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Serum Procalcitonin Level as a Predictor of Outcome in Patients with Pulmonary Tuberculosis

Mohammed Kamal Uddin[1*], Toufiq Ahmed[2], Shirajum Monira[3], Gulnar Yasmin[4], Md Rasul Amin[5], Farzana Reza[6]

[1]Medical Officer, Department of Gastroenterology, Sir Salimullah medical College Mitford hospital, Dhaka, Bangladesh.
*Corresponding author

[2]Junior Consultant, Department of Medicine, Sheikh Russel Gastroliver Institute and Hospital, Dhaka, Bangladesh.

[3]Junior Consultant, Department of Medicine, Dhaka Medical college hospital, Dhaka, Bangladesh.

[4]EMO, Bangladesh secretariet Clinic, Dhaka, Bangladesh.

[5]Associate Professor,Department of Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

[6]Medical officer, National Institute of Traumatology & Orthopaedic Rehabilitaion (NITOR), Dhaka, Bangladesh.

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Abstract

Background: Tuberculosis (TB) is one of the most important causes of mortality in developing countries and is one of the eight leading causes of death due to diseases in the world. Worldwide 9.6 million people are estimated to have fallen ill with TB in 2014. Among them 6 million new cases of TB were reported to WHO. Aim of the study: To evaluate the role of serum procalcitonin level as a predictor of disease outcome in patients with pulmonary tuberculosis. Methods: This prospective observational study was conducted in the department of Internal Medicine of Bangabandhu Sheikh Mujib Medical University Dhaka, from the period of October 2017 to October 2018. A total of 30 patients were included for the study. Sampling technique of this study was convenient sampling. Patients diagnosed as smear positive for AFB or Gene-Xpert for Mycobacterium Tuberculosis Bacilli (MTB) positive pulmonary tuberculosis were selected. Data was entered in Microsoft Excel and analysis was done in STATA version 14. The research protocol was approved by the Institutional Review Board (IRB).Results:The mean age of all patients was 34.6 years with standard deviation of 14.8 years. Median age was found 30 years with minimum and maximum ranges were 19 and 70 years, respectively. Two third (67%) of the patients were male. Fever was found in 83% respondent, which was highest among all four clinical features included in this study. Most of the patients with cough had more than 3 weeks of duration (85%). Hemoptysis was found in 53% of patients and more than two-third of the patients reported weight loss (70%). Total count of WBC was found high in 97% of patients. A strong positive correlation was found in between before and after blood levels of procalcitonin ($r=0.92$, $p<0.001$). In comparison with chest x-ray findings, patchy lesion tended to have higher procalcitonin level in before and after TB treatment. Conclusion: This study assessed serum PCT in patients diagnosed with pulmonary tuberculosis at enrollment and after six months of TB treatment to observe the value of PCT reduction with treatment. PCT level was reduced significantly after getting six-months of TB treatment irrespective of age, sex, BMI and other laboratory parameters.

Keywords: Tuberculosis, Procalcitonin, Predictor.

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INTRODUCTION

Tuberculosis (TB) is one of the most important causes of mortality in developing countries and is one of the eight leading causes of death due to diseases in the world. Worldwide 9.6 million people are estimated to have fallen ill with TB in 2014. Among them 6 million new cases of TB were reported to WHO. About 80% of reported TB cases occurred in twenty two (22) high TB burden countries, over 95% of TB cases are in developing countries where about 7% of all deaths are attributed to TB. Bangladesh ranks sixth among the 22 high TB burden countries in the world. Tuberculosis country profile of Bangladesh reported by WHO1 shows that total new and relapse tuberculosis pulmonary tuberculosis is 79% and bacteriologically confirmed among pulmonary tuberculosis is 72%. Despite of medical advances, pulmonary tuberculos is (PTB) is still one of the major cause of death and disability in our community. Procalcitonin (PCT) is a pro-peptide calciton in hormone consists of 116amino acids which is secreted from neuro-endocrinecells in the thyroid gland, liver and lung in response to endotoxinsandtumornecros is factor-α (TNF-α). The serum level of PCT has a correlation with the severity of pulmonary infections and also prognosis of patients after pulmonary infection. PCT has been used as a biomarker to differentiate viral from bacterial infections. Rasmussen and colleagues[2] found that PCT level in pulmonary tuberculos is patients is higher compared to the healthy control group. They also concluded that the PCT level can be used to predict mortality of TB patients. However it is not exactly known how Mycobacterium tuberculos is infection affects PCT production in adult patients with active pulmonary tuberculos is. It is expected that pro-inflammatory cytokines, TNF-α and lipoarabinomannan (LAM), which play important roles in pulmonary tuberculosis (PTB) pathogenesis,mayalsoincreasePCTlevels.3 Serum PCT level in active pulmonary tuberculosis increases and it decreases after treatment. So it can be used for follow-up differentiating biomarker between active and cured pulmonary tuberculos is and for prediction of treatment response and observing their recovery process, although it cannot be an alternative for bacteriological and pathological diagnosis.[4] The usefulness of PCT indiagnos is and prognos is of tuberculosisis still the matter of some controversy. Further studies are necessary to assess the potential value of PCT form ensuring disease activity. To our knowledge, there was no study to evaluate serum PCT level in pulmonary tuberculosis (PTB) patients in our country. The purpose of this study is to establish the PCT level in PTB patients before & after treatment and evaluate the effect of serum PCT concentration on six-months TB treatment.

Objectives

General objective:

- To evaluate the role of serum procalcitonin level as a predictor of

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disease outcome in patients with pulmonary tuberculosis.

Specific Objectives:

- To determine the serum procalcitonin level in pulmonary tuberculos is patients at the time of diagnosis.
- To determine the serum Procalcitonin level in Pulmonary tuberculos is patients after six months of treatment.
- TocomparetheserumPCTlevelsbetween initial&aftersixmonthsoftreatmentinpul monarytuberculosispatients.
- To observe the effect of serum Procalcitonin level on disease outcome at the end of six months treatment in pulmonary tuberculos is patients.

MATERIALS AND METHODS

This prospective observational study was conducted in the department of Internal Medicine of Bangabandhu Sheikh Mujib Medical University Dhaka, from the period of October 2017 to October 2018. A total of 30 patients were included for the study according to following inclusion and exclusion criteria. Sampling technique of this study was convenient sampling. Patients diagnosed as smear positive for AFB or Gene-Xpert for Mycobacterium Tuberculosis Bacilli (MTB) positive pulmonary tuberculosis were selected. The diagnosis of PTB was made throughrelevant history (fever, cough for 3 weeks or more and weight loss), examination andconfirmationbysputumforAcidFast Bacilli (AFB)or Gene-Xpert for MTBpositive.Serum samples were kept at 2°C - 8°C& was measured within 48 hours of collection.For long-term storage of specimens were kept below -20°C. Samples were prepared according to the standards set. Firstly, labeled monoclonal antibodies added to the additional samples were washed and chromogen solutions was added to them and was being awaited for 10 min at 37°C for reactions. After 10 minutes, the preventive solution was added to the sample. Then the optical density (OD) level of samples was measured under light with a wave length of 450 nm. A machine did all of these steps automatically. The study was done with the existing facilities of Indoor and Outdoor of Department of Internal Medicine and DOTS corner of BSMMU. Data was entered in Microsoft Excel and analysis was done in STATA version 14. The research protocol was approved by the Institutional Review Board (IRB).

Inclusion Criteria

- Newly diagnosed cases of pulmonary tuberculosis confirmed by at least one sputum smear-positive for AFB or positive Gene-X-pert for MTB.
- Age: Over 18 years to 70 years
- Any gender

Exclusion Criteria

- Already on anti-tuberculous therapy
- Extra pulmonary tuberculosis
- H/O previous treatment for TB
- Smear-negative pulmonary tuberculosis
- Patients having Pneumonia, Urinary tract infection, meningitis, HIV infection, Sepsis, other suspected bacterial infections

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RESULTS

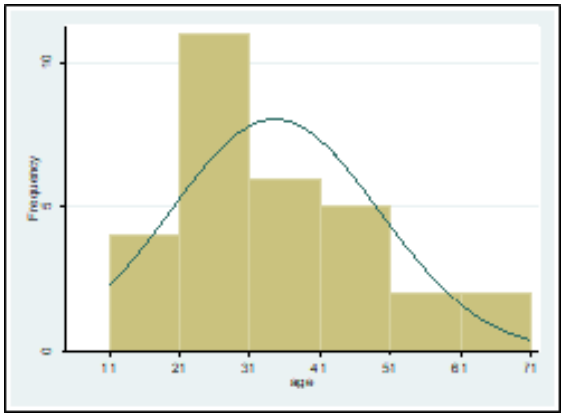

Figure 1: Histogram showing age distribution of participants (n=30).

The mean age of all patients was 34.6 years with standard deviation of 14.8 years. Median age was found 30 years with minimum and maximum ranges were 19 and 70 years, respectively [Figure 1]. Two third (67%) of the patients were male [Figure 2]. Fever was found in 83% respondent, which was highest among all four clinical features included in this study. Most of the patients with cough had more than 3 weeks of duration (85%). Hemoptysis was found in 53% of patients and more than two-third of the patients reported weight loss (70%). Six patients had positive contact with a known case of PTB at the time of enrollment in the study [Table 1]. Two third of the patients had normal BMI and none of them were obese. PCT at enrollment was found weakly & positively correlated with BMI (r= 0.04, p>0.84) [Table 2]. Mean ESR was found 73 mm in first hour with standard deviation of 21 mm in first hour. Total count of WBC was found high in 97% of patients. More than five-sixth of the respondents (87%) had lymphocyte predominant differential count in blood, whereas others showed neutrophil predominant (13%). Almost all patients had abnormal chest x-ray. Only one had normal chest X-ray. Abnormal chest X-ray findings included cavitation (36%), consolidation (20%), military shadow (04%) and patchy opacity (40%).

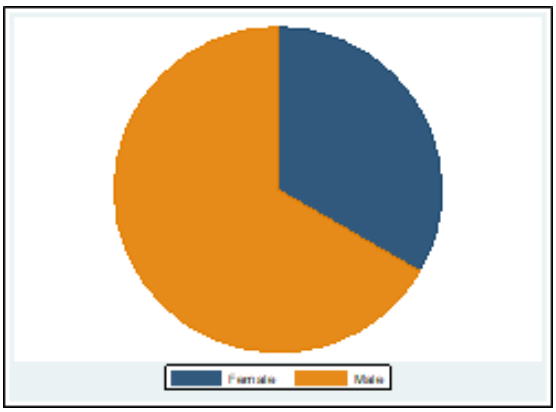

Figure 2: Pie chart showing sex distribution of the participants

Table 1: Clinical features of patients (n=30)

Clinical feature	Number (n=30)	Percentage (%)
Fever	24	83
Cough	27	90
Hemoptysis	16	53
Weight loss	21	70
Contact with sputum positive pulmonary TB	07	23
Data were expressed as frequency & percentage		

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Table 2: BMI of patients (n=30)

BMI	Level (kg/m 2)	Number (n=30)	Percentage (%)
Low Normal Overweight Obese	0 to 18.4 18.5 to 24.9 25 to 30 >30	07 20 03 00	23 67 10 00
Data were expressed as frequency & percentage. Definition of each BMI category was expressed in kg/m2.			

Table 3: Laboratory picture of the respondents (n=30)

Laboratory investigation	Frequency (n=30)	Percentage (%)
ESR (Mean ±SD)	73 ± 21 mm in first hour	
Total count Normal High	 01 29	 03 97
Differential count Neutrophil predominant Lymphocyte predominant	 04 26	 13 87
Chest X-ray Normal Cavity Consolidation	 01 10 05	 03 33 20
Miliary shadow Patchy Opacity	01 13	03 40
Sputum AFB (1+) AFB (2+) AFB (3+) Gene-Xpert+ve	 07 10 08 05	 23 33 27 17
MT (mm) (n=10) Normal Positive	 22 08	 73 27
RBS Normal High	 28 02	 93 07

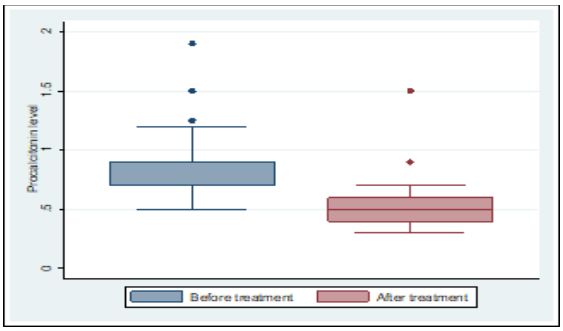

Figure 3: Boxplot showing difference of procalcitonin level due to treatment in TB patients (n=30)

Table 4: Procalcitonin level among patients before and after TB treatment (n=30)

Measures	Before treatment(n=30)	After treatment(n=30)	p value
Category Normal Slightly elevated* Moderately elevated Highly elevated	 00 (00) 30 (100%) 00 (00) 00 (00)	 09 (30%) 21 (70%) 00 (00) 00 (00)	
Mean ± SD (ng/ml)	0.87167 ± 0.2958	0.55± 0.2177	<0.001 (Paired sample t-test)

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Median (IQR) (ng/ml)	0.9	0.5	<0.001 (Sign rank test)
IQR (ng/ml)	0.7-0.9	0.4-0.6	
Range (Min-Max) (ng/ml)	0.5-1.9	0.3-1.5	
Correlation coefficient	0.92		<0.001

Twenty five patients were positive for AFB in sputum, among them 07 were 1+, 10 were 2+ and remaining 8 were 3+. Patients who were negative for AFB in sputum, undergone Gene X-pert and all had positive in Gene X-pert [Table 3]. Procalcitonin level was measured in two time points: before treatment and after treatment. The blood level of procalcitonin was categorized into normal (0 to 0.5 ng/ml), slightly elevated (0.51 to 2ng/ml), moderately elevated (2.01 to 5 ng/ml) and highly elevated (>5 ng/ml). Before treatment, all patients had slightly elevated serum procalcitonin level. After treatment, serum-level of procalcitonin became normal in 30% of respondents. However, mean procalcitonin level was reduced significantly from 0.87 to 0.55 from before treatment to after treatment (p<0.001). Median procalcitonin level after treatment was also significantly reduced from before treatment (p<0.001). A strong positive correlation was found in between before and after blood levels of procalcitonin (r=0.92, p <0.001) [Figure 3 and Table 4]. Male gender had higher procalcitonin level in both before and after treatment than female gender. However, procalcitonin level was lowered more in male gender than female (0.34 vs. 0.29) [Table 5]. In comparison with chest x-ray findings, patchy lesion tended to have higher procalcitonin level in before and after TB treatment [Table 6]. Patients having negative sputum for AFB but positive Gene- Xpert, had highest procalcitonin level at enrollment than others. Similar finding was found among patients after getting TB treatment [Table 7].

Table 5: Association of mean procalcitonin level with TB treatment by gender (n=30)

Variables		**Procalcitonin level**		**Mean difference**	**p value**
		Before treatment(n=30)	**After treatment(n=30)**		
	N	**(Mean ± SD)**	**(Mean ± SD)**		
Sex					
Male	20	0.92 ±0.32	0.58 ±0.25	0.34	<0.001
Female	10	0.79 ±0.22	0.50 ±0.12	0.29	<0.001

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Table 6: Association of mean procalcitonin level with TB treatment by chest x-ray findings at enrollment (n=30)

Variables		Procalcitonin level		Mean difference	p value
		Before treatment(n=30)	After treatment(n=30)		
	N	(Mean ± SD)	(Mean ± SD)		
Chest X-ray					
Normal	01	0.80	0.50	0.30	
Cavity	10	0.79 ±0.18	0.50 ±0.09	0.29	<0.002
Consolidation	05	0.94 ±0.23	0.56 ±0.09	0.38	<0.002
Milliary	01	1.0	0.60	0.40	
Patchy	13	0.94 ±0.41	0.60 ±0.33	0.35	<0.001

Table 7: Association of mean procalcitonin level with TB treatment by sputum examination findings at enrollment (n=30)

Variables		Procalcitonin level		Mean difference	p value
		Before treatment(n=30)	After treatment(n=30)		
	N	(Mean ± SD)	(Mean ± SD)		
Sputum					
AFB (1+)	07	0.80 ±0.35	0.51 ±0.19	0.29	<0.003
AFB (2+)	10	0.80 ±0.11	0.48 ±0.06	0.32	<0.001
AFB (3+)	08	0.88 ±0.29	0.58 ±0.13	0.30	<0.002
Gene- X pert+	05	1.1 ±0.45	0.70 ±0.45	0.31	<0.001

DISCUSSION

In current study, the mean age was 34.6± 14.8 and the majority of patients (70%) were aged between 18 to 40 years. Age pattern in present study is different from other studies and the mean age was lower. However, there have been studies consistent with present study in which most patients were man. PCT level was high among older age patients probably due to having immune compromised, latent co-infection or other autoimmune disorders. Four patients in 18-20 year age group also had comparatively higher PCT. All patients with age more than 50 were male (5 in number), resulting higher PCT level in male than female. The finding of this study show that cough (90%) was the most pre-dominant clinical feature, which also found in other related studies. Presence of fever in 83% patients and weight loss in 70% patients at enrollment also correlate clinical evidence of TB infection among patients at enrollment. The assays differ largely in the detection method of the antibody-PCT-antibody complex and individual characteristics of the assays Gogoset al, Muller et al.[5,6] In all instances, PCT level was decreased significantly after TB treatment. Due to the non-specific

symptoms related to TB infection, such as weight loss, fatigue, persistent coughing, loss of appetite, and night sweats, TB diagnosis is problematic Jeong & Lee.[7] The direct approach includes detection of mycobacteria or its products and the indirect approach includes measurements of humoral and cellular responses of the host against tuberculosis Ramchandran and Paramasivan.[8] It is also important to note that various conditions other than bacterial infection may induce PCT elevation, for example, sever trauma, some autoimmune disorder, prolonged cardiogenic shock, following liver transplantation, in patients with heat stroke, severe pancreatitis, or rhabdomyolysis Meisner et al.[9]However, most of the patients having normal BMI, reduced the scope to compare outcome with other categories. It is peptide of 116 amino acid with an approximate molecular weight of 14.5 kDa, and its structure can be divided into three sections: amino terminus, immature calcitonin, and calcitonin carboxyl-terminus peptide 1 Jinet al.[10] Seven patients had a history of contact with sputum positive pulmonary TB. Mean PCT level was also higher among those having positive contact than those not, indicates possible association between them. Study found evidence of PCT level with prognosis of sepsis patients Nobre et al.[11] The severity of systemic inflammatory response is roughly correlated with the severity of systemic inflammation, although there is no gold standard. Usually, high PCT levels are found in patients with severe sepsis and septic shock Meisner et al9. In this study, laboratory findings were taken only at enrollment, thus correlation of laboratory parameters during before and after treatment could not be evaluated. Therefore, this study focused more on changing PCT level due to six-month TB treatment and level of prediction by baseline laboratory parameters. Patients having more grade at sputum test or undergone Gene- X pert had higher PCT than others, which somehow explains relationship of severity of TB infection and PCT level. However, previous studies suggest not to conclude severity based on sputum examination (both qualitative and quantitative), where there is no opportunity to exclude dead bacilli Wallis et al.[12] Future study can assess same relationship using sputum culture, which could suggest sensitivity and specificity of PCT level at certain cut-offs. Local bacterial infection does not induce significant amounts of PCT Meisner et al.[13] Similarly, PCT levels may be low, if there is no systemic inflammatory response in patients with bacteremia. ESR, chest x-ray findings and WBC picture are established laboratory parameters for pulmonary tuberculosis. At enrollment, patients mean ESR was 73 ± 21 mm in first hour, which was higher than other studies. Negative correlation in between ESR with PCT in both period was found (-0.13 & -0.14), which could not reach statistical significance. In quadratic curve, PCT level (both before and after treatment) was increasing with ESR up to approximately 70mm in first hour of ESR and then it was gradually declined. Previous study found non-

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significant positive correlation in between PCT and ESR. In opinion, positive correlation in between PCT and ESR might exist up to certain point of ESR. Beyond that point, further study including number of TB patients with high ESR is needed to explain. In this study, the mean PCT level before treatment was 0.87± 0.29 and after treatment was 0.55± 0.21. Previous studies shows that plasma level of PCT in healthy individuals are quite low (<0.1 ng/mL) Carrol et al.[14] However, as a cut-off for the diagnosis of sepsis, plasma levels of ≥0.5ng/mL are interpreted as abnormal and suggest presence of sepsis Meisner et al9Therefore, there was limited scope to evaluate relationship of PCT level with multi-organ involvement. The level of procalcitonin in the blood stream of healthy individuals is below the limit of detection (0.01 µg/L) of clinical assays Dendonaet al.[15] However, patients with patchy lesion in chest x-ray had little higher PCT level than cavitary lesion, explaining above statement of having higher PCT in non-localized infections. A persistent increase or failure to decline in the PCT levels has been related to higher mortality rates in various studies Jensen et al.[16] Thus, procalcitonin is superior in identifying and assessing the severity of the infection Reinhart et al.[17]

Limitations of the study:

The study have some limitations such as low sample size, lack of control group, TB diagnosis was based on sputum smear, not excluding the conditions of concomitant other bacterial infection microbiologically, not followed the changing trends of PCT in serum at different points of time during the whole treatment period which reduces the validity of study. This study also did not include extra-pulmonary and MDR-TB.

CONCLUSION

This study assessed serum PCT in patients diagnosed with pulmonary tuberculosis at enrollment and after six months of TB treatment to observe the value of PCT reduction with treatment. PCT level was reduced significantly after getting six-months of TB treatment irrespective of age, sex, BMI and other laboratory parameters. Overall findings indicate significant relationship of PCT level reduction with success of TB treatment. We recommend that PCT should be used as a tool for monitoring of TB patients. Further large-scale study is needed including all type of TB patients (extra pulmonary and MDR-TB) & healthy control group. We also recommend that measurement of PCT should be at different points of time during treatment to observe the changing pattern.

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