

Serum C-Reactive Protein (CRP) - A Dependent Prognostic Marker in Pulmonary Tuberculosis

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ABSTRACT

Introduction: India is the highest Tuberculosis (TB) burden in the world and accounts for nearly 1/4th of the global burden of TB. So study aimed to assess the values of Serum C-reactive protein (CRP) in cases of Pulmonary Tuberculosis (TB) and to evaluate its utility as a serological marker for de novo, treated cases and cases undergoing treatment for Pulmonary TB.

Material and methods: This was a Tertiary hospital based Prospective study of 2 months duration. All patients of pulmonary TB (known as well as newly detected cases) who visited the Respiratory Medicine OPD of this hospital were included in this study.

Results: Of the 50 patients of tuberculosis we assessed, we found 52% newly detected cases of pulmonary TB, 18% undergoing anti-tubercular treatment, 10% Cured cases, 16% treatment defaulters and 4% treatment resistant. The CRP level in the newly detected TB patients was found to be 51.22 ± 30.54 . Those undergoing anti-tubercular treatment had a mean CRP value of 43.29 ± 28.94 and it dropped as the course of treatment progressed. CRP in patients who had started treatment was 66.55 ± 17.22 and those who had completed their treatment were 23.87 ± 26.05 . The patients who had almost completed the treatment had a mean CRP level of 4.78 ± 4.34 . Defaulters had a mean CRP of 66.90 ± 22.66 and the treatment failure had a mean CRP of 87.37 ± 5.83 .

Conclusion: CRP levels are raised in tuberculosis and fall and attain normal values by the end of treatment. If the values are consistently high despite treatment, then there is either resistance to drugs or the patient is not complying with the treatment (Defaulter).

Keywords: PTB, CRP, Defaulter, Resistance, Anti-Tubercular Treatment, Treatment Failure

In 1994 the World Health Organisation (WHO) announced a new strategy, DOTS or Directly Observed Treatment Short course² which has now become the internationally recommended strategy for TB control that has been recognized as a highly efficient and cost-effective strategy. It remains at the heart of the Stop TB Strategy.³⁻⁷ Countrywide coverage was achieved in March, 2006. Since inception till December 2016, more than 2 crore patients were initiated on treatment and more than 35 lakhs additional lives have been saved.

Still, despite the widespread prevalence of TB and the popularity of Directly Observed Short course (DOTS) chemotherapy against TB, there exists no efficient method to successfully monitor the efficacy of anti-tubercular treatment. Presently only sputum smear is widely done to find out the response to the anti-tubercular treatment. However due to the existence of sputum-smear negative tuberculosis, this modality is not very useful.

C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation. Its Physiological role is to bind to Phosphocholine expressed on the surface of dead or dying cells in order to activate the complement system. CRP rises up to 50,000 fold in acute inflammation and as its half-life is constant, its level is mainly determined by the rate of production and hence the severity of the precipitating cause. As CRP is used mainly as a marker of inflammation and infection, measuring and charting CRP values can prove useful in determining the progress of TB and the efficacy of the anti-tubercular treatment. Thus the treatment regimen can be changed timely if the patient response to the drugs is inadequate, leading to not only early recovery but also prevention of Multidrug resistant Tuberculosis. Hence, CRP can serve as a sensitive indicator of activity of the disease and the return to normal values of initially elevated CRP levels may indicate a good therapeutic response. CRP quantitative test is a simple and quick test which detects the level of CRP in serum of the patient.

INTRODUCTION

In 2015, an estimated 2.2 million cases of TB occurred in India out of a global incidence of 9.6 million and 4.8 lakh people died due to TB in India.¹ The estimated TB prevalence figure for 2015 is given as 2.5 million.¹ It is estimated that about 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent TB rather than TB disease.

The table below shows the estimated figures for TB burden globally and for India reported in the 2017 WHO Global TB Report.¹

Estimates of TB burden (2015)	Global	India
Incidence of TB cases	104 lakh	28 lakh
Mortality of TB	14 lakh	4.8 lakh
Incidence of HIV – TB	11.7 lakh	1.1 lakh
Mortality of HIV – TB	3.9 lakh	37,000
MDR – TB	4.8 lakh	1.3 lakh

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This study will use the CRP levels as an indicator of the response of the patients to anti-tubercular treatment. And hence try to determine not only how the patient is responding to the treatment but also whether the patient is a defaulter, whether he is taking medicines regularly or not and at what level of treatment is he in (whether he has just started treatment, whether he is finishing treatment and so on).

Some similar Studies have been done worldwide determining the relationship of response to anti-tubercular treatment and CRP levels. This study will compare the findings of our study with those and if similar results are found then after review and further research this test should be used routinely at regular intervals, during the whole duration of the treatment, to assess response to anti-tubercular treatment.

Study aimed to assess the values of serum C-Reactive Protein in cases of Pulmonary Tuberculosis with the objectives to assess the utility of C-Reactive Protein as a serological marker for de novo and treated cases and cases undergoing treatment for Pulmonary TB, to assess the prognosis and response of patients to treatment of Pulmonary TB by serological estimation of C - reactive protein and to assess the efficacy of CRP to identify the defaulters and resistant cases to anti-tubercular treatment.

MATERIAL AND METHODS

This was a Hospital based Prospective cross sectional conducted in Acharya Vinobha Bhawe Rural Hospital (A.V.B.R.H.), a 1250 bedded Rural Tertiary Hospital of Datta Meghe Institute of Medical Sciences (DMIMS) (Grade "A" Accredited by NAAC), Sawangi (Meghe), Wardha. Institutional ethical committee clearance was taken before starting the study. The duration of study was 6 months. A sample size of 50 Subjects was studied.

Inclusion Criteria

- All patients of pulmonary TB (known as well as newly detected cases) who visited the Medicine and TB chest OPD in AVBRH.
- All the in-house patients of Pulmonary TB admitted in AVBRH.

Exclusion Criteria

- Extra pulmonary Tuberculosis
- Secondary Tuberculosis
- All cases of any other associated Inflammatory Disease

Consent

Verbal consent was obtained from all patients after explaining them the nature of the study.

The subjects were primarily assessed on the basis of a detailed history on a basis of a predesigned questionnaire. Detailed information regarding disease and treatment status was obtained from the patient. To assess the CRP level, 2 ml blood was withdrawn from the patient and was sent was quantitative analysis and the results were obtained. Institutional ethics committee clearance was obtained before starting the study.

STATISTICAL ANALYSIS

The collected data was presented in tabular form and graphs.

It was interpreted statistically and analyzed using the following methods -

- Tukey Multiple Comparison Test
- One Way ANNOVA
- Chi Square Test

$P < 0.05$ was considered significant.

RESULTS

Figure 1 depicts the distribution pattern of all the patients in the study according to their CRP values. Most patients, irrespective of the status of treatment, were found to have CRP levels in the range 80-90 mg/dl (22% of all patients).

Figure 2, depicts the distribution pattern of all those patients who left the treatment in between (Defaulters) according to their CRP levels. It was found that majority of the defaulters had a CRP in the high range, 75% (6) patients had CRP values in the range 50-80 mg/dl. Figure 3, depicts the distribution pattern of the patients who completed the anti-tubercular treatment and were declared cured. All the patients had CRP values less than 20 mg/dl with 80% (4) patients having normal CRP values. This shows that the CRP values reach normal levels when treatment is completed and the patient is cured.

Figure 4, depicts the distribution pattern of treatment resistant patients according to the CRP values. In the study 2 patients completed treatment but were found unresponsive to the drugs and were declared no cured. These patients had a significantly higher CRP values (>80 mg/dl).

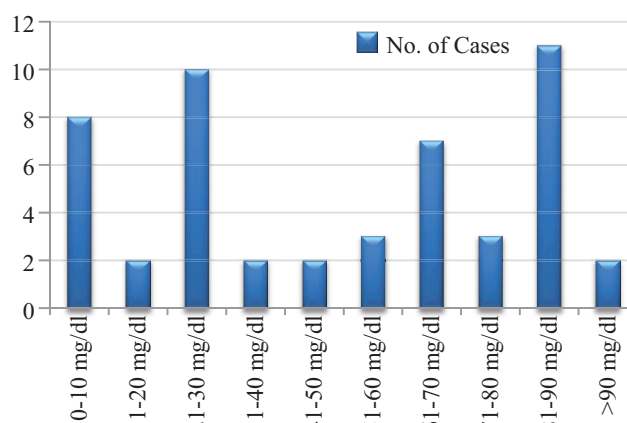


Figure-1: CRP values in all patients of Tuberculosis.

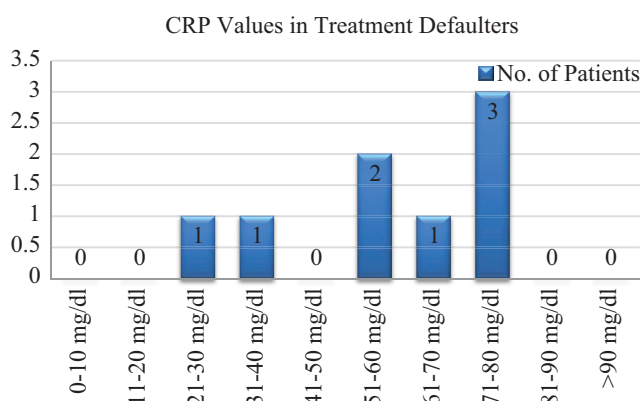


Figure-2: CRP values in Treatment Defaulters.

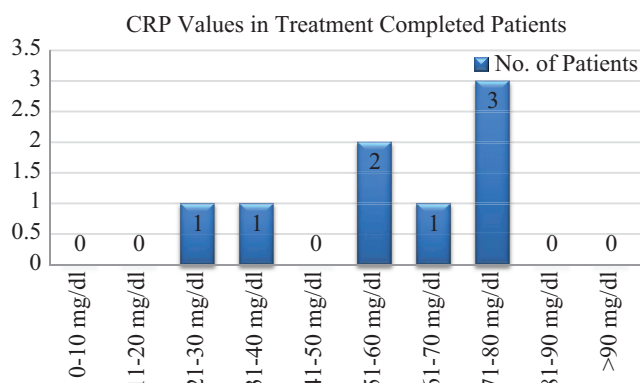


Figure-3: CRP values in Treatment Completed Patients

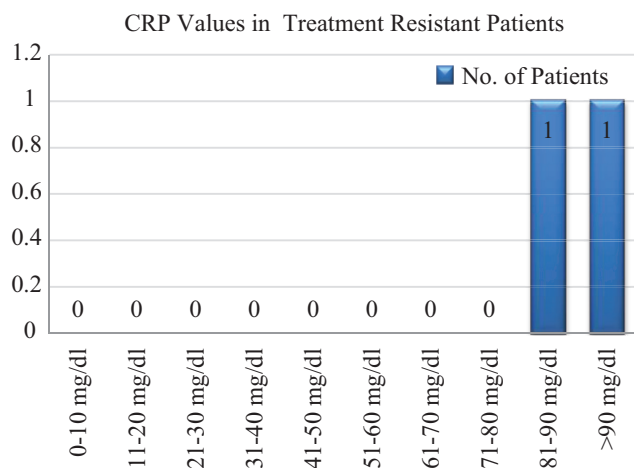


Figure-4: CRP values in Treatment Resistant Patients

DISCUSSION

According to the World Health Organization, Tuberculosis is a highly prevalent disease in India, accounting for about one-fifth of the global figure - making it the most TB prevalent country. However what is surprising is its prevalence despite a cure and control strategy. And the continuing lack of an efficient mark to evaluate the effect of the treatment in a patient.

Hence our study aim to establish CRP as not only as an effective but also economic marker, to detect the response of patient to anti-tubercular treatment and to timely change the treatment regimen in cases where the treatment is not effective so as to suppress the emergence of multidrug resistant TB (MDR TB).

The cases of tuberculosis which we came across were divided into the following categories -

1. Newly detected cases
2. Cases undergoing treatment
3. Cured
4. Treatment defaulters
5. Treatment resistant cases

The values of serum CRP was compared within each category, with other categories of TB cases and with the normal standard (CRP in normally below 10mg/dl). Correlation and reasoning, then finally evaluation and interpretation were done to establish the value of CRP levels as a serological marker for the assessment of response to tuberculosis. Our

study has many findings which are comparable to findings of the studies done worldwide.

In our study, 52% patients out of 50 were males and 48% patients were females. Majority of the patients were within the ages of 21-50 yrs and least number of patients were below 20 yr and more than 70 yrs.

Of the 50 patients of tuberculosis we assessed, we found 52% newly detected cases of pulmonary TB, 18% undergoing anti-tubercular treatment, 10% Cured cases, 16% treatment defaulters and 4% treatment resistant. 56% of the patients were sputum smear positive and the remaining 44% were sputum smear negative.

The mean CRP level in the newly detected TB patients was found to be 51.22 ± 30.54 which is higher than the normal value. Lawn et al⁸, Sukhesh Rao et al⁹, Douglas Wilson et al¹⁰, F C de Beer et al,¹¹ Bajaj G et al,¹² yoon et al,¹³ and Kannapiran M et al,¹⁴ in their studies found that the CRP levels were higher in the patients who had not yet undergone treatment.

Sukhesh Rao et al,⁹ correlated CRP levels with extent of disease and revealed that these values were significantly higher in stage III disease (52.44 ± 17.78). Bajaj G et al,¹² found mean initial levels of CRP in tuberculosis group was $18.52 \mu\text{g/ml}$ and Kannapiran M et al,¹⁴ found moderate or markedly elevated concentrations ($\geq 1 \text{ mg/dl}$) were observed in 58 (87 percent) of the 67 tuberculous patients.

The patients who were undergoing anti-tubercular treatment had a mean CRP value of 43.29 ± 28.94 and it was found that the value dropped as the course of treatment progress as the mean value of CRP in patients who were in the initial stages of treatment was 66.55 ± 17.22 and those who had almost completed their treatment was 23.87 ± 26.05 . In accordance, the patients who had completed the treatment had a mean CRP level of 4.78 ± 4.34 which was within normal values.

F C de Beer et al,¹¹ from their study concluded that C-reactive protein levels decreased rapidly after initiation of treatment in the patients with post-primary tuberculosis without significant pulmonary destruction. Bajaj G et al,¹² noticed that the elevated CRP levels fell significantly to $5.93 \mu\text{g/ml}$ after one month of treatment and by 3 to 6 months of treatment had fallen to normal values. The patients who had left the treatment in between, treatment defaulters, and the treatment resistant patients had higher CRP values. The defaulters had a mean CRP of 66.90 ± 22.66 and the treatment resistant had a mean CRP of 87.37 ± 5.83 .

Hence, the CRP levels are raised in tuberculosis and these levels fall and attain normal values by the end of treatment. But if the CRP values are consistently high despite treatment, then there is either resistance to drugs or the patient is not complying with the treatment (Defaulter).

Thus, CRP can be established as an efficient biomarker to detect the response to anti-tubercular treatment.

Rao Sukhesh MD et al,⁹ concluded that Serum CRP levels may have a role in identifying the advanced and extensive disease patients thereby indirectly helping the health workers to pick up delayed convertors/potential defaulters, so as to guide them to put in extra efforts on these groups, in

tuberculosis control programs. F C de Beer et al, found that C-reactive protein levels decreased rapidly after initiation of treatment in the patients with post-primary tuberculosis. Bajaj G et al,¹² found that the elevated CRP levels fell to normal by 3 to 6 months of treatment.

Considering the above mentioned studies on CRP and its levels vis-a-vis tuberculosis, it can well be stated that there seems to be a definitive variation in the levels not only beyond the normal limits, but also the higher levels show definitive increase depending on the stage as well as the drug response and treatment of the subject.

CONCLUSION

Tuberculosis is a highly prevalent infectious disease in India, especially rural India, which claims many human lives and stunts the socioeconomic progress of the country. Despite the availability of Directly Observed Treatment Short-course (DOTS), the disease still remains highly prevalent, with many people failing to complete the treatment course and an alarming number of multidrug resistant cases coming up. There exists a positive correlation between the CRP levels and tuberculosis. The correlation exist in the form of a definite rise seen in untreated and treatment resistant states of TB and a fall in the CRP in cases of effective treatment in the same. As CRP shows a definite rise and fall pattern in the course of tuberculosis and its treatment, it can behave as a marker for the following categories- CRP can be utilized as a biomarker for not only identifying the sero-prevalence of the disease but also predicting the therapeutic and immune outcome of the subject. In rural setup economics of CRP and the financial liabilities on a patient of tuberculosis definitely seems to come as a relief. It can be henceforth concluded that CRP can definitely server as a marker to detect the patient response and compliance to the anti-tubercular treatment.

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