Original Research Article

Correlation of serum parameters with disease severity, exacerbations and hospitalizations in patients with Non-cystic fibrosis bronchiectasis

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ABSTRACT

Background: The factors essential to define the severity and the prognosis of subjects with NCFB have not been sufficiently assessed. A prospective observational study was conducted to assess the serum parameters, their correlation with BSI (bronchiectasis severity index) and FACED (FEV1% predicted, age, chronic colonization by pseudomonas aeruginosa, extension by radiological assessment and dyspnoea) score in assessing disease severity and respiratory hospitalizations in patients with NCFB.

Methods: About 76 clinically stable patients diagnosed as NCFB were included. Data extraction was done using structured proforma. The BSI and FACED scores were calculated. The serum parameters albumin, CRP (C-reactive protein), ANC (Absolute neutrophil count) and Hb (hemoglobin) levels were estimated. The number of exacerbations and hospitalizations during the 6 months follow up period were recorded.

Results: The mean value of the serum parameters albumin, CRP, absolute neutrophil count (ANC) and Hb were 3.86 (95% CI 3.77- 3.95), 19.61 (95% CI 15.53 -23.68), 8632.95 (95% CI 7258.5-10068) and 12.3 (95% CI 11.84- 12.74) respectively. There was strong negative correlation between serum albumin and the BSI and FACED score. The mean exacerbations and hospitalizations during the 6 months follow up period were 3.3 (95% CI 2.93-3.65) and 1.14 (95% CI 0.85-1.44) respectively.

Conclusions: The serum albumin level exhibited strong correlation and was identified as a variable associated with the BSI and FACED scores. Further studies in this direction are needed for use of serum parameters in severity assessment.

Keywords: Albumin, ANC, BSI, CRP, FACED, Hb, NCFB

INTRODUCTION

Bronchiectasis is defined as a progressive respiratory disease characterized by permanent dilatation of the bronchi. It is associated with symptoms of cough, sputum production and recurrent respiratory infections.[1] Causes of bronchiectasis include cystic fibrosis (CF), previous lung infections, connective tissue diseases, inflammatory bowel disease, immune deficiencies and gastro-oesophageal reflux, and this may impact on the management and outcome.[1]

The prevalence of bronchiectasis is increasing depending on the population studied.[2,3] Bronchiectasis is associated with asthma, interstitial lung disease and chronic obstructive pulmonary disease (COPD). Hence it has wider relevance in respiratory medicine. In the presence of other respiratory diseases, bronchiectasis is associated

with more persistent infections, prolonged hospital admissions and increased healthcare costs.[4]

Bronchiectasis is associated with significant morbidity and mortality.[5,6] Exacerbation of bronchiectasis leading to admission to hospital is associated with high readmission and increased mortality rates. Increasing readmission rates following an infective exacerbation of bronchiectasis have been reported.[7]

Characterizing patients by combining clinical, radiological, inflammatory, and microbiological data allows identification of those individuals who have a more rapid disease progression or exacerbate frequently.[8] Chronic colonization of *P. aeruginosa* in the sputum, low FEV1 on spirometry, and/or multi-lobe involvement on computerized tomography scan are associated with worse prognosis.[9] So, a predictive tool for assessment of the disease severity in routine practice is needed which would help in focusing on therapies most likely to benefit the patients and improve their quality of life.[10]

Hence this study was conducted to estimate the serum parameters, study the correlation between serum parameters, BSI (bronchiectasis severity index) and FACED (FEV1% predicted, age, chronic colonization by *pseudomonas aeruginosa*, extension by radiological assessment and dyspnoea) scores and to find out the number of exacerbations and respiratory hospitalizations during the 6 months follow up period.

METHODS

After getting clearance from institutional ethical committee, a prospective observational study was conducted in a tertiary teaching institution in central Kerala, India. All patients diagnosed as NCFB and clinically stable in the study period were included. Patients with active malignancy, active mycobacterial disease, human immunodeficiency virus (HIV) infection, and chronic liver/kidney failure were excluded from the study.

Sample size was calculated by the formula:

$$N = [(Z\alpha + Z\beta)/C]2 + 3$$

$$C = 0.5 * \ln[(1+r)/(1-r)]$$

Where, r= the expected correlation coefficient

Sample size obtained by substituting r=0.316 was 76.[11]

All patients diagnosed as NCFB and clinically stable at the time of initial assessment were enrolled in the study. Basic demographic details and smoking status of the patients were asked and entered in the proforma.

All the patients were informed about the study and their written informed consent was obtained.

The FACED score and the bronchiectasis severity index (BSI) were calculated for the individual patients enrolled in the study.

The FACED score

The FACED score is an assessment of severity tool validated for patients with bronchiectasis. It consists of 5 dichotomised variables

- F-FEV1 % predicted (cut-off 50%, maximum value 2 points),
- A - Age (cut-off 70 years, maximum value 2 points),
- C-Chronic colonization by *pseudomonas aeruginosa* (dichotomic, maximum value 1 point),
- E- Extension by radiological assessment (number of lobes affected, cut-off 2 lobes, maximum value 1 point)
- D-Dyspnoea (cut-off grade II on the medical research council (MRC0 scale, maximum value 1 point).

Bronchiectasis was classified into 3 severity classes based on the scores derived:

- Mild bronchiectasis (overall score 0-2 points),
- Moderate bronchiectasis (overall score 3-4 points) and
- Severe bronchiectasis (overall score 5-7 points).[12]

BSI

The BSI uses a combination of clinical, radiological and microbiological features as an assessment of severity tool. It uses the following criteria

- Age: less than 50 years (0 points); 50-69 years (2 points), 70-79 years (4 points), more than 80 years (6 points),
- Body mass index (BMI): less than 18.5 (2 points), more than 18.5 (0 points),
- FEV1 % predicted: less than 80% (0 points), 50-80% (1 point), 30-49% (2 points), less than 30% (3 points),
- Hospitalizations in previous year: no (0 points), yes (5 points),
- Exacerbations in previous year: 0-2 (0 points), 3 or more (2 points),
- MMRC dyspnoea score: 1-3 (0 points), 4 (2 points), 5 (3 points),
- Colonization with pseudomonas aeruginosa: no (0 point) yes (3 points),
- Colonization with microorganisms other than Pseudomonas aeruginosa: no (0 point), yes (1 point),

- Severity on HRCT imaging (more than 3 lobes involved or cystic bronchiectasis): no (0 points), yes (1 point).

Based on the overall score obtained, the patients with bronchiectasis were classified into 3 BSI classes

- low BSI score (overall score 0-4 points),
- intermediate BSI score (overall score 5-8 points) and
- high BSI score (overall score 9 or more points).[13]

The following serum parameters were evaluated in the enrolled subjects

- Serum albumin
- C- reactive protein (CRP),
- Absolute neutrophil count (ANC),
- Hemoglobin (Hb) level.

The enrolled subjects were followed-up on a monthly basis for 6 months. During the follow-up, the patients were enquired regarding exacerbations and hospitalizations in the interim period.

Exacerbations were defined as acute deterioration (usually over several days) with worsening local symptoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness, hemoptysis) and/or systemic upset (BTS guidelines). These may result in antibiotic usage, increased use of reliever medications, emergency visits and/or hospitalizations.

The number of exacerbations and hospitalizations during the 6-month follow-up period were recorded.

Statistical analysis

Data was appropriately coded and entered in Microsoft Excel and analysed using SPSS version 21.

Descriptive statistics

Data for quantitative variables were expressed as mean value with standard deviation (S.D.). The mean BSI and FACED scores were calculated. The mean serum albumin, CRP, absolute neutrophil count (ANC) and Hb levels were estimated.

Inferential statistics

Correlation between the serum parameters and the BSI and FACED score was assessed by using the SPSS version to calculate the correlation coefficient. Correlation between the serum parameters and the number of exacerbations and hospitalizations was also done to estimate the correlation coefficient.

Mean difference between 2 groups is tested using t-test. Mean difference between 3 groups is tested using ANOVA. Statistical significance is fixed at 5% (0.05).

RESULTS

The age and sex distribution of study subjects were as shown in (Table 1). The mean age of the study population was 56.82 with standard deviation 13.53.

Table 1: Age and sex distribution of study subjects.

Age group	Male	Female	Total
15-40	5 (50%)	5 (50%)	10 (100%)
41-65	24 (57.1%)	18 (42.9%)	42 (100%)
>65	16 (66.7%)	8 (33.3%)	24 (100%)
Total	45 (59.2%)	31 (40.8%)	76 (100%)

Out of the total 76 patients, 45 (59.2%) were male and 31 (40.8%) were female. The sex distribution varied according to the age group. There were 5 (50%) males and 5 (50%) females in the 15-40 years age group. There were 24 (57.1%) males and 18 (42.9%) females in the 41-65 years age group. There were 16 (66.7%) males and 8 (33.3%) females in the >65 years age group. Majority of the patients were in the 41-65 years age group 42/76 (55.2%).

The mean value of the serum parameter albumin was 3.86 (95% CI 3.77-3.95). Figure 1 shows box and whisker plot of descriptive of serum albumin. The median value of the distribution was 3.85. The distribution of serum albumin followed the pattern for normal distribution.
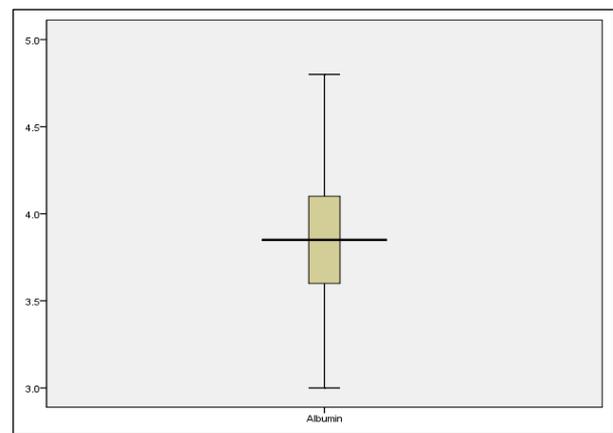

Figure 1: Box and whisker plot showing descriptive of serum albumin.

The mean and median values of serum CRP were 19.61 (95% CI 15.53-23.68) and 11.0 respectively. Figure 2 is the box and whisker plot showing descriptive of serum CRP. Majority of the patients had CRP values higher than the median as shown in the figure.
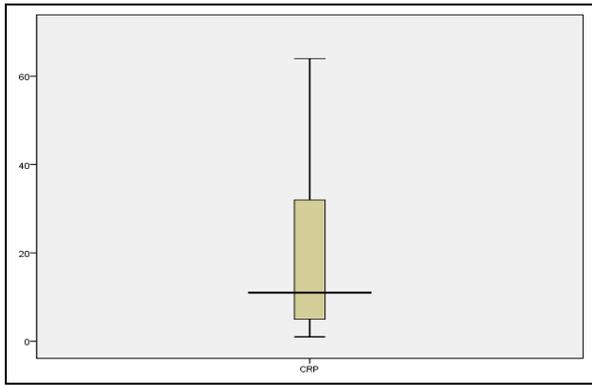
Figure 2: Box and Whisker plot showing descriptive of CRP (C-reactive protein).

Figure 3 is the box and whisker plot showing descriptive of ANC (absolute neutrophil count). The mean value of serum ANC was 8632.95 (95% CI 7258.5 -10068). The median value of the distribution was 7801.
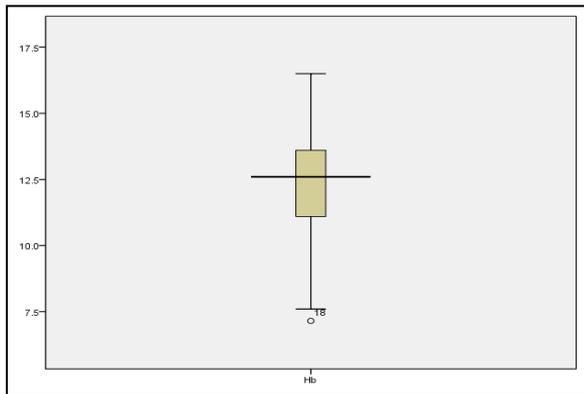

Figure 3: Box and whisker plot showing descriptive of ANC (absolute neutrophil count).

The Box and Whisker plot showing descriptive of Hb is as in Figure 4. The mean and median values of the distribution of Hb were 12.3 (95% CI 11.84-12.74) and 12.6 respectively.
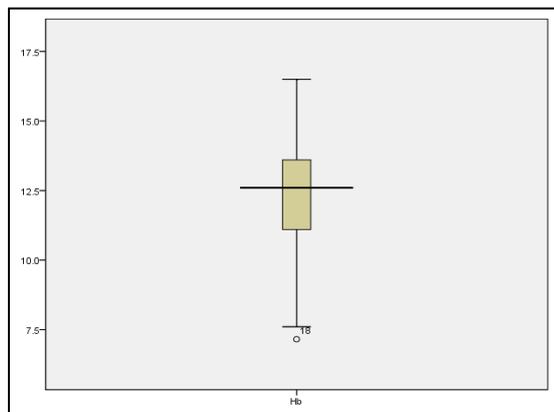

Figure 4: Box and Whisker plot showing descriptive of Hb (Haemoglobin).

The mean BSI and FACED scores were 11.63 (SD 3.34) and 3.33 (SD 1.4) respectively. FACED score showed a strong negative correlation with serum albumin levels (r=-0.240) which was statistically significant with a p value 0.04. There was positive correlation of FACED score with CRP (r=0.192, p value 0.097) and ANC (p value 0.963) levels but was not statistically significant. Negative correlation of FACED with Hb level (r=-0.1, p value 0.39) was also not statistically significant. BSI score also showed a strong negative correlation with serum albumin levels (r=-0.242) which was statistically significant with a p value 0.035. There was positive correlation of BSI score with CRP (r=0.149, p value 0.2) and ANC (r=0.108, p value 0.35) but was not statistically significant. Negative correlation of BSI with Hb level (r=-0.027, p value 0.81) was also not statistically significant.

Based on the obtained FACED score, authors found 28 patients (36.8%) with mild bronchiectasis, 31 patients (40.8%) with moderate bronchiectasis and 17 patients (22.4%) with severe bronchiectasis. Based on the obtained BSI score, authors found 2 patients (2.6%) with low BSI score, 13 patients (17.1%) with intermediate BSI score and 61 patients (80.3%) with high BSI score. Since there were only 2 patients with low BSI score, for the analysis purpose only 2 groups were included (intermediate and high).

The mean exacerbations and hospitalizations during the 6 months follow up period were 3.3 (95% CI 2.93-3.65) and 1.14 (95% CI 0.85-1.44) respectively. The mean exacerbations during follow up in patients with FACED category mild, moderate and severe bronchiectasis were 2.5 (95% CI 2.06-2.94), 3.65 (95% CI 3.17-4.12) and 3.94 (95% CI 2.87-5.01) respectively (Figure 5).
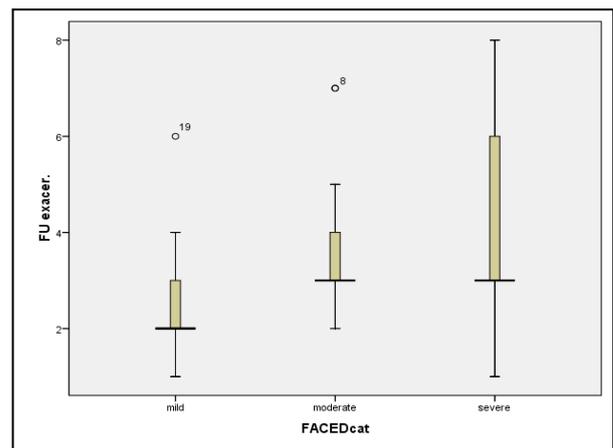

Figure 5: Box and whisker plot showing descriptive of follow up exacerbations.

The mean hospitalizations during follow up in patients with FACED category mild, moderate and severe bronchiectasis were 0.64 (95% CI 0.34 - 0.95), 1.13 (95%

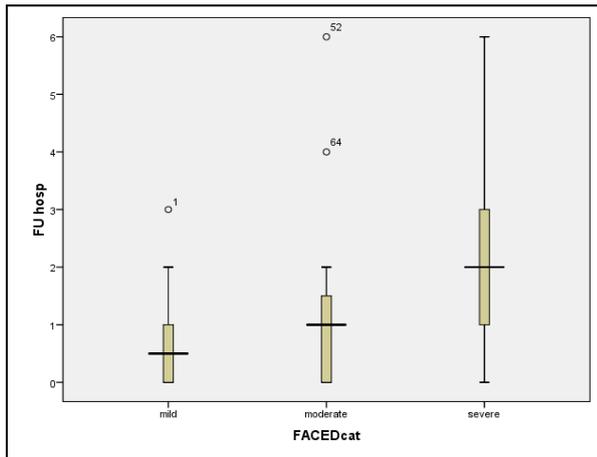CI 0.7-1.6) and 2 (95% CI 1.17-2.83) respectively (Figure 6).

Figure 6: Box and Whisker plot showing descriptive of follow up hospitalizations.

The mean follows up exacerbations in patients with intermediate and high BSI scores were 2.15 (SD 0.69) and 3.57 (SD 1.6) respectively. The mean follows up hospitalizations in patients with intermediate and high BSI scores were 0.7 (SD 0.95) and 1.25 (SD 1.37) respectively. The serum parameters albumin (r=-0.131) and Hb (-0.046) had negative correlation, ANC (r=0.159) and CRP (r=0.081) had positive correlation with follow up exacerbations, but none was statistically significant. Similarly, the serum parameters albumin (r=-0.029) and Hb (r=-0.104) had negative correlation, ANC (r=0.047) and CRP (r=0.068) had positive correlation with follow up hospitalizations, none being statistically significant. 2 patients expired during the course of the follow-up. 2 patients lost to follow up following the first hospitalization.

DISCUSSION

The BSI and FACED scores have been developed to assess the severity and predict the prognosis of patients with NCFB. Systemic inflammatory response is enhanced in patients with exacerbation of bronchiectasis. But the role of serum inflammatory markers in predicting outcomes in patients with stable bronchiectasis has not been studied.

Present study tried to assess the correlation between serum parameters and the number of exacerbations and hospitalizations with respect to the BSI and FACED scores. This was done with the aim of developing predictive tools for the assessment of severity of bronchiectasis with respect to its prognosis.

The mean value of the serum parameters albumin, CRP, absolute neutrophil count (ANC) and Hb were 3.86, 19.61, 8632.95 and 12.3 respectively. There was a strong negative correlation between serum albumin and the FACED and BSI scores respectively. The mean exacerbations and hospitalizations in the 6 months follow up period were 3.3 and 1.14 respectively. As expected, the number of exacerbations and hospitalizations increased according to the increasing severity of bronchiectasis as per both FACED and BSI scores.

The serum albumin level exhibited statistically significant negative correlation and can be considered as a simple and relevant variable associated with the BSI and FACED score. The other serum parameters did not show a statistically significant correlation. Similar results of serum albumin levels as predictor of prognosis of bronchiectasis were obtained in other studies.[14,15]

Bronchiectasis patients were studied for systemic evidence of inflammation indicated by lower serum albumin and higher total leucocyte count.[16] But in present study, low serum albumin levels instead of a negative phase reactant may be a marker of malnutrition rather than degree of inflammation, since the other serum parameters indicative of systemic inflammatory response (ANC, CRP) did not correlate.

Malnutrition is highly prevalent in patients with bronchiectasis. Association between nutritional depletion and chronic respiratory diseases has been recognized but little information regarding bronchiectasis is available.[17] Hypoalbuminemia, in present study, may be a marker of nutritional depletion or may be secondary to chronic protein loss through expectoration. Thus, assessment and correction of hypoalbuminemia may offer benefits to patients with bronchiectasis. Nutritional supplementation may influence the severity of bronchiectasis and therefore may result in decrease in exacerbations and hospitalizations. Further studies in this direction are necessary to ascertain the role of serum albumin as a relevant marker for assessing the severity of patients with bronchiectasis. The main limitation of the study was that most of the patients had severe bronchiectasis and may have implications on the data interpretation.

CONCLUSION

The serum albumin level can be considered as a simple marker correlating with both the scoring systems. Further studies are needed for the precise determination of its role as a marker of inflammation or nutritional depletion.

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