

# Study of the Serum Levels of C-Reactive Proteins as an Indicator of Disease Activity in Pulmonary Tuberculosis and Monitoring Response to Treatment.

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## ABSTRACT

**Background:** Pulmonary Tuberculosis is caused by mycobacterium tuberculosis. C-reactive proteins (CRP) are produced in the body by liver in response to inflammation caused by Mycobacterial infection. Insufficient information is available in medical literature, correlating serum CRP levels to the severity of pulmonary tuberculosis. The present study was undertaken to correlate the validity of serum CRP levels to clinical findings. Severity of pulmonary tuberculosis, need for ventilator support, response to anti-tubercular therapy and mortality. Objectives: To correlate the serum CRP levels with clinical findings, mortality, radiological severity and response to anti-tubercular treatment in patients suffering from pulmonary tuberculosis. **Methods:** The present study was conducted in 50 new sputum positive pulmonary TB patients and 50 healthy individuals. The patients were evaluated for clinical and radiological findings, which were correlated to baseline CRP levels. CRP levels were measured at 2 months and after completion of treatment and correlated to treatment end results. **Results:** Mean baseline CRP levels in pulmonary tuberculosis patients were 55.32mg/L (range 16-144mg/L). CRP levels among normal healthy individuals were 4.46 mg/L (range 2-8mg/L). CRP levels were significantly higher in TB patients with fever, tachycardia, tachypnea, hypotension, respiratory distress and the need for ventilatory support when compared to patients without these features. The study showed significant correlation between CRP levels and radiological extent of disease. Baseline CRP levels were significantly higher in mortality group when compared to survivor group. CRP levels showed progressive decline in patients who were cured. **Conclusion:** The CRP levels in pulmonary tuberculosis patients before initiating anti-tubercular therapy showed a positive correlation with features like presence of fever, tachycardia, tachypnea, hypotension, respiratory distress, need for ventilator support, radiological severity and in patients who died. Thus, serum CRP levels can be used as a surrogate marker for severity of pulmonary tuberculosis in the patients. This is probably the first study conducted in North India correlating CRP levels and disease severity of pulmonary Tuberculosis to the best of our knowledge.

**Keywords:** Pulmonary tuberculosis, C-Reactive proteins, Radiological severity, Mortality.

## INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* and usually affects lungs. It is estimated that between 19 and 43% of the world's population is infected with *Mycobacterium tuberculosis*.<sup>[1]</sup>

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C-reactive protein (CRP) is produced by the liver in response to inflammation and its levels are also elevated in patients with pulmonary tuberculosis.<sup>[2,3]</sup>

At present, there is insufficient information correlating CRP levels to clinical findings, radiological severity and response to anti-tubercular treatment.<sup>[4,5]</sup>

The identification of biomarkers that are predictive of adverse outcomes can help in risk stratification of patients for early intervention and better patient management. Biomarkers for early detection of treatment failure measurable during early treatment of TB may help in identification and shifting of these patients to newer drugs.

In the present study, we tested the validity of CRP as a biomarker by correlating its values to clinical findings, radiological severity, need for ventilator support, mortality and treatment outcome. Measuring and charting CRP values may prove useful in determining disease severity or the effectiveness of treatments.

### Aims and Objectives

To correlate the serum CRP levels with clinical findings, radiological severity and response to anti-tubercular treatment in patients of pulmonary tuberculosis admitted to Guru Nanak Dev Hospital, Govt. Medical College, Amritsar.

## MATERIALS AND METHODS

This study was conducted in 50 patients with new sputum positive pulmonary tuberculosis presenting to Government Medical College, Amritsar and 50 individuals from healthy population served as control group. Diagnosis of pulmonary TB was based on symptoms, x-ray findings and positive sputum smear microscopy for *M tuberculosis*. Inclusion and exclusion criteria for the study group were as under-

### Inclusion Criteria

Patients with age of more than 18 years with sputum positive pulmonary tuberculosis

### Exclusion Criteria

Patients with age less than 18 years, those with HIV sero-positive status, liver failure, chronic inflammatory conditions such as autoimmune diseases, malignancies, Inflammatory Bowel Disease and patients not willing to give informed consent.

Before initiating treatment, baseline serum CRP levels were measured and the values were correlated to clinical and radiological findings. Serum CRP levels were correlated with age, BMI, presence or absence of fever, dyspnea, hemoptysis, tachycardia, tachypnea, hypotension, respiratory distress and mortality. Repeat estimations of CRP levels were done at 2 months and 6 months and the values were correlated to treatment end result.

The extent of radiographic disease was graded by using the U.S. National Tuberculosis and Respiratory Disease Association scheme.<sup>[6]</sup> It classifies the disease into-

(1) **Minimal disease:** slight to moderate density, or no visible radiological pathology, without cavitations. Total extent not to exceed the volume equivalent to the area on one side above the second costochondral junction and the spine of the fourth or body of the fifth thoracic vertebra.

(2) **Moderate disease:** disseminated lesions of slight to moderate density that may extend throughout the total volume of one lung or the equivalent in both

lungs; dense and confluent lesions that are limited in extent to one-third the volume of one lung; total diameter of cavitations not more than 4cm.

(3) **Advanced disease:** Greater than the above.

Statistical analysis was performed with SPSS (Version 16.0; SPSS Inc.) and Graph Pad Prism 5.01. Data was expressed as mean  $\pm$  SD. Differences among groups were analysed by one-way analysis of variance (ANOVA). P value  $<$  0.05 was considered significant. Informed consent of patients and ethical committee's approval was obtained before starting the study.

## RESULTS

Fifty new sputum positive pulmonary tuberculosis patients were enrolled for the study. [Table 1] shows the general trend of characteristics of the pulmonary TB patients selected for this study. Thirty-eight patients (76%) were males and 12 (24%) were females. Mean age of study population was found to be 38.2 years (range 20-60 years). In hematological parameters, mean haemoglobin levels were found to be 9.38 gm% (range 7-13gm%). Mean BMI of the patients was 16.94 Kg/m<sup>2</sup>(range 14-20Kg/m<sup>2</sup>). Serum CRP levels in the study group before initiating anti-tubercular treatment were 55.32 mg/L(range 16-144mg/L) as compared to 4.46 mg/L(range 2-8mg/L) in the normal population. Mean CRP levels in TB patients after treatment in treated patients were 5.39 mg/L (range 3-10mg/L). Mean CRP levels in TB patients after treatment in treatment failure group were 35.3mg/L.

**Table 1: showing general trends of characteristics of pulmonary TB patients selected for the study.**

Characteristics		
Number of TB patients	50	
Mean Age(years)	38.2 $\pm$ 12.4	20 to 60 years
Sex		
• Males	38	76%
• Females	12	24%
Mean CRP levels in TB patents before initiating treatment (mg/L)	55.32 $\pm$ 34.32	16-144 mg/L
Number of Patients with fever	35	70%
Number of Patients with hemoptysis	3	6%
Number of TB patients with tachycardia	33	66%
Number of TB patients with tachypnea	28	56%
Number of TB patients with Respiratory distress	15	30%
Number of TB patients with hypotension	10	20%
Number of TB patients in the study group who required Ventilatory support	3	6%
Number of TB patients with miliary TB	2	4%

Number of TB patients with cavitary disease	12	24%
Mortality in TB patients	6	12%
Mean Haemoglobin (gms/dL)	9.38±1.47	7-13gm%
Mean BMI ( Kg/m <sup>2</sup> )	16.94±1.5	14-20Kg/m <sup>2</sup>
Mean CRP levels in TB	5.39±1.74	3-10mg/L

patients after treatment in cured patients		
Mean CRP levels in TB patients after treatment completion in treatment failure patient group.	35.33±9.23	30-46mg/L

Table 2: showing mean CRP levels in patients with and without clinical findings.

Parameters in TB patients	CRP levels(mg/L) (Mean±SD)		'p' value	Level of Significance
	Present	Absent		
Fever	66.20±34.92	29.93±13.19	<0.0003	Highly significant
Hemoptysis	49.00±29.31	55.72±34.85	0.74	Not significant
Tachycardia	70.18±33.30	26.47±7.03	<0.001	Highly significant
Tachypnea	77.18±31.17	27.50±7.12	<0.001	Highly significant
Hypotension	106.20±22.35	42.60±23.12	<0.001	Highly significant
Respiratory distress	96.60±26.15	37.63±18.48	<0.001	Highly significant
Need for ventilatory support	131.67±14.39	50.45±29.00	0.002	Highly significant
Mortality	115.50±20.18	47.11±26.84	<0.001	Highly significant

CRP levels were significantly higher in patients with fever, tachycardia, tachypnea, hypotension, respiratory distress, need for ventilatory support and

mortality when compared to patients without these findings.

### Radiological Severity

Table 3: Relationship between mean baseline CRP levels and radiological severity of disease in patients with pulmonary tuberculosis.

Radiological Severity	No. Of Patients	Baseline CRP levels (mg/L) MEAN±SD	'p' value	Level of significance
Minimal Disease	10	22.70 ± 4.76	< 0.001	Highly Significant
Moderate Disease	22	41.95 ± 18.48		
Advance Disease	18	89.78 ± 29.11		

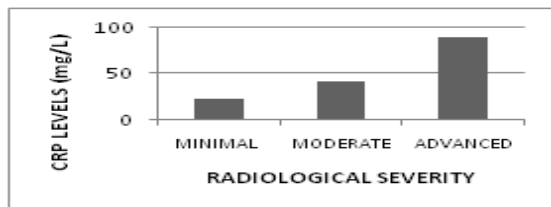


Figure 1: Radiological Severity.

Table 3 shows significant correlation between mean baseline CRP levels and radiological severity of the disease. The mean baseline CRP levels for minimal, moderate and advanced disease were 22.70 mg/L, 41.95 mg/L and 89.78 mg/L, respectively.

Table 4: showing correlation between serum CRP levels and end results of treatment in patients with pulmonary tuberculosis.

	Treatment Failure	Cured	'p' value	Level of Significance
No of Patients	3	41		
CRP levels before initiating treatment (mg/L) (Mean±SD)	59.67±27.57	46.20±26.90	0.40	Not significant
CRP levels after 2 months of treatment(mg/L)(Mean±SD)	21.67±5.77	12.27±4.70	0.10	Not significant
CRP levels at completion of treatment(mg/L)(Mean±SD)	35.33±9.23	5.39±1.74	0.03	Significant

[Table 4] shows comparison between serum CRP levels (before, at 2 months and after completion of treatment) of cured patients and treatment failure group. The cured group had progressive reduction in CRP levels after initiation of treatment. The treatment failure group had a reduction in the CRP levels which again increased by the end of treatment. Although the mean baseline and 2 months CRP

levels were higher in treatment failure group, the values were statistically not significant. The difference in the CRP levels at the end of treatment was however statistically significant.

The present study showed that CRP levels were significantly raised in patients with pulmonary tuberculosis (mean 55.32mg/L) when compared to healthy population (4.46 mg/L). The serum CRP

levels at time of diagnosis showed a statistically significant correlation with clinical findings like fever, tachycardia, tachypnea, hypotension, respiratory distress, need for ventilatory support, mortality and radiological severity of disease. Six patients died of the disease during study. Mean baseline CRP levels in non-survivor group were 115.50 mg/L. The CRP levels did not show significant correlation with age, BMI or hemoptysis. The highest levels of CRP were seen in patients with miliary TB. All patients who were cured after treatment had CRP levels in the normal range at completion of treatment. Treatment failure patients had significantly higher CRP levels at the end of treatment.

## DISCUSSION

In the present study CRP levels were significantly elevated in the patients with pulmonary TB (55.32 mg/L) at the time of diagnosis when compared to healthy population (4.46 mg/L). Peresi E et al<sup>[7]</sup> and Abakay O et al<sup>[8]</sup> obtained similar results in their studies.

The data showed that the mean baseline CRP levels were significantly higher in patients with fever, dyspnea, tachycardia, tachypnea, respiratory distress, hypotension, need for ventilatory support when compared to patients without these findings. A study by Caner SS et al<sup>[9]</sup> showed that CRP levels were significantly higher in patients with fever. Another study by Kaminskaia GO et al<sup>[10]</sup> showed similar correlation between degree of intoxication and CRP levels. The correlation between CRP levels and presence or absence of haemoptysis was statistically not significant.

When we compared the mean CRP levels for survivor and non-survivor group (47.11 mg/L and 115.50 mg/L) from our study to the study conducted by Chong Whang Kim et al<sup>[11]</sup> (69.5 mg/L and 123.8 mg/L) the results showed similar trends and were statistically significant.

When comparing baseline CRP levels with radiological disease severity, the correlation between the two was statistically significant. Similar findings were reported by Chong Whang Kim.<sup>[11]</sup>

Serum CRP levels before, during and after treatment in cured patients as compared to treatment failure group showed that the group that responded to anti-tubercular treatment had progressive lowering of C-reactive protein levels after initiation of treatment. The subjects in treatment failure group had an initial fall in the CRP levels which again increased by the end of treatment. Although the mean baseline and 2 months CRP levels were higher in treatment failure group, the values were statistically not significant. The difference in the CRP levels at the end of treatment was however statistically significant. Similar results were reported by Mohammad

Shameemet al<sup>[12]</sup>, Peresi E et al<sup>[7]</sup>, Lee JH et al<sup>[13]</sup> and Plit ML<sup>[14]</sup>.

## CONCLUSION

Patients with sputum positive pulmonary TB had significantly elevated levels of serum CRP at the time of diagnosis. The baseline serum CRP levels showed a positive correlation with important markers of severity of disease like fever, tachycardia, tachypnea, hypotension, respiratory distress, need for ventilatory support, mortality and radiological extent of disease. The patients who were cured after treatment had CRP levels in the normal range after completion of treatment. Patients who didn't respond to treatment had significantly higher CRP levels at the end of treatment. Thus, CRP may be used as a marker of disease severity and to monitor response to treatment in patients with pulmonary tuberculosis. Although CRP levels at 2 months were higher in treatment failure group when compared to cured group, the values were statistically not significant. This is probably the first study conducted in north India correlating severity of disease and serum CRP levels.

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