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.

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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 al6 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
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 bronspumut 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. In this study three systemic inflammatory markers were being studied in association with COPD i.e., procalcitonineopterin and CRP. 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. CRP is an acute phase reactant also associated with systemic chronic inflammatory conditions. 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. 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 diagnosed 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 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. 164 sputum samples from patients a with exacerbation and with pneumonia were taken and sent to micro lab Op polymorphonuclears. Diagnosis was based on culture report. All relevant data from the patients like age, gender, clinical., ts. After one year all the data exacerbations and number Out of 116 exacerbation patients, 20 samples were collected after a month and stored–20°C till 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 neotrin 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: 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: Number of isolates and levels of PCT, CRP, and neopterin according to the microorganism isolated

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

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 constitute a heterogeneous group with various clinical manifestations. Several factors influence the prognosis of COPD patients. Circulating biomarkers specific for inflammation have been studied in this research work these biomarkers levels can be influenced by various factors like any co morbid condition, 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. In some studies it was found that corticosteroids decreases the levels of these biomarkers. 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. 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. 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. 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.
6. Acknowledgement

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7. Source of Funding

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8. Conflict of Interest

Authors have no conflict of interest whatsoever.

References

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