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The role of procalcitonin as a biomarker for acute pulmonary exacerbation in subjects with cystic fibrosis and non-cystic fibrosis bronchiectasis

Firuz MAMMADOV[1], Sehnaz OLGUN YILDIZELI[2], Derya KOCAKAYA[1], Huseyin ARIKAN[2], Caner CINAR[2], Emel ERYUKSEL[2], Berrin CEYHAN[2]

[1] Pulmonary Medicine, Bona Dea International Hospital, Baku, Azerbaijan
[2] Department of Pulmonary Medicine and Critical Care, School of Medicine, Marmara University, Istanbul, Turkey

Corresponding Author: Derya KOCAKAYA
E-mail: drderyagun@gmail.com

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ABSTRACT

Objective: Patients with cystic fibrosis (CF) and non-CF bronchiectasis are prone to exacerbations of pulmonary infections. C-reactive protein (CRP) and procalcitonin (PCT) are inflammatory markers. The aim of this study is to evaluate the role of CRP and PCT on exacerbations of CF and non-CF bronchiectasis.

Patients and Methods: The medical records of 18 CF (52 hospitalizations) and 20 non-CF bronchiectasis patients (51 hospitalizations) were reviewed retrospectively. CRP, PCT levels and, white blood cell (WBC) counts on admission and follow-up were evaluated.

Results: C-reactive protein levels correlated with PCT levels on admission in all patients. Baseline PCT levels were markedly higher (>0.5μg/L) in 12% of CF and 10% of non-CF bronchiectasis patients, however, baseline CRP values were markedly higher (>5mg/L) in 96% of CF and non-CF bronchiectasis patients (p=0.760 and p=0.100, respectively). Baseline CRP and PCT levels were positively correlated with hospitalization length (r=0.501, p=0.001 and r=0.289, p=0.04, respectively) in CF patients, but not in non-CF bronchiectasis.

Conclusion: Our study shows the potential utility of these biomarkers to determine the severity of the exacerbation particularly predicting hospitalization length in CF patients. Both biomarkers could be able to guide antibiotic treatment of infective exacerbations in CF and non-CF bronchiectasis patients.

Keywords: Cystic fibrosis, Bronchiectasis, Exacerbation, Infection, Procalcitonin, C-reactive protein

1. INTRODUCTION

Cystic fibrosis (CF) is a multisystem disorder caused by mutations in cystic fibrosis transmembrane conductance regulator (CFTR) gene. Patients with CF have periodic flare-ups or exacerbations associated with increased mortality and morbidity [1, 2]. Most patients develop pulmonary symptoms that worsen following exacerbations and 25% of cases do not return to baseline pulmonary function test values despite treatment [2]. Most clinicians use clinical signs and symptoms with microbiology and imaging modalities. Antibiotic therapy is recommended for bacterial exacerbations, and treatment response can be seen even in cases of infection with pan-resistant strains [3].

Non-CF bronchiectasis is a chronic lung disease characterized by chronic and recurrent lower respiratory tract infection. Although, management and follow-up strategies for non-CF bronchiectasis are usually extrapolated from CF; patients with non-CF bronchiectasis have different distribution, rate of progression, degree of inflammation of the area of bronchiectasis without multiorgan disease and the data about acute exacerbation in this group is scarce. Physicians prefer to rely on biomarkers in addition to clinical features and radiologic changes to define exacerbations. The specific diagnostic marker and optimal duration of treatment for CF and non-CF bronchiectasis exacerbations are currently unknown. Unlike sputum, blood sampling is simple and feasible to monitor the severity of inflammation in entire lung. The ideal biomarker in blood should be clinically relevant to demonstrate high sensitivity and specificity for diagnosis and treatment effects, also it should predict the prognosis of exacerbation process.

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Nonspecific markers of inflammation, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and elevated white blood cell (WBC) count are well established and widely used in clinical practice to diagnose inflammation including bacterial infection. It has been reported that CRP is correlated with high resolution computerized tomography (HRCT) scores in stable non-CF bronchiectasis patients [4]. In a prospective observational 2-year cohort study, CRP crossed the upper normal limits at onset of acute exacerbation and related with symptoms in 32 outpatients with non-CF bronchiectasis [5]. Although, there is no gold standard marker for diagnosis of exacerbations in CF and non-CF bronchiectasis patients, one of the most studied biomarkers for CF pulmonary exacerbation is CRP that is increased during CF exacerbations and decreased with antibiotic treatment [6, 7]. However, it is a fact that new biomarkers are necessary for diagnosis, treatment and follow-up of CF and non-CF bronchiectasis patients because of limited specificity for bronchiectasis.

Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin which also is a newly identified marker for infection. It can be detected at high levels in bacterial diseases [8]. In the absence of infection in the body, PCT is synthesized by thyroidal C-cells and stored in secretory glands in the form of calcitonin. In the presence of bacterial infections, calcitonin gene expression is upregulated via a process that may be mediated by microbial toxins and cytokines, leading to an increased release of PCT from non-thyroid tissues into the bloodstream. Contrarily, down-regulation of calcitonin by secreted cytokines during viral infections increases PCT specificity in bacterial infections [8]. A meta-analysis has shown that PCT is more sensitive (88% vs 75%) and specific (81% vs 76%) in bacterial infections than CRP. PCT also has shorter durations for reaching peak levels than CRP (8 h vs 36 h) [9]. Apart from diagnosis, clinical assessment and routine blood tests may be insufficient and serial PCT measurements would be recommended to determine the duration of antibiotic use. Therefore, PCT guidance protocols inform the decision to start and stop the antibiotics in lower respiratory tract infections with a shorter duration of antibiotic use. [10, 11]. However, as a reliable marker to diagnose and guide the antibiotic treatment in patients with CF and non-CF bronchiectasis, the data about PCT is lacking. Louw et al., found that baseline PCT was not statistically elevated in pediatric CF acute pulmonary exacerbation group [12]. Similarly, Roderfeld et al., found significant change of CRP but not PCT in CF exacerbation period in adult patients [13]. It is a fact that, based on current international guidelines, there are no recommendations for PCT use in managing acute exacerbations of chronic lung diseases including bronchiectasis [14]. In a study assessing non-CF bronchiectasis patients, it has been reported that PCT levels in outpatient bronchiectasis patients were lower than hospitalized patients who needed intravenous antibiotics and PCT was significantly correlated with CRP. High PCT levels were related with increased likelihood antibiotic prescription and authors commented that PCT seems likely to be able to guide the treatment of an exacerbation in non-CF bronchiectasis patients [15].

We suggest that biomarkers could be helpful to define antibiotic treatment response and the length of hospitalization in severely acute exacerbated CF and non-CF bronchiectasis patients. This study aimed to determine whether CRP and PCT levels may play a role in the clinical care of CF and non-CF bronchiectasis patients with acute pulmonary exacerbations.

2. PATIENTS and METHODS

This was a retrospective study including patients aged ≥18 years with acute exacerbation of CF and non-CF bronchiectasis that were followed by Marmara University Hospital Adult Pulmonology Clinic between May 2013 and December 2016. The research project was approved by Marmara University School of Medicine Clinical Research Ethics Committee with the approval number 09.2016.515.

Patient Selection and Data Collection

A total of 102 non-CF bronchiectasis and 76 CF patients were screened, and 119 hospitalizations were reviewed. However, 4 hospitalized patients were excluded because of transfer to other intensive care units, and 12 were excluded since we could not reach all data. Inclusion criteria; age ≥18years with exacerbation requiring hospitalization as determined by the treating physician, exclusion criteria; antibiotics initiated more than 48 hours prior to admission (other than chronic azithromycin use) and pregnancy. Finally, a total of 52 hospitalizations of 18 CF patients and 51 hospitalizations of 20 non-CF bronchiectasis patients were included in the study. Medical records were reviewed by questioning patients' age, gender, body mass index (BMI), smoking history, duration of disease, comorbidities, medications, colonization status, pulmonary function tests performed during last stabilization period, exacerbation and hospitalization rate within last year. Antibiotics used during hospitalization, microbiological analyses of sputum, white blood cell (WBC) counts, CRP, and PCT levels at enrollment day and 3, 7, 10 days after starting antibiotics were recorded.

Diagnosis of CF and non-CF Bronchiectasis and Acute Exacerbations

Cystic fibrosis was diagnosed based on pilocarpine iontophoresis-induced sweat chloride levels ≥60 mEq/L or genetic analyses revealing two CF-related mutations and two CF-consistent clinical findings. Pulmonary CF exacerbation was defined according to the Clinical Practice Guidelines Signs and Symptoms of Pulmonary Exacerbation. Pulmonary exacerbation was defined as the emergence of 4 of 12 signs or symptoms, prompting changes in therapy and initiation of antibiotics (modified from Fuchs' criteria). These criteria included: change in sinus congestion, sputum, or hemoptysis; increased cough, dyspnea, malaise, fatigue or lethargy; fever; hypoxia or weight loss; change in chest physical exam; or forced expiratory volume in the first second (FEV_1) decrease >10% from a previous value [16].

Non-CF bronchiectasis patients were defined by excluding CF but confirming bronchiectasis by HRCT. Exacerbation was defined as a patient with non-CF bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 hours; cough, sputum volume and/or consistency; sputum purulence, breathlessness and/or exercise intolerance,

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Marmara Med J 2022;35(2): 164-171

fatigue and/or malaise, hemoptysis and a clinician determined change in bronchiectasis treatment was required [17].

Procalcitonin was measured in duplicates using 50 µL serum by the time-resolved amplified cryptate emission technology (Brahms, England), whereas CRP was measured using 25µL serum by an automated analyzer (Abbott Architect, Illinois, USA). Cut-off values of 0.5 µg/mL for PCT and 5 mg/L for CRP were accepted as higher than normal and WBC counts >10000/mm3 indicated leukocytosis.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 23.0 for Windows® system (SPSS® Inc., Chicago, Illinois, USA). Normal distribution of variables was examined using histogram graphs and the Kolmogorov–Smirnov test. The mean ± standard deviation, median and minimum–maximum values were used when descriptive analyses were presented, and 2 × 2 tables were used to compare variables with the Pearson's chi-squared and Fisher's exact tests. When normally distributed (parametric) variables were evaluated, the Student's *t*-test was used for independent groups; when non-normally distributed variables were evaluated between groups, the Mann–Whitney U Test was used. Pearson's correlation analysis for normally distributed and Spearman correlation test for non-normally distributed data were used. A p value of <0.05 was considered statistically significant.

3. RESULTS

Demographics

In the present study, 11/18 (61%) adult CF patients and 11/20 (55%) adult non-CF bronchiectasis patients were females. The mean age of CF and non-CF bronchiectasis patients was 23.9 ± 4.8 and 47.2 ± 15.3 years, respectively (p<0.001). The characteristics of the patients are summarized in Table I. Compared with other comorbidities, pancreatic insufficiency was significantly more common in CF patients. Chronic obstructive pulmonary disease (COPD) was more frequently detected in non-CF bronchiectasis patients when compared with CF patients (p<0.011) (Table I).

Table I. *Patient Characteristics*

	Cystic Fibrosis (n:18)	Non-Cystic Fibrosis Bronchiectasis (n:20)	p value
Age, years (mean ± SD)	23.9 ± 4.8	47.2 ± 15.3	0.001*
Female, n (%)	11 (61)	11 (55)	0.703
BMI, kg/m² (mean ± SD)	20.6 ± 2.5	23.7 ± 6.2	0.075
Current or ex-smoker, n (%)	1 (6)	6 (30)	0.052
Asthma, n (%)	6 (33)	8 (40)	0.671
COPD, n (%)	0 (0)	6 (30)	0.011*
Pancreatic Insufficiency, n (%)	15 (83)	0 (0)	0.001*
Hypertension, n (%)	0 (0)	3 (15)	0.087
DM, n (%)	4 (22)	5 (25)	0.841
CRF, n (%)	0 (0)	1(5)	0.336
Pulmonary Embolism, n (%)	1 (6)	1 (5)	0.939
Colonization, n (%)	14 (78)	6 (30)	0.004*
Pulmonary function tests			
FEV_1/FVC (% predicted)	64.0±10.7	59.0±13.1	0.210
FVC (% predicted)	57.6±25.7	56.0±24.5	0.869
FEV_1 (% predicted)	44.7±25.6	43.7±25.6	0.947
Attack numbers	n=52	n=51	
CRP ** (mg/L)	55.3 (3.44-321.0)	53.5 (3.44-296.0)	0.864
PCT ** (µg/L)	0.10 (0.02-13.51)	0.10 (0.02-3.72)	0.236
WBC ** (/mm3)	11.000 (5600-33100)	11.200 (2500-31600)	0.877
Hospitalization length, days	10.7±2.5	10.0±1.9	0.191

BMI: Body Mass Index, COPD: Chronic Obstructive Pulmonary Disease, DM: Diabetes Mellitus, CRF: Chronic Renal Failure, CRP: C-Reactive Protein, PCT: Procalcitonin, WBC: White blood cell.
**p < 0.05 is statistically significant, **Measurements on enrollment day, Data are given as mean ±SD and median (min-max).*

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Marmara Med J 2022;35(2): 164-171

Pulmonary Function Testing

There was no statistically difference between pulmonary function tests of CF and non-CF bronchiectasis patients. (Table I). Ten patients of CF group (56%) and thirteen (65%) of non-CF bronchiectasis patients had severe pulmonary obstruction (FEV_1 < 50% of predicted value).

Bacterial Colonization

Sputum samples from patients with CF were colonized with bacteria at a significantly higher rate compared with non-CF bronchiectasis cases (78% vs 30%, respectively, p<0.004) (Table I). Upon examination of bacterial colonization in both groups, *Pseudomonas aeruginosa* was observed to be the most commonly colonized bacteria in both groups (67 % of CF and 30 % of non-CF bronchiectasis patients)

Signs and Symptoms

Upon evaluation of signs and symptoms; such as fever, increased sputum volume, sputum thickening, increased breathlessness, and hemoptysis during admission to the ward; there was no relation between high levels of CRP, PCT, WBC counts and these signs and symptoms.

Sputum Culture

Examination of sputum cultures obtained from patients during admission to the clinic revealed that 42 of 52 attacks (83%) of CF patients and 16 of 51 attacks (31%) of non-CF bronchiectasis patients demonstrated culture growth (Table II). *Pseudomonas aeruginosa* was observed to be the most commonly cultured bacteria (56 % of CF patients vs 16 % of non-CF bronchiectasis patients).

Table II. *Microbiological analysis of sputum samples at enrollment day in patients with CF and non-CF bronchiectasis*

Sputum Culture	Cystic Fibrosis n=52 (%)	Non – cystic fibrosis bronchiectasis n=51(%)
Pseudomonas aeruginosa	29 (56%)	8 (16%)
Achromabacter	6 (12%)	
MSSA	2 (4%)	2 (4%)
Acinetobacter baumannii	2 (4%)	
Hemophilus influenza	1 (2%)	1 (2%)
MRSA	1 (2%)	4 (8%)
Stenotrophomonas maltophilia	1 (2%)	
Serratia	1 (2%)	
Streptoccoccus pneumonia		1 (2%)
Total	43 (83%)	16 (31%)

MSSA: Methicillin-sensitive staphylococcus aureus, MRSA: Methicillin-resistant staphylococcus aureus

Length of Hospitalization

The mean duration of hospitalization was 10.7 ± 2.5 days and 10.0 ± 1.9 days for CF and non-CF bronchiectasis patients, respectively. BMI, FEV_1, PCT and CRP levels and WBC counts were examined as factors possibly affecting the duration of hospitalization. In both groups, there was no relation between BMI, FEV_1% predicted, forced vital capacity (FVC) % predicted, FEV_1/FVC%, WBC counts at the enrollment day and duration of hospitalization, whereas the length of hospitalization was significantly longer in all patients with high CRP and PCT levels at the enrollment day (r=0.315, p<0.001 and r=0.289, p<0.003, respectively). Moreover, when we analyzed the length of hospitalization in the participants who had CF and non-CF bronchiectasis separately, these linear correlations remained statistically significant for CRP levels in CF patients but not in non-CF bronchiectasis patients (r=0.501, p<0.0001 and r=0.100, p<0.479, respectively). Similarly, when we correlated the length of hospitalization with PCT levels at the admission, there was positive correlation in patients with CF (r=0.289, p<0.040) but not in non-CF bronchiectasis patients (r=0.223, p<0.112) (Figures 1 and 2). In either group, no significant difference was found between the patients colonized with *Pseudomonas aeruginosa* and the other bacteriological pathogens in terms of length of hospitalization.

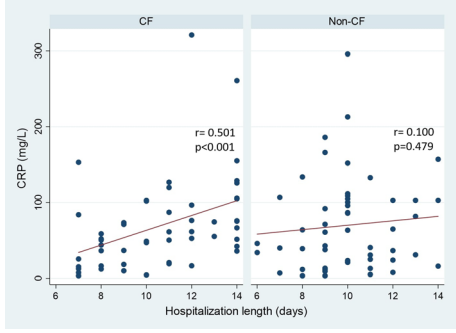

Figure 1. *Correlation between hospitalization length and CRP level in patients with CF and non-CF bronchiectasis*

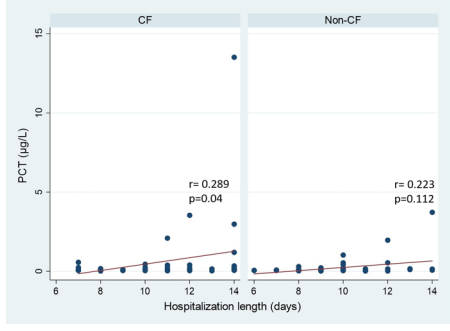

Figure 2. *Correlation between hospitalization length and PCT level in patients with CF and non-CF bronchiectasis*

Inflammatory Biomarkers

Upon examination of all attacks, median CRP level at the enrollment day was 55.3 (min-max: 3.44-321.0) mg/L in patients with CF and 53.5 (min-max: 3.44-296.0) mg/L in non-CF

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Marmara Med J 2022;35(2): 164-171

bronchiectasis (p<0.864). Median PCT level was 0.10 (min-max: 0.02-13.51) μg/L in patients with CF and 0.10 (0.02-3.72) μg/L in patients with non-CF bronchiectasis (p<0.236) (Table I). We correlated the CRP with PCT levels at the time of enrollment in all patients and found a significant linear correlation between CRP and PCT levels (r=0.573, p<0.0001). Of the 51 attacks, CRP was high (>5 mg/L) in 49 (96%) in patients with CF and 50/52 (96%) of attacks in patients with non-CF bronchiectasis (p<1.000). PCT was high (>0.5 μg/L) in 6/51 (12%) of attacks in patients with CF and 5/52 (10%) of attacks in patients with non-CF bronchiectasis (p<0.760). There was no statistically significant difference between the CRP and PCT positivity rates when we analyzed the patients with CF and non-CF bronchiectasis separately (p<1.000 and p<1.000, respectively). There was no correlation between WBC count and CRP and PCT at the admission. The median WBC, CRP and PCT levels at the enrollment day in these two bronchiectasis groups with and without positive sputum cultures did not result in any significant difference (Table III). Likewise, neither the existence of colonization nor the colonizing species did not affect CRP, PCT levels and WBC counts at the enrollment day in patients with CF and non-CF bronchiectasis.

Table III. *Relationship between sputum cultures and acute phase reactants at the enrollment day*

	Cystic Fibrosis			Non-Cystic Fibrosis		
Sputum culture	**Positive**	**Negative**	**p value**	**Positive**	**Negative**	**p value**
	n=42	**n=9**		**n=16**	**n=36**	
WBC * (10^3/mm3)	12.6 (5.6-14.4)	10.9 (5.6-33.1)	0.776	11.95 (3.0 – 31.6)	10.3 (2.5 – 20.0)	0.211
CRP * (mg/L)	60.1 (3.44–321.0)	48.9 (7.53-102)	0.266	72.9 (5.18 – 296.0)	40.3 (3.44 – 213.0)	0.234
PCT * (μg/L)	0.1 (0.03-13.51)	0.1 (0.02-0.57)	0.435	0.11 (0.03 – 1.97)	0.08 (0.02 – 3.72)	0.110

WBC: White Blood Cell, CRP: C-Reactive Protein, PCT: Procalcitonin
*Data are given as median (min-max), * Measurements on enrollment day*

In all participants, we recorded PCT and CRP levels at admission as well as after 10 days of treatment. Most PCT and CRP levels did decrease, however observation of the decreasing effect of inflammatory markers with antibiotic response at 24 h and 72 h revealed that CRP and PCT levels at 24 h did not show any significant change from baseline in CF and non-CF bronchiectasis patients (p<0.053 and p<0.479, respectively). At 72 h, there were significant decreases in both inflammatory markers, particularly in CRP in both CF and non-CF bronchiectasis patients (48% in CRP and 30% in PCT, p<0.039 vs 69% in CRP and 45% in PCT, p<0.006, respectively). When patients' CRP and PCT levels were analyzed under antibiotic treatment during the first 10 days after admission, the decrease in CRP levels was linear and the decrease in PCT levels was biphasic (Figures 3 and 4).

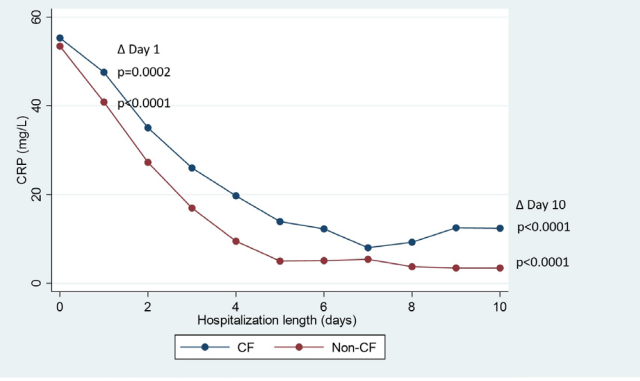

Figure 3. *10-day treatment response in CRP level in patients with CF and non-CF bronchiectasis*

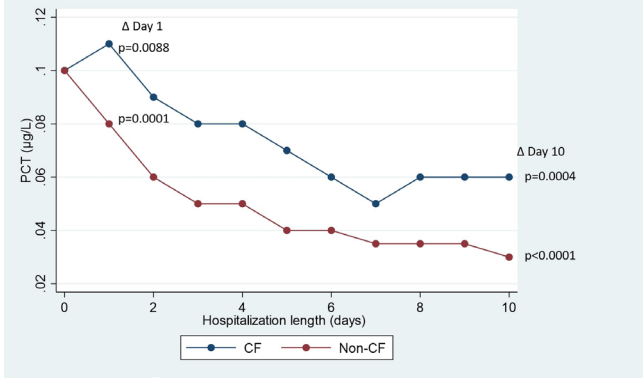

Figure 4. *10-day treatment response in PCT level in patients with CF and non-CF bronchiectasis*

4. DISCUSSION

Despite the importance of managing pulmonary acute exacerbations in the clinical course of adult CF and non-CF bronchiectasis patients, there is limited data related to the role of inflammatory biomarkers during follow-up. A serum biomarker that was able to accurately predict an acute infective exacerbation requiring antibiotic therapy and the length of hospitalization would be a great benefit for management of these patients. Our study is the first to examine the utility of PCT levels in the acute exacerbations in patients with CF and non-CF bronchiectasis requiring hospitalization. Unlike prior

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Marmara Med J 2022;35(2): 164-171

studies, we also determined the response of CRP and PCT values of CF and non-CF bronchiectasis patients in severe acute exacerbations who needed intravenous antibiotic treatment during a 10-day hospitalization. In this study, no significant differences in baseline PCT and CRP levels were noted in patients with CF and non-CF bronchiectasis.

The precise contribution of bacterial infection is difficult to define because of chronically colonized airways in these diseases. The role of acquisition of new bacteria or reactivation of colonized bacteria remains as an important factor in the pathogenesis of acute exacerbation [18]. In our study, only 12 % of exacerbated patients with CF and 10 % of non-CF bronchiectasis had PCT levels >0.5 μg/L as an evidence of bacterial infection. Thus, the contribution of bacterial infection in CF and non-CF bronchiectasis has been markedly overestimated or PCT values do not differentiate localized bacterial infection in bronchial wall from other noninfectious etiologies. It might be suggested that slight elevations of PCT may be reflective of low grade invasive bacterial infections on the mucosal surface with limited inflammation thus, low PCT levels may indicate bacterial colonization, while higher levels of PCT indicate more invasive infections. The traditional cut-off to diagnose systemic bacterial infection with PCT has been interpreted as serum PCT level<0.1 μg/L antibiotics strongly discarded, <0.25 μg/L discouraged, >0.25 μg/L encouraged, >0.5 μg/L strongly encouraged in pneumonia and COPD exacerbation [19, 20]. Our study suggested PCT and CRP as useful outcome predictors of acute pulmonary exacerbations in CF and non-CF bronchiectasis patients. PCT was significantly correlated with CRP. Although, we found detectable PCT (>0.5 μg/L) levels in 12% of attacks in CF patients and 10% of attacks in non-CF bronchiectasis patients while detectable CRP (>0.5 mg/L) levels in 96% of attacks in both groups; duration of hospitalization was longer with higher CRP and PCT levels. However, considering all patients, these correlations were noted in only CF patients but not in non-CF bronchiectasis. Furthermore, the positive sputum culture and colonization in sputum did not affect the inflammatory marker response in acute exacerbations of both groups. In case of response to antibiotic therapy, we showed that CRP and PCT levels decreased statistically significantly at 72 h in both groups and maintained during the 10-day follow-up of hospitalization.

One of the most studied biomarkers for CF and non-CF bronchiectasis acute exacerbation is CRP. CRP is an acute phase reactant and increased during acute exacerbation and decreased with antibiotic treatment [7]. In a meta-analysis, it has been reported that CRP consistently increased in exacerbation state in 5 of 6 studies and decreased statistically significantly after treatment in 18 of 20 studies [21]. CRP has previously been shown to be increased in CF pulmonary exacerbations [22]. In agreement with previous studies, PCT was found to be a less promising marker than CRP in CF patients since detectable levels of PCT was found in a small number of patients in this study. In an earlier study, Louw et al., found that PCT values did not rise significantly at the onset of a respiratory exacerbation of pediatric CF patients while CRP increased significantly [12]. Likewise, in adult CF patients, PCT did not increase however, CRP significantly increased during exacerbation, additionally higher levels of CRP predicted frequent exacerbations within a year [23]. Furthermore, in a study comparing the biomarkers of adult CF patients at an acute attack with those of stable state, CRP significantly increased however, PCT did not increase at the admission [13]. In a recent study by Bailey et al., evaluated adult CF patients with acute exacerbation. Of 40 patients, 23 had detectable levels of PCT ≥0.05 μg/L that was lower than accepted level in our study therefore numbers of patients with detectable PCT were higher than ours. There was no correlation between WBC and PCT levels but there was linear correlation between PCT and CRP at the time of enrollment as similar to our results. Moreover, PCT levels were significantly associated with pulmonary exacerbation scores and decrease in FEV_1. Those who had worsening PCT during treatment or detectable PCT at admission were more likely to be readmitted to the hospital sooner [24].

This is the first study assessing the PCT use in the acute exacerbations of adult patients with non-CF bronchiectasis. We found small number of patients with non-CF bronchiectasis have detectable PCT levels however, CRP levels increased in 96% of patients. Loebinger et al., compared CRP and PCT levels of inpatient and outpatient groups with non-CF bronchiectasis and they found that PCT levels were generally lower in outpatients than those of inpatients. PCT was significantly correlated with CRP levels. Higher PCT levels were associated with increased likelihood of high levels of symptoms and increased inpatient antibiotic prescription. The big confounding factor in that study is that they did not exclude patients who had taken antibiotics before admission. In that study, the other interesting point is the lack of relationship between the original PCT level and the likelihood of re-exacerbating over the next 6 months in patients with non-CF bronchiectasis [15].

Although, there was a linear correlation between PCT and CRP on admission in CF patients, only PCT showed correlation with admission symptoms and the authors emphasized that similar relationship could not be demonstrated with conventional CRP [24]. Similarly, Sequeiros et al., evaluated 168 acute attacks of 58 adult patients with CF who had worse symptom score did not have higher CRP level at the beginning of treatment [25].

In most adult CF patients, the lungs are chronically infected with *Pseudomonas aeruginosa* and colonization has been shown to be related to progression of disease. Furthermore, Pseudomonas colonization means that many of patients will not have an oral antibiotic option for acute exacerbation, this population is likely to have inpatient management with at least two intravenous antibiotics. In our study, *Pseudomonas aeruginosa* is the first among the microorganisms grown in sputum culture in both groups that is compatible with similar publications [15]. Upon examination of initial and follow-up PCT values, no relation was observed between sputum cultures, colonization and detectable PCT levels in patients with CF and non-CF bronchiectasis.

For the first time, we have described that high CRP and PCT levels were related to prolonged admission time in CF patients but not non-CF bronchiectasis patients. In a similar study

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Marmara Med J 2022;35(2): 164-171

predicting duration of exacerbation, baseline CRP levels were studied however, it was found not to be predictive of the duration required to control CF acute exacerbation [25]. We suggest that elevated PCT and CRP values correlated with longer hospitalization period suggesting the possibility of severe illness at admission. Thus, high PCT and CRP alert clinicians to the unresponsiveness of the antibiotics and consequently the need of longer hospitalization.

There is limited literature about the role of PCT in monitoring the response against antibiotics regarding infective exacerbations of adult CF and non-CF bronchiectasis patients. While most reports evaluating the guidance of PCT on antibiotic therapy revealed that PCT follow-up reduces the duration of antibiotic use in lower respiratory tract infections, there are some reports that are contradicting. Ito et al., also suggested that high PCT and CRP levels in diagnosis and follow-up of community-acquired pneumonia were useful in predicting early mortality [26]. Our study adds to the growing body of literature which questions the utility of PCT levels to guide antibiotic treatment in CF and non-CF bronchiectasis patients. When CRP and PCT levels in response to antibiotic therapy were evaluated at admission in the present study, it was observed that evaluation of the antibiotic response showed a statistically significant decrease in 72-h CRP and PCT levels in CF and non-CF bronchiectasis patients. In addition, PCT tends to decrease biphasically, whereas CRP tends to decrease linearly and superiority to each other was not detected. However, in another study, it was found no statistically significant change of PCT level after 10 days of antibiotic treatment in CF patients [24]. In contrast, Roderfeld et al., followed only 7 CF inpatients during antibiotic treatment and did obtain serum samples after completion of antibiotic therapy, however neither CRP nor PCT were significantly changed after antibiotic therapy for pulmonary exacerbation [13]. In a study evaluating non-CF patients, Loebinger et al., monitored acute exacerbation of non-CF bronchiectasis patients after starting antibiotic treatment and there was no significant difference in PCT concentrations between the measurements at days 0, 5, and 10 in contrast to our results [15].

Considering the shortcomings of this study, only a limited number of patients could be included because of lack of data due to the retrospective nature of the study. Also, long-term outcomes of patients were not monitored. We have not clinical scoring data for grading acute exacerbation. Additionally, sampling from a single center limits the generalizability of these principal findings.

This is the first study assessing the use of CRP and PCT in patients with CF and non-CF bronchiectasis together. We showed that PCT may be a useful biomarker in CF exacerbations to determine the outcome. Furthermore, high PCT values at the time of diagnosis of acute infective exacerbations requiring hospitalization in patients with CF but not non-CF bronchiectasis, were shown to be related to prolonged admission time. Follow-up of response to treatment with a trend of superiority were anticipated because of statistically significant decrease starting from 3rd day of antibiotic treatment. We conclude that PCT and CRP should be located in the follow-up of infective acute exacerbations of adult CF and non-CF bronchiectasis patients to determine its potential in guiding management decisions. Further studies are needed to determine PCT cut-off values and to assess PCT efficacy in acute bacterial exacerbations of CF and non-CF bronchiectasis patients.

Compliance with Ethical Standards

Ethical Approval: This study was approved by Marmara University School of Medicine Clinical Research Ethics Committee with the approval number 09.2016.515.

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