthy Volunteers. *J Toxicol Environ Health* . 2012;75(24):1456–70. doi:10.1080/15287394.2012.722186.
7. Andreo F, Ruiz-Manzano J, Prat C, Lores L, Blanco S, Malet A, et al. Utility of pneumococcal urinary antigen detection in diagnosing exacerbations in COPD patients. *Respir Med*. 2010;104(3):397–403. doi:10.1016/j.rmed.2009.10.013.
8. Barnes PJ, Chowdhury B, Kharitonov SA, Magnussen H, Page CP, Postma D, et al. Pulmonary Biomarkers in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2006;174(1):6–14. doi:10.1164/rccm.200510-1659pp.
9. Lacoma A, Prat C, Andreo F, Dominguez J. Biomarkers in the management of COPD. *Eur Respir Rev*. 2009;18(112):96–104. doi:10.1183/09059180.00000609.
10. Bathoorn E, Liesker JJ, Postma D, Koeter G. Change in inflammation in out-patient COPD patients from stable phase to a subsequent exacerbation. *Int J Chron Obstruct Pulmon Dis*. 2009;4:101–9. doi:10.2147/copd.s4854.
11. Karadag F, Karul AB, Cildag O, Yilmaz M, Ozcan H. Biomarkers of Systemic Inflammation in Stable and Exacerbation Phases of COPD. *Lung*. 2008;186(6):403–9. doi:10.1007/s00408-008-9106-6.
12. Prat C, Dominguez J, Andreo F, Blanco S, Pallares A, Cuchillo F, et al. Procalcitonin and neopterin correlation with aetiology and severity of pneumonia. *J Infect*. 2006;52(3):169–77. doi:10.1016/j.jinf.2005.05.019.
13. Müller B, Prat C. Markers of acute inflammation in assessing and managing lower respiratory tract infections: focus on procalcitonin. *Clin Microbiol Infect*. 2006;12(9):8–16. doi:10.1111/j.1469-0691.2006.01654.x.
14. Tang H, Huang T, Jing J, Shen H, Cui W. Effect of Procalcitonin-Guided Treatment in Patients with Infections: a Systematic Review and Meta-Analysis. *Infect*. 2009;37(6):497–507. doi:10.1007/s15010-009-9034-2.
15. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. *J Clin Investig*. 2003;111(12):1805–12. doi:10.1172/jci200318921.
16. de Torres JP, Cordoba-Lanus E, López-Aguilar C, de Fuentes MM, de Garcini AM, Aguirre-Jaime A, et al. C-reactive protein levels and clinically important predictive outcomes in stable COPD patients. *Eur Respir J*. 2006;27(5):902–7. doi:10.1183/09031936.06.00109605.
17. Weis N, Almdal T. C-reactive protein — can it be used as a marker of infection in patients with exacerbation of chronic obstructive pulmonary disease? *Eur J Internal Med*. 2006;17(2):88–91. doi:10.1016/j.ejim.2005.09.020.
18. Berdowska A, Zwirska-Korczala K. Neopterin measurement in clinical diagnosis. *J Clin Pharm Ther*. 2001;26(5):319–29. doi:10.1046/j.1365-2710.2001.00358.x.
19. Barbera JA, Peces-Barba G, Agusti AG. Clinical guidelines for the diagnosis and treatment of chronic obstructive pulmonary disease. *Arch Bronconeumol*. 2001;37(6):297–316.
20. Rodriguez-Roisin R. Toward a Consensus Definition for COPD Exacerbations. *Chest*. 2000;117(5):398S–401S. doi:10.1378/chest.117.5_suppl_2.398s.
21. Bartlett JG, Dowell SF, Mandell LA, File TM, Musher DM, Fine MJ, et al. Practice Guidelines for the Management of Community-Acquired Pneumonia in Adults. *Clin Infect Dis*. 2000;31(2):347–82. doi:10.1086/313954.
22. Isenberg HD. Clinical Microbiology Procedures Handbook. In: 2nd Edn. Washington: ASM Press; 2007.
23. Murray PR, Washington JA. Microscopic and baceriologic analysis of expectorated sputum. *Mayo Clin Proc*. 1975;50(6):339–44.
24. Coonrod JD, Rytel MW. Detection of type-specific pneumococcal antigens by counterimmunoelectrophoresis. I. Methodology and immu- nologic properties of pneumococcal antigens. *J Lab Clin Med*. 1973;81(5):770–7.
25. Dominguez J, Gali N, Blanco S. Detection of Streptococcus pneumoniae antigen by a rapid immunochromatographic assay in urine samples. *Chest*. 2001;119(1):243–49.
26. Perren A, Cerutti B, Lepori M, Senn V, Capelli B, Duchini F, et al. Influence of Steroids on Procalcitonin and C-reactive Protein in Patients with COPD and Community-acquired Pneumonia. *Infection*. 2008;36(2):163–6. doi:10.1007/s15010-007-7206-5.
27. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA, et al. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106(2):196–204.
28. Yanbaeva DG, Dentener MA, Creutzberg EC, Wesseling G, Wouters EFM. Systemic Effects of Smoking. *Chest*. 2007;131(5):1557–66. doi:10.1378/chest.06-2179.
29. de Kruif MD, Lemaire LC, Giebelen IA, Struck J, Morgenthaler NG, Papassotiriou J, et al. The influence of corticosteroids on the release of novel biomarkers in human endotoxemia. *Intensive Care Medicine*. 2008;34(3):518–522. Available from: https://dx.doi.org/10.1007/s00134-007-0955-x. doi:10.1007/s00134-007-0955-x.
30. Christ-Crain M, Muller B. Biomarkers in respiratory tract infections: diagnostic guides to antibiotic prescription, prognostic markers and mediators. *Eur Respir J*. 2007;30(3):556–73. doi:10.1183/09031936.00166106.
31. Hurst JR, Donaldson GC, Perera WR, Wilkinson TMA, Bilello JA, Hagan GW, et al. Use of Plasma Biomarkers at Exacerbation of Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 2006;174(8):867–74. doi:10.1164/rccm.200604-506oc.
32. Stolz D, Christ-Crain M, Morgenthaler NG, Leuppi J, Miedinger D, Bingisser R, et al. Copeptin, C-Reactive Protein, and Procalcitonin as Prognostic Biomarkers in Acute Exacerbation of COPD. *Chest*. 2007;131(4):1058–67. doi:10.1378/chest.06-2336.
33. Stolz D, Christ-Crain M, Morgenthaler NG, Miedinger D, Leuppi J, Müller C, et al. Plasma Pro-Adrenomedullin But Not Plasma Pro-Endothelin Predicts Survival in Exacerbations of COPD. *Chest*. 2008;134(2):263–72. doi:10.1378/chest.08-0047.
34. Lacoma A, Prat C, Andreo F, Lores L, Latorre I, Pérez M, et al. Usefulness of mid regional pro-atrial natriuretic peptide in the exacerbations of chronic obstructive pulmonary disease. *Clin Chim*

Acta. 2011;412(5-6):470–5. doi:10.1016/j.cca.2010.11.032.

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