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CORRELATION OF ERYTHROCYTE SEDIMENTATION RATE (ESR) AND C-REACTIVE PROTEIN (CRP) WITH GRADE OF SPUTUM POSITIVITY IN PULMONARY TUBERCULOSIS PATIENTS

Pulmonary Medicine

Dr. Shaheed Arman Khondekar Junior Resident, GMC Amritsar, Department of Pulmonary Medicine.
Dr. Guneet Sharma Associate Professor, GMC Amritsar, Department of Pulmonary Medicine.
Dr. Naveen Pandhi Professor and Head ,GMC Amritsar, Department of Pulmonary Medicine.
Dr. Arjun Sharma Junior Resident, GMC Amritsar, Department of Pulmonary Medicine.

ABSTRACT

This study investigates the correlation between C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and sputum grades in pulmonary tuberculosis patients. Conducted in the Department of Pulmonary Medicine at Government Medical College, Amritsar, 100 sputum-positive TB patients were analyzed. The study found that CRP and ESR levels significantly correlate with sputum smear grades, indicating that higher levels of these markers reflect increased disease severity. Specifically, the highest ESR and CRP values were observed in patients with Grade 3 sputum smears. The study concludes that ESR is strongly correlated with disease severity,and it could be a valuable diagnostic tool in resource-limited settings. Both CRP and ESR are recommended as adjunctive markers for assessing severity of the disease.

KEYWORDS

INTRODUCTION

Tuberculosis (TB) is a contagious and serious disease caused by the Mycobacterium tuberculosis complex (MTBC). It predominantly affects the lungs and is spread through coughing, with an infectious dose of fewer than 10 bacteria.[1] The mortality rates for untreated active pulmonary tuberculosis can approach nearly 60%.[2] Significant medical advancements beginning in the 1940s brought about excellent treatment that could cure the great majority of clinical cases.[3] Each year, tuberculosis (TB) claims the lives of over a million people globally. Globally, the impact of tuberculosis (TB) is not uniformly spread, with those from resource-poor backgrounds and those living in poverty being disproportionately affected.[4]

The World Health Organization (WHO) deemed tuberculosis (TB) a worldwide emergency in 1990. The WHO responded by endorsing the directly observed therapy strategy (DOTS), which vowed to eradicate tuberculosis by identifying and treating infected cases in environments with limited resources.[5] Within a few years of its design, the World Bank labeled the DOTS strategy the most cost-effective health intervention ever deployed.[6] The frequency of tuberculosis has been gradually declining since 2004, with a 2.3% decline between 2018 and 2019. The 90/90 targets were set by the Joint United Nations Programme on HIV/AIDS with the intention of reaching at least 90% of TB patients and guaranteeing that more than 90% of them successfully complete their treatment. However, at the current pace of advancement, it is improbable that these goals will be accomplished by 2030. Furthermore, these advantages might be lessened by the disruption of TB control efforts during the COVID-19 pandemic.[7]

C-reactive protein (CRP) is a protein found in the blood, the levels of which was seen to rise during inflammation. Its physiological function involves binding to phosphocholine which were present on the surface of deceased or dying cells, which activates the complement system. In order to determine the progress of tuberculosis and the effectiveness of antitubercular therapy, CRP values can be useful in measuring and marking them, since they are mainly used as a determinant of inflammation and infection. CRP may serve as a important indicator of the disease's activity, and its revert to normal baseline values after initial elevated levels can be indicative of good therapeutic response.[8]

Erythrocyte sedimentation rate (ESR) is a simple, cheap, and commonly used test which has been in use since the early 20th century. It is sensitive to inflammation or the so-called acute-phase response. It measures aggregation of red blood cells and fall in a vertical column when held vibration free at room temperature.[9,10] When it comes to pulmonary tuberculosis, the liver is stimulated by inflammatory cytokines to create acute-phase proteins like fibrinogen, which raises the ESR.[11]

Sputum positivity is a crucial aspect of TB management, aiding in diagnosis, treatment monitoring, and prognostication. However, its predictive value for treatment outcomes is not absolute and should be interpreted in the context of other clinical, radiological, and microbiological data.

The correlation between the grade of sputum and pulmonary tuberculosis (TB) is significant, as higher sputum smear grades are associated with increased infectivity and disease severity.

Studies have shown that higher grades of sputum acid-fast bacilli (AFB) smears correlate with a higher risk of Mycobacterium tuberculosis transmission. For instance, Lohmann et al. found that the highest sputum AFB grades (+4/+5) were associated with the highest relative risk (≥ 8) of extensive transmission or active TB among contacts.[12] This indicates that patients with higher sputum smear grades are more likely to transmit TB to others.

Additionally, Gopalan et al. demonstrated that a 3+ smear grade was a significant predictor of unfavorable TB treatment outcomes, with an adjusted hazard ratio (HR) of 1.94.[13] This suggests that higher sputum smear grades are also indicative of more severe disease and poorer prognosis.

Ko et al. further supported this by showing that CT findings such as cavitation and consolidation were more frequent and extensive in patients with higher sputum AFB grades, indicating a correlation between radiological severity and sputum smear grade.[14]

In summary, higher sputum smear grades are correlated with increased transmission risk, greater disease severity, and poorer treatment outcomes in pulmonary tuberculosis.

AIMS AND OBJECTIVES

1. To determine the grade of sputum positivity by AFB staining [Ziehl-Neelsen stain (ZN) method].
2. To determine the levels of CRP and ESR in blood in pulmonary tuberculosis patients.
3. To evaluate the correlation between CRP and ESR levels in blood with grade of sputum positivity.

MATERIALS AND METHODS

This observational study was carried out on 100 sputum positive pulmonary tuberculosis patients in the department of Pulmonary Medicine, Government Medical College, Amritsar. For these 100 patients blood samples were collected and their serum values of C-reactive protein and Erythrocyte Sedimentation Rate were evaluated. The patients were enrolled at department of Pulmonary Medicine, Govt. Medical College, Amritsar. This study was conducted after approval from Institutional Thesis and Ethics Committee, Government Medical College, Amritsar(Memo number 10803/D-26/2021 Batch,

Date:03-04-2023)

Inclusion Criteria:
1. Patient consenting for the study.
2. Newly diagnosed sputum positive tuberculosis patients of either gender admitted in Government Medical College, Amritsar under National Tuberculosis Elimination Program.
3. Age >18 years to <80 years.

Exclusion Criteria:
1. Patients not giving consent for the study.
2. Patients <18 years of age.
3. Patients of chronic obstructive pulmonary disease and bronchial Asthma.

All patients were enrolled in the study after taking written and informed consent in the local language that the patient could understand. A pre- structured proforma was filled in those cases, which are included in the study.

Statistical Analysis:
Data have been documented, tabulated and analyzed using appropriate statistical methods wherever applicable.

OBSERVATIONS
All the observations were compiled in a proforma and were subjected to statistical analysis using appropriate test. The results were as follows
1. The maximum number of cases belonged to the age group of 21-30 years i.e. 32% followed by 16% in the age group of 41-50 years. Minimum cases were in age group >70 years i.e. 5%. Mean age was 40.59±17.77 years. The youngest case was 19 years old and the oldest case was 79 years in age
2. Maximum cases were males (58%), while females contributed (42%) of cases.
3. It was seen that 41% were farmers, followed by 40% were housewifes and 18% were laborers, and 1% students as well.
4. Most of the cases taken in the study were having more than one complaint. It was seen that the most common symptom was cough which was present in 100% cases and fever which was present in 100% cases. Breathlessness was present in 90% cases and hemoptysis was present in 12% cases, while 1% cases had chest pain.
5. The above table of comorbidities shows that 11% cases had hypertension and 8% cases had diabetes mellitus.
6. The table of general physical examination shows that 97% cases had pallor, 13% cases had clubbing, 9% cases had icterus and 13% had lymphadenopathy.
7. In my study it was seen that the mean of Pulse rates of case were 80.56±12.12 beats per minute, the mean of respiratory rate was 20.26±3.87 breaths per minute, the mean of Systolic Blood pressure was 116.70±15.38 mm Hg and that of Diastolic Blood Pressure was 75.23±10.09 mm Hg
8. It was seen that the mean of pulse rates of case were 80.56±12.12 beats per minute, the mean of respiratory rate was 20.26±3.87 breaths per minute, the mean of systolic blood pressure was 116.70±15.38 mm Hg and that of diastolic blood pressure was 75.23±10.09 mm Hg
9. It was seen that mean of hemoglobin was 9.40±1.16 g/dl, total leucocyte count was 12.21±10.88 per microliter ,random blood sugar was 121.5±47.98 mg/dl, serum urea was 28.52±10.43 mg/dl, serum creatinine was 0.85±0.26 mg/dl ,serum bilirubin was 0.80±0.46 mg/dl, SGOT is 76.26±93.66 IU/liter , SGPT was 73.32±84.16 IU/liter.
10. This study showed that Mean value of ESR of 100 cases was 96.11±33.77 mm/hr and Mean value of CRP of 100 cases was 39.33±34.11 mg/dl
11. This study showed that mean of ESR and CRP in grade 1 sputum was 81.61±21.49 mm/hr and 24.95±20.92 mg/dl respectively that of in grade 2 sputum was 101.42±36.21 mm/hr and 39.92±55.31 mg/dl respectively that of grade 3 sputum was 108.58±37.78 mm/hr and 44.10±13.90 mg/dl respectively.
12. In my study it was seen that the mean value of ESR in sputum grade 1 was 81.61±21.49 mm/hr, sputum grade 2 was 101.42±36.21 mm/hr and sputum grade 3 was 105.58±37.78 mm/hr. In my study it was seen that the Spearman correlation coefficient of ESR with Grade of sputum was Significant(p=0.0001).
13. In my study it was seen that the mean value of CRP in sputum Grade 1 was 34.95±20.92 mg/dl, sputum grade 2 was 39.92±55.31 mg/dl and sputum Grade 3 was 44.10±13.90 mg/dl. It was also seen that correlation of grade of sputum with CRP was significant(p=0.002).
14. Study showed that the comparison of ESR vs CRP in each Grade of sputum 1,2,3 and it was seen that the 'p' value was less than 0.0001 (Highly Significant).

Table 1: Showing Sputum Grade Wise Distribution Of ESR And CRP

	Grade I	Grade II	Grade III	Total
ESR (mm/hr)	81.61±21.49	101.42±36.21	108.58±37.78	96.11±33.77
CRP (mg/dl)	24.95±20.92	39.92±55.31	44.10±13.90	39.33±34.11

Table 2: Showing Comparison Of ESR vs CRP In Each Grades Of Sputum

Difference	-56.660
Standard error	2.999
95% CI	-62.5743 to -50.7457
't' statistic	-18.892
d.f.	198
Significance level	'p' < 0.0001

GRADE 1 ESR VS CRP

Difference	-61.500
Standard error	6.611
95% CI	-74.5368 to -48.4632
t-statistic	-9.303
DF	198
Significance level	P < 0.0001

GRADE 2 ESR vs CRP

Difference	-64.480
Standard error	4.026
95% CI	-72.4185 to -56.5415
't' statistic	-16.018
d.f.	198
Significance level	P < 0.0001

GRADE 3 ESR vs CRP

DISCUSSION:
Tuberculosis (TB) is a disease which is infectious, primarily caused by the Mycobacterium tuberculosis. It predominantly affects the lungs but can also impact other organs of the body.[15,16] The disease is transmitted via droplets which are aerosolized from individuals with active pulmonary TB.[16] Globally, tuberculosis is a primary cause of illness and mortality, especially in developing nations. The disease is further compounded by co-infections like HIV and problems with healthcare systems.[17]

Presence of tubercular bacilli in sputum samples, which is a direct indicator of active disease and infectiousness, is indicative of the relationship between sputum positivity as well as pulmonary tuberculosis. Sputum positivity, typically evaluated by AFB smear, culture or PCR in association with certain radiographic and clinically relevant features which indicate a greater extent of the disease.

Research has shown that individuals with sputum AFB-positive pulmonary tuberculosis (TB) have much higher frequencies and larger extent of specific computed tomography (CT) abnormalities, such as centrilobular micronodules, tree-in-bud opacities, consolidation, and cavitation, than patients with AFB-negative TB.[18] These radiological features not only suggest active disease but also correlate with higher grades of AFB smear positivity, indicating a higher bacterial load.

Overall, sputum positivity is an important indicator of active infection and response to treatment in pulmonary tuberculosis, which has significant implications for the transmission and management of the disease.

C-reactive protein and Erythrocyte sedimentation rate are inflammatory markers that play a role in the assessment and management of pulmonary tuberculosis. CRP and ESR and levels were seen to be higher in patients with active pulmonary TB, reflecting the response of acute phase and inflammation associated with the disease.[19,20]

CRP, in particular, correlated with disease severity and extent of lesions in pulmonary tuberculosis . Patients with more extensive

disease and those with lesions in both lungs had higher values of CRP and it decreased significantly following effective treatment.[21] This makes CRP a useful marker for disease progression and response to therapy in pulmonary TB. Additionally, it's levels are associated with T-cell profiles, specifically reflecting a shift towards a Th2 response in active disease.

ESR, while less specific, also correlates with pulmonary TB activity. It is generally elevated in active cases and can be used alongside other markers to assess the inflammatory status of the patient. However, its role is more limited compared to CRP due to its low specificity and slow response to changes in disease activity.[19,21]

In summary, both ESR and CRP are valuable in the initial assessment of disease severity and monitoring response to treatment in pulmonary tuberculosis, with CRP providing a more dynamic and specific measure of inflammatory activity related to pulmonary TB.

My study revealed that the most (32%) of cases were from the age of 21 to 30 years that had pulmonary tuberculosis. The minimum age of cases that was affected was 19 years and that of maximum age was 79 years. So it was evident that the younger population was affected most. In a study led by Cruz AT et al. (2013) and Starke JR, 145 adolescent tuberculosis patients were included. Their average age was 15.4 years, with an equal gender distribution (50% female, 50% male). Among them, Fifty five% were Hispanic, twenty six % Black, thirteen % Asian, and one % White. A total of 54 patients were born outside the country. Diagnoses were established primarily through symptomatic presentation in 79% of cases, during contact investigations in 14%, and following tuberculin skin testing in the remaining cases.[22]

In my study it was seen that males(58%) were affected more than females(42%). Tuberculosis (TB) affects more males than females globally. The literature consistently reported a higher incidence, prevalence, and mortality of TB in males compared to females. Studies had shown that men are more likely to develop active pulmonary TB and also experience poorer treatment outcomes. In summary, males were more affected by tuberculosis than females, with a combination of biological and socio-behavioral factors contributing to this disparity.

In a study conducted by Jiménez-Corona ME et al. (2006), 623 pulmonary TB patients were included. The study found that men were more prone to treatment default and mortality from TB compared to women. This study concluded that these higher rates of disease transmission and reactivation, and poor treatment outcomes in men, highlighted gender disparities in the diagnosis and management of pulmonary TB. The findings suggest the need for targeted strategies in endemic areas to address these specific challenges.[23]

In my study it was seen that 41 were Farmers(41%), followed by 40 were housewives (40%) and 18 were labourers (18%), as well as students were 1(1%).

In a study conducted by Torres-Gonzalez P et al (2013). it has been shown that workers that were exposed to farm animals infected with Mycobacterium Bovis had a high incidence of latent and pulmonary tuberculosis (TB), and that occupational exposure in non-ventilated rooms enhanced the chance of contracting the disease. In this context, interspecies transmission is common and poses a workplace risk.[24]

My study showed that most of the cases taken in the study were having more than one complaints. Most common symptom was cough which was present in 100 (100%) cases and fever which was present in 100 (100%) cases. Breathlessness was present in 90 (90%) cases and in 12 (12%) cases hemoptysis was seen, while 1 (1%) cases had chest pain.

In a study conducted by Akkara SA et al., 264 patients in total were included. Most of them were in their 40s and 50s and were men. Expectoration from a cough was the most frequent complaint. A chest X-ray revealed different levels of lung loss, with Wilcox Grade II involvement seen in 38% of the patients. Thirty-four instances had normal spirometry, while the other cases showed signs of restrictive pattern and reversibility associated with varied degrees of obstructive airway disease. Pulmonary hypertension was evident in seventy-two cases. These results are in line with what has been published in the literature.[25]

In my study it was seen that (11%) cases had Hypertension and 8 (8%) cases had Diabetes Mellitus as comorbidities.

In a study by Bhattacharya P et al. (2020) involving 173 patients, it was found that 53.17% of them had comorbidities, with diabetes mellitus (DM) (26.58%) and hypertension (17.34%) being the most common conditions. Comorbidities were significantly more prevalent among Pulmonary TB patients compared to those with extrapulmonary tuberculosis (EPTB). The study also observed that HbA1c levels were higher in PTB patients than in those with EPTB. Notably, half of the patients had comorbidities, predominantly diabetes mellitus, and PTB patients exhibited poorer glycemic control.[26]

My study showed that in general physical examination 97(97%) cases had pallor, 13(13%) cases had clubbing, 9((%) cases had icterus and 13(13%) had lymphadenopathy.

In their study (Minchella PA et al.,)(2015) it was found that anemia was more prevalent among tuberculosis patients (67%) compared to TST-positive controls (36%) and TST-negative controls (21%).At the time of tuberculosis diagnosis, autoimmune (AI) anemia was the most frequently observed type, declining from 36% to 8% after six months of treatment. However, there was no corresponding decrease observed for anemia with iron-responsive components. Iron-related indicators effectively differentiated between active untreated tuberculosis and treated cases, as well as between TST-positive or TST-negative controls and tuberculosis patients undergoing treatment. Notably, hepcidin levels exhibited the most significant decrease, reducing from a median of 84.0 ng/mL at diagnosis to 9.7 ng/mL after two months ($P < 0.001$).[27]

In my study it was seen that Mean value of ESR of 100 cases is 96.11±33.77 mm/hr and Mean value of CRP of 100 cases is 39.33±34.11 mg/dl.

Significant correlations were found between SAA, CRP, and ESR in a study by Furuhashi K et al., Among them, the association between SAA and CRP was particularly substantial ($r = 0.88$). CRP levels were greater in bilateral lesions and had a strong correlation with both the sputum smear scale and the size of lesions. Patients with pleural effusion had greater levels of all indicators, but SAA values corresponded with the sputum smear scale. The ratio of Th1/Th2 was inversely linked with both CRP and SAA levels. ESR, on the other hand, had a negative correlation with the Tc1/Tc2 ratio.[28]

It was shown that CRP accurately represented the severity of the illness prior to treatment. While ESR was linked to cytotoxic T-cell proportions, levels of CRP and SAA were linked to helper T-cell proportions; both were type 2 predominant.

In my study it was seen that the mean of Pulse rates of case were 80.56±12.12 beats per minute, the mean of respiratory rate was 20.26±3.87 breaths per minute ,the mean of Systolic Blood pressure was 116.70±15.38 mm Hg and that of Diastolic Blood Pressure was 75.23±10.09 mm Hg.

In a study conducted by Seegert AB et al., 1544 patients in total were enrolled. At the time of inclusion, 12.8% of patients had hypertension. Patients with hypertension had a little less severe case of tuberculosis (TB), but at the 2-year follow-up, their mortality rate was 64% higher and they were also less likely to have a good treatment outcome. Patients over 45 years old and female hypertension patients had the highest mortality rates.[29]

It was concluded that hypertensive patients at the start of TB treatment had a increased rate of mortality at two year follow-up. Mortality rates were highest in hypertensive females and patients aged ≥45 years.

In my study it was seen that the mean value of ESR in sputum grade 1 was 81.61±21.49 mm/hr, sputum grade 2 was 101.42±36.21 mm/hr and sputum grade 3 was 105.58±37.78 mm/hr showed that the mean value of ESR increased with grade of sputum. It was also seen that correlation of ESR and Grade of sputum was significant.

In my study it was seen that the Spearman correlation coefficient of ESR with Grade of sputum was 0.0001(Significant).

In a study done by Romero-Tamarit A et al, it was seen that the study indicated that higher ESR values are associated with greater bacillary

load in TB patients. This suggested that there might be a positive correlation between ESR and sputum positivity grades, as both are indicators of disease activity and severity.[30]

In my study it was seen that the mean value of CRP in sputum Grade 1 was 34.95±20.92 mg/dl, sputum grade 2 was 39.92±55.31 mg/dl and sputum grade 3 was 44.10±13.90 mg/dl showed that the mean value of CRP increased with grade of sputum. It was also seen that correlation of CRP with grade of sputum was significant.

In my study it was seen that the Spearman correlation coefficient of CRP with Grade of sputum was 0.002(Significant).

In a study done by Azam K, Khosa C, Viegas S, et al. It was seen that The Pearson correlation coefficient between C-reactive protein (CRP) levels and the grade of sputum positivity in pulmonary tuberculosis patients was reported to be 0.70, indicating a strong positive correlation. This correlation suggested that as the sputum bacillary load increases, the CRP levels also tend to be higher.[31] This relationship underscored the utility of CRP as a biomarker that reflects the bacterial burden in pulmonary tuberculosis, aligning with clinical observations that higher mycobacterial loads provoke stronger inflammatory responses, as evidenced by elevated CRP levels.

In my study it was seen that the mean of ESR and CRP in grade 1 sputum was 81.61±21.49 mm/hr and 24.95±20.92 mg/dl respectively that of in grade 2 sputum was 101.42±36.21 mm/hr and 39.92±55.31 mg/dl respectively that of in grade 3 sputum was 108.58±37.78 mm/hr and 44.10±13.90 mg/dl respectively.

In my study it was seen that in comparison of ESR and CRP in each grades of sputum the P value is less than 0.0001.

CONCLUSION

Tuberculosis is one of the leading causes of death from a single infectious agent worldwide. The study concludes that ESR and CRP are valuable adjunctive markers in the diagnosis of severity of tuberculosis. Their levels correlate well with disease severity and treatment response, making them useful for both initial assessment and ongoing monitoring. ESR and CRP values increased with higher sputum grades, showing a correlation between disease severity and these markers. Specifically, the mean ESR and CRP values were highest in Grade 3 sputum cases.ESR was determined to be a better marker than CRP for indicating disease severity.The study concluded that ESR, being more affordable, could serve as a useful tool for assessing disease severity in resource-limited settings, where advanced diagnostic techniques are less available.Thus, both ESR and CRP can help assess tuberculosis severity, but ESR is a more reliable and cost-effective marker.

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