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SERUM PROCALCITONIN LEVELS IN ACUTE EXACERBATION OF INTERSTITIAL LUNG DISEASE PATIENTS ADMITTED AT A TERTIARY CARE CENTER

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ABSTRACT

Background: Acute exacerbation of ILD can be attributed to varying etiologies ranging from infection, aspiration, and pulmonary embolism. An elevated procalcitonin (PCT) is a marker of infection. This study was done to evaluate serum PCT levels in patients with acute exacerbation of ILD admitted and correlate the serum PCT with clinical course and outcome of hospital admission. **Methods:** In this hospital based observational study data was captured from patients admitted with an acute exacerbation of ILD. Along with history, clinical examination, serum PCT levels were measured along with other baseline investigations including sputum pyogenic culture and sensitivity. **Result:** 53 patients with acute exacerbation were included in the study, 3 patients died due to the event (mortality rate 6%). Serum PCT levels (Mean±SD) in acute exacerbation of ILD patients were 0.83+/- 0.51. Serum PCT correlated with total leukocyte counts (TLC) ($p<0.05$) and inversely correlated with SPO2 levels ($p<0.005$). There was significant association of serum PCT level groups and the outcome of the sputum pyogenic culture and sensitivity results ($p<0.005$). It was found that there was no significant correlation between raised serum PCT levels with duration of hospitalization and mortality. **Conclusion:** Mortality rate in our study with acute exacerbation of ILD was around 6%. Raised PCT was noted in 13% of patients which inversely correlated with oxygen saturation. We conclude that serum PCT is a useful biomarker for ruling out infection and it guides appropriate pharmaco-therapy including steroids and antibiotics.

KEYWORDS :

INTRODUCTION

Diffuse parenchymal lung diseases, often collectively referred to as the interstitial lung diseases (ILDs), are a heterogeneous group of disorders that are classified together because of similar clinical, radiographic, physiologic, or pathologic manifestations [1,2,3,4,5,6]

Acute exacerbation of ILD has a clinical presentation of rapid onset progressive dyspnoea, cough with or without sputum, fever and hypoxemia with presence of new lung infiltrates on chest imaging. However these features are not specific to acute exacerbation of ILD nor do they ensure an accurate differentiation of bacterial pneumonia (since a variety of infections can cause interstitial opacities on chest radiograph, including COVID pneumonia, fungal pneumonias, Pneumocystis jirovecii , atypical bacterial pneumonias, and viral pneumonias), pulmonary embolism and heart failure. Hence it is essential to rapidly recognize these conditions for their specific and targeted therapy.[60-62]

Procalcitonin (PCT) is a calcitonin precursor hormone, in the absence of systemic inflammation, PCT synthesis is restricted to thyroid neuroendocrine cells, and the protein is not released into the blood until it is cleaved into its mature form, calcitonin. Thus, serum PCT is typically undetectable in healthy persons when standard assays are used.[7] It is raised in bacterial sepsis and septic shock.

Acute exacerbation of ILD can be due to varying etiologies ranging from infection, aspiration, and pulmonary embolism. An elevated PCT will therefore help distinguish bacterial infection from other causes of infection or inflammation. In patients with acute exacerbation of ILD, PCT can serve as a helpful adjunct to clinical judgment for guiding antibiotic therapy and resolving diagnostic uncertainty.

Our study aims to evaluate serum PCT levels in patients presenting with acute exacerbation of ILD admitted at a tertiary care center. The secondary aim was to correlate the serum PCT with clinical course and outcome of hospital admission.

MATERIALS AND METHODS

This was a hospital-based observational study, conducted on all acute onset dyspnoea patients of ILD who were admitted at the Institute of respiratory diseases, SMS medical college, Jaipur. This study was approved from the research review board and ethics committee of SMS Medical college, Jaipur. It was conducted over a period of one year (January 2021-December 2022). Institute of respiratory diseases is a tertiary care center for respiratory diseases in Rajasthan. We included patients in the study who presented with: (1) acute onset of dyspnoea with ILD and were admitted, (2) those who gave written informed consent and (3) were above 18 years of age. Patients were excluded from the study if they had: (1) pulmonary oedema (cardiogenic and non cardiogenic) (2) pancreatitis (3) all other conditions that present with false positive PCT.

Patients satisfying the inclusion criteria of this study were enrolled after providing written informed consent for this study. A detailed history was elicited from the patients and general physical examination and systemic examination was carried out. Routine blood investigations including complete blood count, renal function test, liver function tests, random blood sugar, serum electrolytes, chest x ray, sputum pyogenic culture, sensitivity, and serum PCT were done for all patients.

High resolution computed tomography (HRCT) of chest was done to diagnose new onset acute presentation of ILD patients. The diagnosis of ILD was made as per the guidelines outlined in the American thoracic society (ATS) and British thoracic society (BTS).[27,18]

All the data were entered in an excel sheet and statistical analysis was done. The data entry was done in google excel

spreadsheet and the final analysis was done using the statistical package for social sciences (SPSS-20) software, IBM manufacturer, Chicago, USA, ver2.1.0. The presentation of categorical variables such as age, sex, occupation, residential area, symptoms, past history, exposures, multi-disciplinary diagnosis, type of connective tissue disease (CTD), treatment received by patients, duration of hospital stay were analyzed and presented in terms of number and percentage. Quantitative data like serum PCT levels were presented in terms of mean plus or minus standard deviation. Pearsonian Chi square tests were applied for association between serum PCT and mortality, serum PCT and duration of hospital stay, serum PCT and sputum pyogenic culture and sensitivity. Student-T tests were applied for comparison between serum PCT and TLC, serum PCT and oxygen saturation (SPO2). For statistical significance, P value of less than 0.05 was considered significant and p value less than 0.005 was considered highly significant.

RESULTS

A total of 53 patients with ILD were admitted with acute exacerbation, 29 females (55%) and 24 males (45%) during the study period. Majority of patients were more than 40 years of age (90%) and the rest were between 20 and 40 years of age, the majority of the patients, around 67% were resided in urban areas, 22% belonged to suburban areas and 11% belonged to rural areas. All patients had shortness of breath and cough as their main presenting complaint, followed by fever and weight loss of around 42% and 43% respectively. Some patients presented with symptoms of CTD like difficulty in swallowing (8%), dry mouth (8%), dry eyes (8%) and skin changes (13%).

In the study sample, 32% of the patients were current or ex-smokers. Systemic hypertension (23%) was the most common comorbidity, followed by diabetes mellitus type 2 (17%), coronary artery disease (8%) and past history of tuberculosis (8%). 20% of the population had connective tissue disorders for many years and eventually developed ILD in later stages. The common exposures in the ILD patients included biomass fumes (10%), dust (10%), pigeon feathers and excreta (4%) and air cooler (2%). Physical examination revealed bibasilar crackles (92%) and clubbing (42%). Around 94% patients had new chest infiltrates on X ray at the time of admission. Recent COVID infection was noted in 34% patients, and pulmonary hypertension (PAP >20 mm of Hg at rest) was noted in 25% patients. Almost a third (32%) patients had raised total leukocyte counts (TLC >11000), and 13% had raised serum PCT (levels>0.5). The mean serum PCT levels were 0.83±0.51 (Mean standard±deviation, SD).

The sub-type of ILD in the studied population included CTD related ILD (26%), post COVID- ILA (23%), chronic hypersensitivity pneumonitis (17%), idiopathic pulmonary fibrosis (IPF) including combined pulmonary fibrosis and emphysema (CPFE) (17%), idiopathic non specific interstitial pneumonia (NSIP)(5%), sarcoidosis (4%) and there were one case each of cryptogenic organising pneumonia (COP), drug induced ILD due to infliximab, desquamative interstitial pneumonia (DIP) and neurofibromatosis ILD. The most common subtype of CTD was rheumatoid arthritis (50%), systemic sclerosis (14%), sjogrens syndrome (14%) and other undifferentiated CTD (22%). The common radiological diagnosis were NSIP (25%), post COVID-ILA (23%), usual interstitial pneumonia (UIP) (19%), undifferentiated (5%), and some rare ILD's like sarcoidosis (4%), COP(2%), DIP (2%), diffuse alveolar damage (2%) and lymphocytic interstitial pneumonia (LIP)(2%).

There was no significant correlation between serum PCT levels with the subtypes of ILD (P value >0.05). The treatment comprised of parenteral steroids (91%) in the form of either Methylprednisolone or hydrocortisone. 53% of patients received antibiotics during their hospitalization period. Out of the 50 patients who received steroids, 40 patients received methylprednisolone (80%) and 10 patients received hydrocortisone (20%) for treatment. Of the 53 patients, 53% stayed in the hospital for a period of 6-10 days, 45% were admitted for a period of 0-5 days, and 2% were admitted for more than 10 days. Three patients died during their hospital admission due to the current exacerbation event. It was found that there was no significant correlation between serum PCT levels with the duration of hospitalization period and mortality (p=0.56) (Table 1).

The serum PCT levels were significantly associated with TLC (p<0.05) (Figure 1). They were also significantly associated with SPO2 levels; higher PCT levels were associated with lower SPO2 levels (p<0.005) (Figure 2). We also found that there was significant association with the serum PCT level groups and the outcome of the sputum pyogenic culture and sensitivity results. Out of the 46 patients (100%) who had normal serum PCT, only one patient (3%) turned out to be sputum positive for bacterial growth. Whereas out of the total 7 patients (100%) who had raised serum PCT levels, almost around 6 patients (86%) turned out to be sputum positive for bacterial growth (p<0.005) (Table 2).

DISCUSSION

Of the 53 patients who were admitted with acute exacerbation of ILD, 13% (7 patients) had raised PCT levels. Mortality rate was 6% (3 patients) in the studied population. Raised PCT levels were not significantly associated with mortality (P value = 0.56), and duration of hospital admission (P value = 0.29). However, raised PCT was significantly associated with raised TLC (P value = 0.02), growth on bacterial culture (P value = 0.001), and low oxygen saturation (P value = 0.001). The most common ILD in our study was CTD related ILD (26%) and the most common radiological pattern was NSIP (25%). Among the CTD-related ILD, the most common observed CTD was rheumatoid arthritis (50%). However there was no significant association of raised PCT levels and the type of ILD (P value = 0.36). Steroids remained the mainstay of treatment in the majority of cases (91%) during the admission period.

In our study, 55% of patients were females and 45% of patients were males. Our study had more females compared to males since most cases were due to CTD related ILD which predominated in women. Most of the patients (90%) in our study were of the age group >40 years of age suggesting that middle aged women and old aged men were affected more depending on sub-type of ILD.

The duration of hospitalization also varied with 53% patients being hospitalized for a period 6-10 days and 45% patients being hospitalized for a period 0-5 days and only 2% were hospitalized for more than 10 days. The mortality rate amongst the patients was 6 % especially in cases with advanced fibrosis and co-morbidities complicating the primary disease. Please quote mortality rates from previous studies. Out of the 6% (3 patients) who suffered mortality, only 1 patient had a raised PCT value while the remaining 2 patients had a normal PCT value (p>0.05).

There was a significant correlation between the serum TLC levels and serum PCT levels in these patients. Those patients who had normal serum PCT levels (<0.5) had lower mean TLC values of 10.05 ±3.85 compared to those patients with a raised serum PCT levels (>0.5) had higher mean TLC values of 15.44 ± 5.67 (p<0.05). Raised serum TLC values could be due to various reasons but most common, being due to an infectious cause in our clinical settings. Steroids also lead to leukocytosis, thereby serum PCT is valuable for differentiating leukocytosis due to steroids versus due to infection. As mentioned earlier, the serum PCT levels follow infections in

our body, this data from our study proved that serum PCT could be used as a marker to assess an infectious tiology that would have led to exacerbation in these patients.

J kyeom sim et al [78] performed a prospective observational study in ILD patients (n=25) and studied the usefulness of serum PCT as a biomarker for differential diagnosis of acute exacerbation and bacterial pneumonia in patients with ILD. They found that the PCT level in the acute exacerbation group was significantly lower than that in the bacterial pneumonia group (0.05 versus 0.91ng/mL, respectively; P value 0.001). Our study supports these findings, supporting the role of serum PCT in the differentiating diagnosis of acute exacerbation and bacterial pneumonia in patients of ILD with acute onset breathlessness.

Also, it was found in our study that there was a significant inverse relation between the serum PCT levels and measured mean SPO2 levels via pulse oximetry. Those patients who had normal serum PCT levels (<0.5) had higher mean SPO2 levels of 86 ± 0.07 when compared to patients with a raised serum PCT levels (<0.5) having a lower mean SPO2 levels of 83± 0.08 (P value of <0.001). This inverse relation observed here could be due to the infection, resulting in parenchymal infiltrates in the ILD patients who already have compromised lungs. These could have resulted in a decrease in SPO2 levels in these patients.

It was observed in our study that there was a significant association between the serum PCT levels and outcome of the sputum pyogenic culture and sensitivity in these patients. Out of the 46 patients (100%) who had normal serum PCT, only one patient (3%) turned out to be sputum positive for bacterial growth. Whereas out of the total 7 patients (100%) who had raised serum PCT levels, 6 patients (86%) turned out to be sputum positive for bacterial growth (p<0.005). Bacterial cultures are time consuming with a delay of 48 to 72 hours for the growth to demonstrate. Patients who are unable to expectorate sputum are also a challenge. PCT in these cases provides rapid results and timely intervention can be sought. Our study proves that the serum PCT levels are raised in cases of infectious etiology and prompt results guide initiation of anti-bacterial treatment in an acute setting like exacerbation of ILD.

The study center was situated in urban area, however patients in our study resided in urban, suburban and rural, the majority (67%) belonged to urban areas. The common symptoms in the patients included shortness of breath (100%) and cough (100%). Previous studies from India have a similar case profile. Apart from these two main symptoms some patients had CTD-related symptoms like fever (42%), weight loss (23%), joint pain (15%), chest pain (30%), difficulty in swallowing (8%), dry mouth or dry eyes (8%) and some skin related changes (13%). These extra pulmonary symptoms were the manifestation of the chronic underlying inflammatory disease process in the patient due to CTD's.

It was found in our study that 32% of patients were chronic smokers that led to smoking related ILDs like DIP, CPFE and IPF. Few others had exposure to biomass fuel (10%) particularly in those patients residing in suburban and rural areas in our country. Apart from these exposures, 10% patients had dust exposure, 4% had pigeon exposure and 2% had air cooler exposure which has most likely contributed to development of ILDs like hypersensitivity pneumonitis.

The common comorbids included in the study were: hypertension (23%), diabetes mellitus type 2 (17%), coronary artery disease (8%) likely due to the past history of smoking or due to the known and dose independent side effects of steroid that is been used to achieve long term control of ILD.

Our study population consisted of various different ILD's ranging from common to very rare ILD's. Among the various different multidisciplinary diagnosis, our study predominantly had CTD-ILD (26%) comprising of rheumatoid arthritis (50%), systemic sclerosis (14%), Sjogrens (14%), undifferentiated (22%) as the most common ones, which explains the predominant female population in our study, followed by Post COVID-ILA (23%). Since this study was undertaken during the ongoing COVID pandemic in India, our study had a significant number of patients with post COVID fibrosis. This was followed by chronic hypersensitivity pneumonitis (17%) and IPF (17 %). There was no significant correlation between serum PCT levels and sub-type of ILD (P value>0.05).

Radiologically, most common diagnosis was NSIP (25%), post COVID-ILA (23%), UIP (19%), undifferentiated (5%), and some rare ILD's like sarcoidosis (4%), COP (2%), DIP (2%), diffuse alveolar damage (2%) and LIP (2%).

Post COVID ILA

All our patients received treatment with parenteral corticosteroids like Methylprednisolone or Hydrocortisone (91%) and antibiotics (53%). There was less use of antibiotics compared to steroids since once the treatment was initiated it was later tailored according to blood reports like TLC, PCT and sterile sputum culture of the patient. The treatment of acute exacerbation of ILD is a controversial topic with various studies advocating the use of pulse or high doses of corticosteroids.

There are certain limitations of the study. First, we did not categorize our patients into acute exacerbation group and bacterial pneumonia groups, we considered all cases as acute exacerbation of ILD and assessed the PCT levels in them. This methodology was adopted because bacterial infection is a causative factor for exacerbation rather than a separate entity. Secondly, serial measurement of PCT for guiding antibiotic therapy was not done due to logistic issues.

Nevertheless, this simple non-invasive and reliable investigation is important in decision making for treating the patients in the best possible way. Third, it was a single center study and the number of patients in each sub-type of ILD was less. Data can thus, only be used to assess acute exacerbation as a whole group of ILD rather than specific sub-types.

CONCLUSION

Our study demonstrates that acute exacerbation of ILD is a serious condition that needs to be addressed and treated promptly. The mortality rate in our studied population was 6%, which is considerably high and acute exacerbation of ILD carries a poor prognosis for patients with progressive fibrotic disease as it leads to lowering of lung function. Thirteen percent of patients admitted with acute exacerbation of ILD had raised PCT levels. The serum PCT levels did not correlate with the sub-type of ILD (P>0.05), duration of hospital admission (P>0.05) and mortality (P>0.05).

Raised PCT in the 13% of patients suggest an infective cause of exacerbation, which was further confirmed by laboratory investigations like raised TLC counts (>11000) and positive sputum pyogenic culture. Further, we found a significant inverse relation between the SPO2 levels and serum PCT levels (P<0.05), this could be due to infections like pneumonia complicating the ILD that has led to an increased fall in SPO2 levels in these patients. Hence, we conclude from our study that serum PCT is a useful and resourceful biomarker for ruling out infection. It can guide appropriate therapy including steroids and antibiotics.

Figure legends

Figure 1: Scatter diagram of serum procalcitonin and TLC in the studied ILD population

Figure 2: Scatter diagram of serum procalcitonin and SPO2 in the studied ILD population

Table 1: Association of duration of disease with serum procalcitonin levels

Serum Procalcitonin Duration (Days)	Normal (<0.5)	Infected (≥0.5)	χ2 Value	P-Value
0-5	22	02	1.18	0.56
6-10	23	05		
>10	01	00		
Mortality	02	01	1.12	0.29

Table 2: Association of serum procalcitonin with sputum pyogenic cultures

Serum ProcalcitoninSputum pyogenic cultures	Normal (<0.5)	Infected (≥0.5)	χ2 Value	P-Value
Negative	45	01	36.99	<0.001*
Positive**	01	06		

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