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Original Research Article

Study of Acute Phase Inflammatory Markers (ESR, CRP, Ferritin, Albumin/ Globulin Ratio) in Active Tuberculosis, Its Correlation with Disease Severity and Response to Treatment

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Abstract

Tuberculosis (TB) is one of the leading causes of morbidity and mortality. TB induces an acute phase response, resulting in elevated levels of blood reactants like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), ferritin and albumin/globulin ratio (AGR). This study aims to evaluate values of acute phase inflammatory markers, including ESR, CRP, ferritin and AGR prior to treatment, end of intensive phase (IP), and end of continuation phase (CP). Material & Methods: This hospital-based prospective observational study was carried out over 14 months (January 2023 to March 2024) in the Department of Pulmonary Medicine at Gauhati Medical College and Hospital, Guwahati. A total of 73 adult patients with newly diagnosed pulmonary TB and treated with anti-tubercular treatment (ATT) were enrolled. Inflammatory markers such as CRP, ESR, ferritin and AGR were measured at baseline, end of IP (8 weeks) and end of CP (16 weeks). Results: The cohort predominantly comprised females (57.53%) with a mean age of 48.49 ± 10.74 years. Most patients presented with a cough (95.89%) and 13% had a history of TB. Moderate pulmonary TB was found in 49.32% of the patients. A majority of patients were microbiologically positive and showed nodular patterns on radiological exams (50.68%). At the end of CP, significant reductions were noted in ESR, CRP and ferritin levels, while the AGR increased significantly ($p < 0.0001$). Conclusion: Treatment during the IP and CP led to a significant decrease in inflammatory markers, including ESR, CRP, and ferritin, with a notable increase in AGR. These changes suggest a positive response to ATT, observed across varying severities of pulmonary tuberculosis.

Keywords: APR- Acute phasereactant, ESR-Erythrocyte sedimentation rate, CRP-C reactive protein, PTB-Pulmonary tuberculosis.

Introduction

The leading infectious disease that causes morbidity and mortality is tuberculosis (TB). [1] Around a million people succumb to death from TB every year, and an around 10 million people get the disease globally. [2] According to estimates from the World Health Organization (WHO), about 2 million people worldwide die from TB each year and about 8 million people worldwide get active TB every year. One out of every ten individuals with Mycobacterium tuberculosis (MTB) infection may go on to develop an active disease at the some point in their lifetime. [3] With an approximate incidence of TB of 277 million in the year 2022, India makes up about 25% of the tb cases of the world. [4] The country has made a commitment to ending TB by 2025. [5]Ninety percent of cases of active TB are reactivation of TB disease. It is the most prevalent form of the TB. The most frequently affected organ is the lung [6].A cellular immune response is one of the characteristics of TB infection. [7] The cytokines generated during the immune response are involved in both effector and regulatory processes. They also activate and proliferate macrophages and T lymphocytes, which in turn secrete cytokines (interleukins [IL-6, IL-8 and IL-12] and tumour necrosis factor-alpha [TNF-α]) that facilitate the cellular immune response's development. [8] TNF-α and IL-6, in particular, have an impact on the maturation of the cells of the thrombopoietic lineage and the release of platelets

in the blood. [9] As a result, certain antigens of the mycobacteria interact with other and "toll-like receptors (TLRs)" which are present on the surface of the dendritic cells and macrophages, causing a cellular immune response that is primarily proinflammatory. [10] "The acute-phase response" (APR), a systemic reaction, coexists with the inflammatory reaction11 C-reactive protein (CRP) is unique among APR proteins because acute inflammation causes a thousand-fold increase in its serum level. [12] A negative acute-phase protein called albumin has been observed to decrease in response to chronic infections-associated inflammation. [13] On the other hand, high levels of globulin have been linked to rheumatic diseases and cancer. [14] During the two-month IP, TB patients who showed a negative culture result did not show significantly elevated values of albumin or albumin to globulin ratio (AGR) than those with a positive culture. [15]

Beyond merely reflecting inflammatory responses, biomarkers of the iron metabolism pathway, such as ferritin, which also function as APP, may be useful as treatment response markers. In fact, autoimmune disorders, cancer, infections and other diseases are associated with elevated levels of ferritin which is surrogate marker of iron storage that is used as a gauge of status of iron and inflammatory response. High ferritin levels have been observed in pulmonary TB (PTB) patients; however, limited research has examined whether ferritin levels are indicative of treatment response. Conversely, circulating levels of CRP have been found to be correlated with radiographic improvement and the severity of TB after two months of antitubercular therapy (ATT). [16,17] CRP and ferritin levels were found to be elevated in TB disease patients, about to start ATT and to decrease over the first two months of anti tb drug treatment. Ferritin levels were not correlated with mycobacterial load, although elevated CRP levels are indicative of higher Acid-Fast Bacilli (AFB) smear grades. Based on this observation, we hypothesize that MTB-driven inflammatory tissue damage may significantly increase CRP production, while ferritin may be indirectly induced through the activation of other, as of yet unidentified, inflammatory pathways. Finally, after 60 days of ATT, ferritin proved to have a promising role as a TB biomarker as the predictor of the outcome of ATT. [17]

The majority of biomarkers tend to show a significant decline in levels following ATT initiation. [15] APPs that are highly accurate baseline predictors of ATT failure include CRP, ESR, ferritin and AGR. These markers have the potential to be a quick prognostic test for unfavourable treatment outcomes in PTB if they are validated. Therefore, the aim of this present study was to assess acute phase inflammatory marker values before starting of treatment, after the end of the IP and after the end of the continuation phase (CP), including ferritin, ESR, CRP and AGR.

Aims and Objectives: To evaluate values of acute phase inflammatory markers – ESR, CRP, ferritin and AGR prior to treatment, at the end of the IP period and end of CP period.

To evaluate the relationship of acute phase protein with the severity of the disease.

Materials & Methods

This was a prospective observational study conducted over a period of 14 months - from January 2023 to March 2024 in the Department of Pulmonary Medicine and allied specialities of Gauhati Medical College, Guwahati, Assam.73 Adult patients with newly diagnosed pulmonary tuberculosis (PTB) who were treated with ATT were included in the study .Excluded patients were those who were diagnosed with MDR tuberculosis, pregnant women.

Important parameters Included presenting symptoms, severity of PTB, and diagnosis of PTB based on clinical examination, radiological examination and microbiological examination. A previously validated "clinical tuberculosis (TB) score", developed by "Bandim", was employed to evaluate the severity of the disease. Laboratory parameters Included diagnosis of PTB based on microbiological examination as well as estimation of inflammatory markers, including CRP, ESR, ferritin and AGR. Inflammatory markers such as CRP, ESR, ferritin and AGR were measured at baseline, end of IP (8weeks) and end of CP (16weeks). Serum CRP and Serum Ferritin were measured by sandwich immunoassay of chemiluminescence type, reagent manufacturer is Biorad. Albumin and globulin by reflectance spectrophotometry and ESR by automated analyser (vesmatic cube30) Cure was defined as negative AFB smear at the end of CP of ATT. "Treatment failure" was defined as positive sputum smear at the end of CP of ATT.

Observations and Results

A total of 73 adult patients who are being newly diagnosed with PTB and treated with ATT were enrolled in the study. A comprehensive clinical history, thorough physical examination, and laboratory tests were performed in each instance. The results and observations of the data were recorded in tabular form, bar diagram, and pie diagram wherever necessary. Appropriate statistical methods were applied, calculated and presented. The majority of the patients were in the age group

of 41 – 50 years (34.25%). Majority of the patients were females (57.53%) with a female-to-male ratio of 1.35. Out of a total of 73 patients, 10 (13.70%) had a history of TB, while the remaining 63 (86.30%) did not report any history of TB.

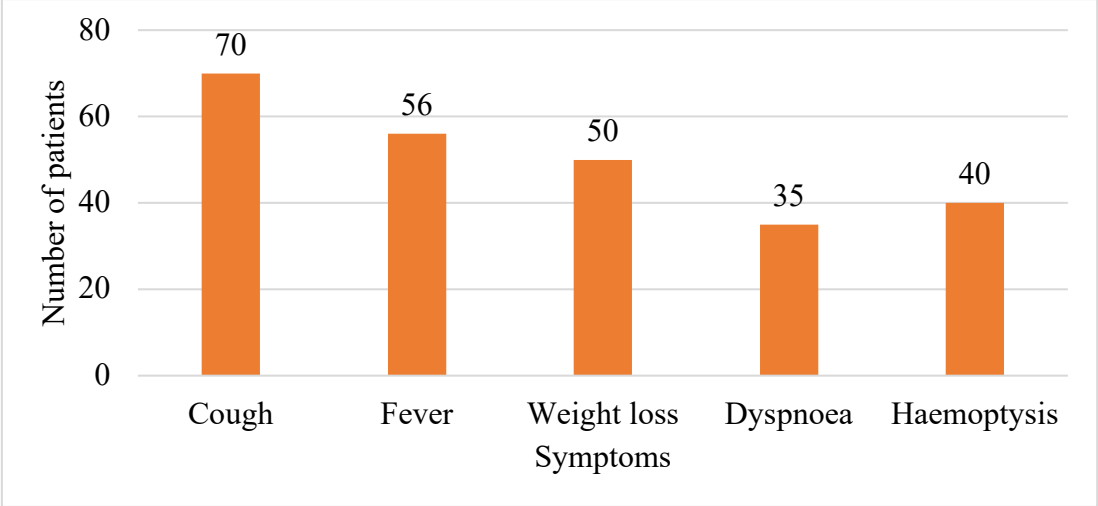

Figure 1: Distribution of Patients Based On Presence of Symptoms

Out of a total of 73 patients, 70 (95.89%) had a cough succeeded by fever (76.70%), weight loss (68.40%), dyspnoea (47.90%) and haemoptysis (54.79%).

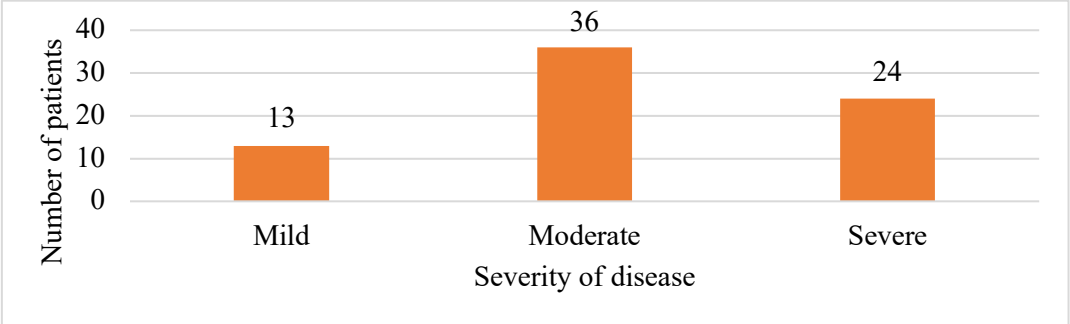

Figure 2: Distribution of Patients Based On Severity Of Disease

According to Bandim TB score Out of a total of 73 patients, 36 (49.32%) had a moderate disease succeeded by 24 (32.88%) had severe disease and 13 (17.80%) mild disease.

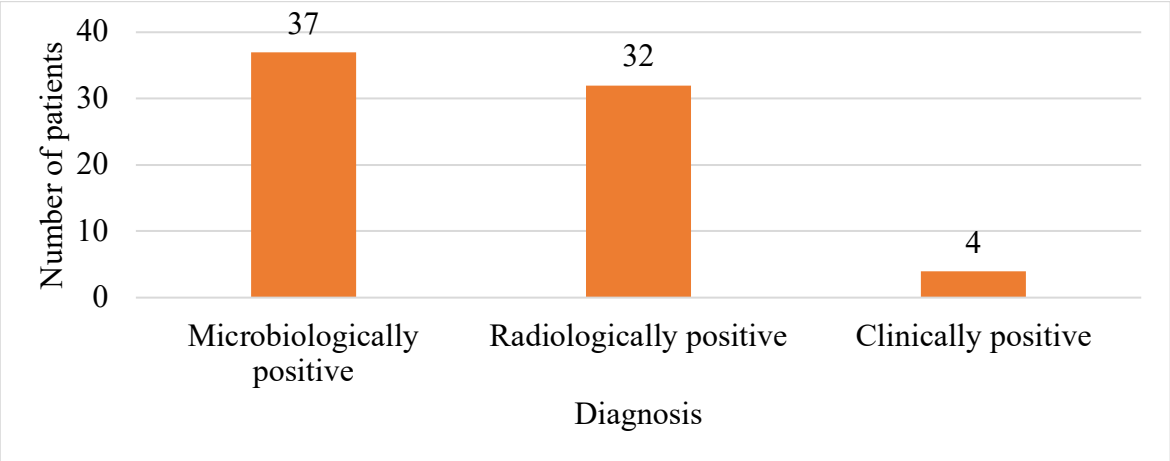

Figure 3: Distribution of Patients Based on Diagnosis

Out of a total of 73 patients, 37 (50.68%) patients were microbiologically positive, 32 (43.84%) were radiologically positive, and 4 (5.48%) were clinically positive for PTB.

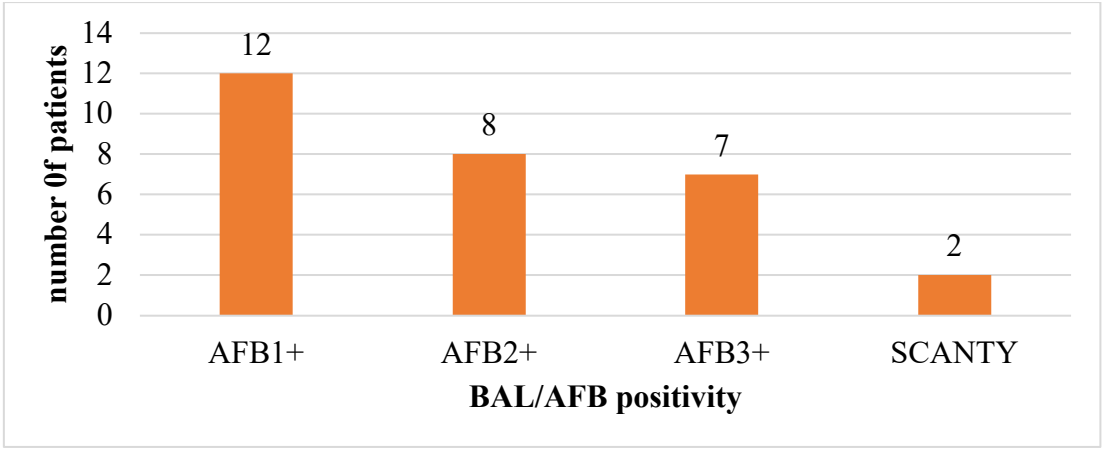

Figure 4: Distribution of Patients According To Sputum/BAL AFB Positivity

Among the 29 patients who tested positive AFB, the results were distributed as follows: 12 patients (41.37%) had a 1+ AFB result, while 8 patients (27.58%) had a 2+ AFB result. Additionally, 7 patients (24.13%) presented with a 3+ AFB result. There were 2 patients (6.89%) who had a scanty AFB result.

Table 1: Change in ESR over the Study Duration

ESR (mm/hr)	Baseline	End of IP	End of CP	P
Mean ± SD	129.44 ± 6.34	76.42 ± 7.23	25.71 ± 6.07	<0.0001

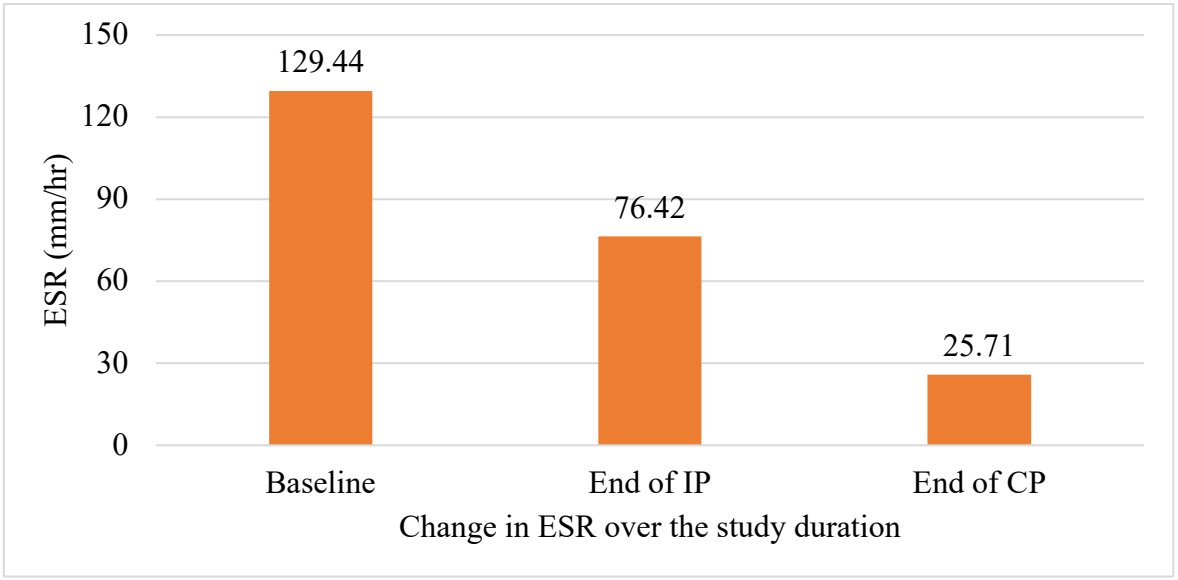

Figure 5: Change in ESR over the study duration

Analysis by repeated measure ANOVA revealed significant change in ESR over the study duration (p <0.0001). Post-hoc analysis by 'Bonferroni test' revealed significant decrease in ESR at the end of CP from baseline and end of IP (both p <0.0001). Moreover, significant decrease in ESR was observed at the end of CP relative to end of IP (p <0.0001).

Table2: Change in CRP over the study duration

CRP (mg/L)	Baseline	End of IP	End of CP	P
Mean ± SD	94.48 ± 2.65	54.08 ± 2.84	29.64 ± 2.70	<0.0001

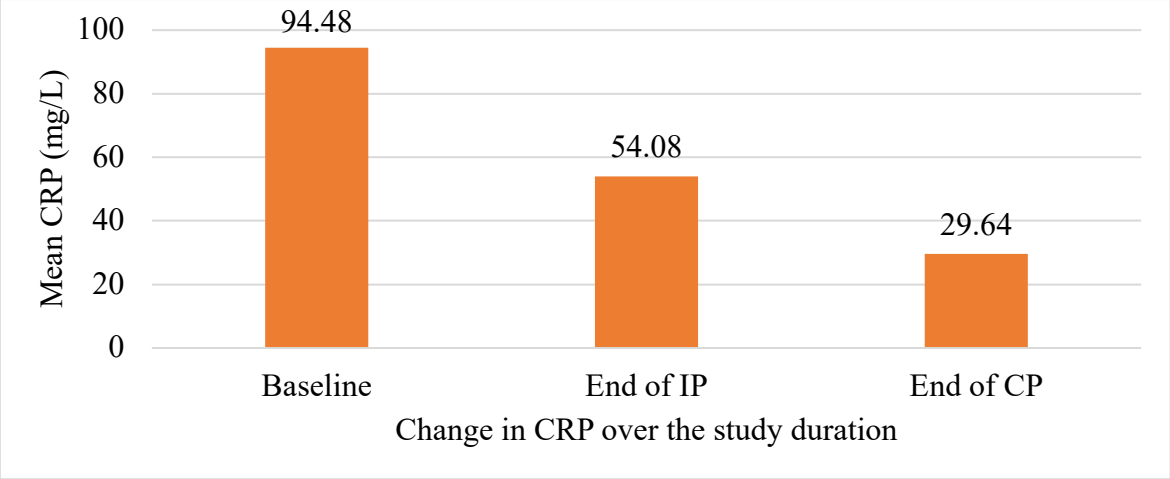

Figure 6: Change in CRP over the study duration

Analysis by repeated measure ANOVA revealed significant change in CRP over the study duration (p <0.0001). Post-hoc analysis by 'Bonferroni test' revealed significant decrease in CRP at the end of CP from baseline and end of IP (both p <0.0001). Moreover, significant decrease in CRP was observed at the end of CP relative to end of IP (p <0.0001).

Table 3: Change in ferritin over the study duration

Ferritin (ng/ml)	Baseline	End of IP	End of CP	P
Mean ± SD	869.01 ± 41.63	794.79 ± 61.24	681.69 ± 66.33	<0.0001

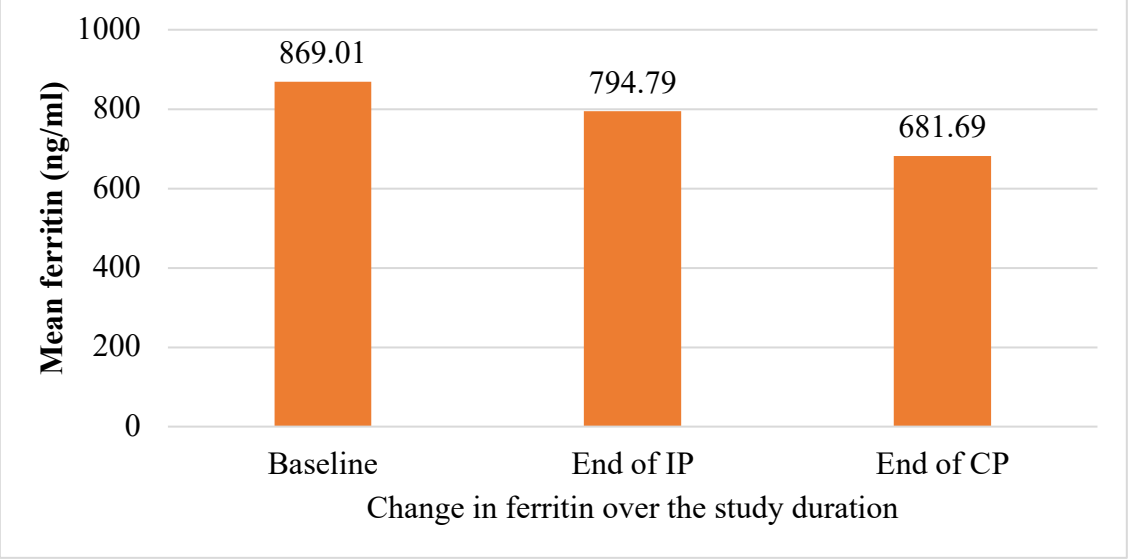

Figure 7: Change in ferritin over the study duration

Analysis by repeated measure ANOVA revealed significant change in ferritin over the study duration (p <0.0001). Post-hoc analysis by 'Bonferroni test' revealed significant decrease in ferritin at the end of CP from baseline and end of IP (both p <0.0001). Moreover, significant decrease in ferritin was observed at the end of CP relative to end of IP (p <0.0001).

Table 4: Change in Albumin-Globulin Ratio over the Study Duration

Alb-glob ratio	Baseline	End of IP	End of CP	P
Mean ± SD	0.45 ± 0.10	0.70 ± 0.10	1.14 ± 0.13	<0.0001

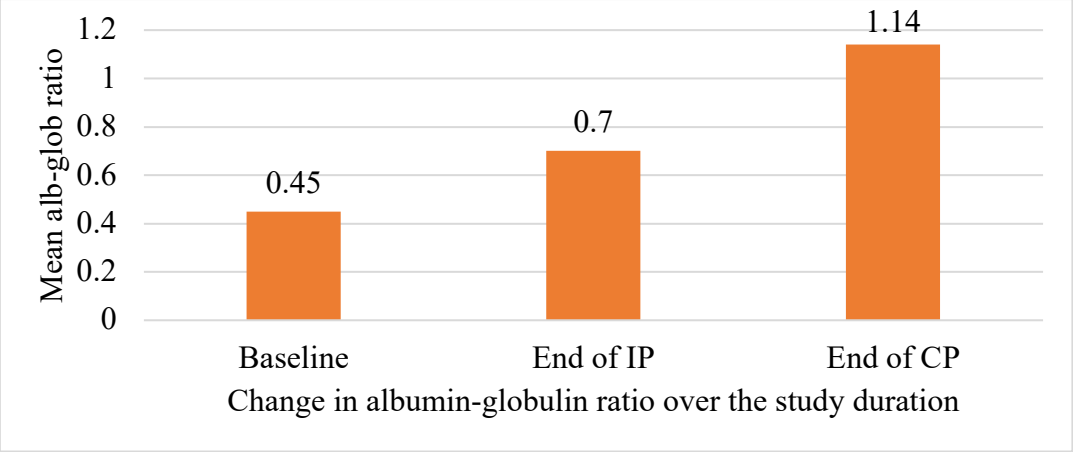

Figure 8: Change in albumin-globulin ratio over the study duration

Analysis by repeated measure ANOVA revealed significant change in AGR over the study duration. Post-hoc analysis by 'Bonferroni test' revealed significant increase in AGR at the end of CP from baseline and end of IP (both p <0.0001). Moreover, significant increase in AGR was observed at the end of CP relative to end of IP (p <0.0001).

Table 5: Association of Disease Severity with Inflammatory Markers

	Severity	Baseline	End of IP	End of CP	p
CRP	Mild	50.00 ± 12.40	35.00 ± 10.30	15.00 ± 2.50	<0.0001
	Moderate	78.00 ± 14.40	54.00 ± 8.60	24.00 ± 4.60	<0.0001
	Severe	98.00 ± 16.40	74.00 ± 14.40	35.00 ± 8.40	<0.0001
ESR	Mild	64.00 ± 13.50	44.00 ±10.20	12.00 ± 8.30	<0.0001
	Moderate	98.00 ± 8.40	76.00 ± 10.20	32.00 ± 4.30	<0.0001
	Severe	140.00 ± 4.60	80.00 ± 4.60	40.00 ± 10.20	<0.0001
Ferritin	Mild	400.00 ± 32.00	350.00 ± 46.80	190.00 ± 38.40	<0.0001
	Moderate	850.00 ± 45.00	740.00 ± 60.20	548.00 ± 20.50	<0.0001
	Severe	960.00 ± 40.50	885.00 ± 57.40	680.00 ± 35.80	<0.0001
Alb/Glb ratio	Mild	0.90 ± 2.30	1.12 ± 0.60	1.24 ± 0.50	<0.0001
	Moderate	0.56 ± 0.20	0.77 ± 0.35	1.14 ± 0.35	<0.0001
	Severe	0.44 ± 0.52	0.78 ± 0.25	0.94 ± 0.54	<0.0001

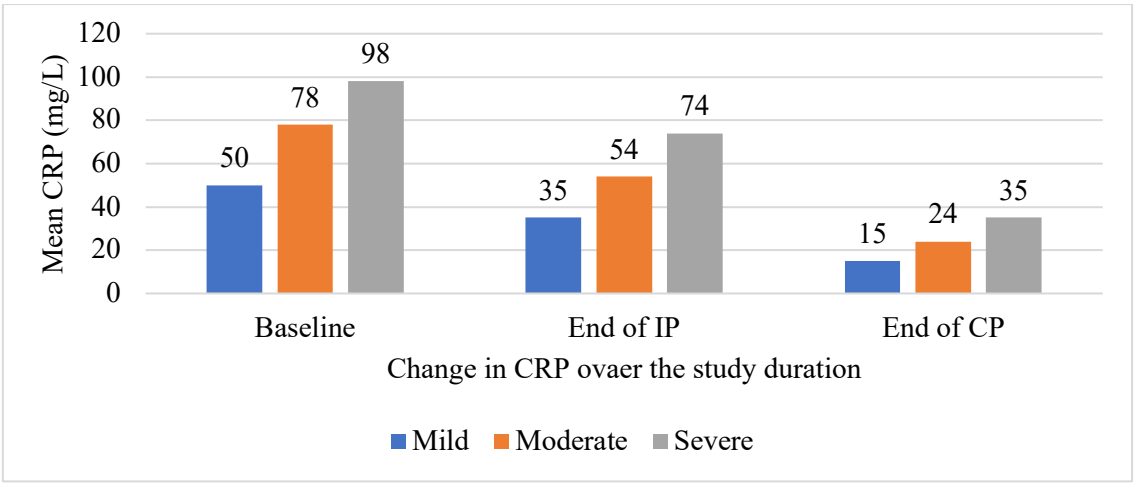

Figure 9A: Change in CRP ovaer the study duration

Analysis by repeated measure ANOVA revealed significant change in CRP over the study duration. Post-hoc analysis by 'Bonferroni test' revealed significant decrease in CRP at the end of CP and IP compared to baseline (both p<0.0001), as well as between end of CP and IP (p<0.0001) in patients with mild, moderate, and severe PTB.

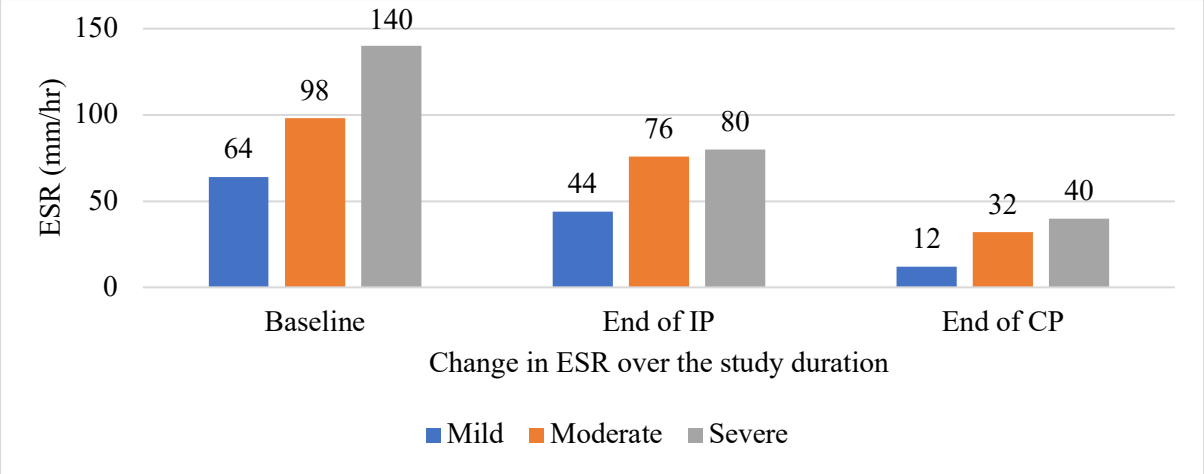

Figure 9B: Association of disease severity with ESR

Analysis by repeated measure ANOVA revealed significant change in ESR over the study duration. Post-hoc analysis by 'Bonferroni test' revealed significant decrease in ESR at the end of CP and IP compared to baseline (both $p<0.0001$), as well as between end of CP and IP ($p<0.0001$) in patients with mild, moderate, and severe PTB.

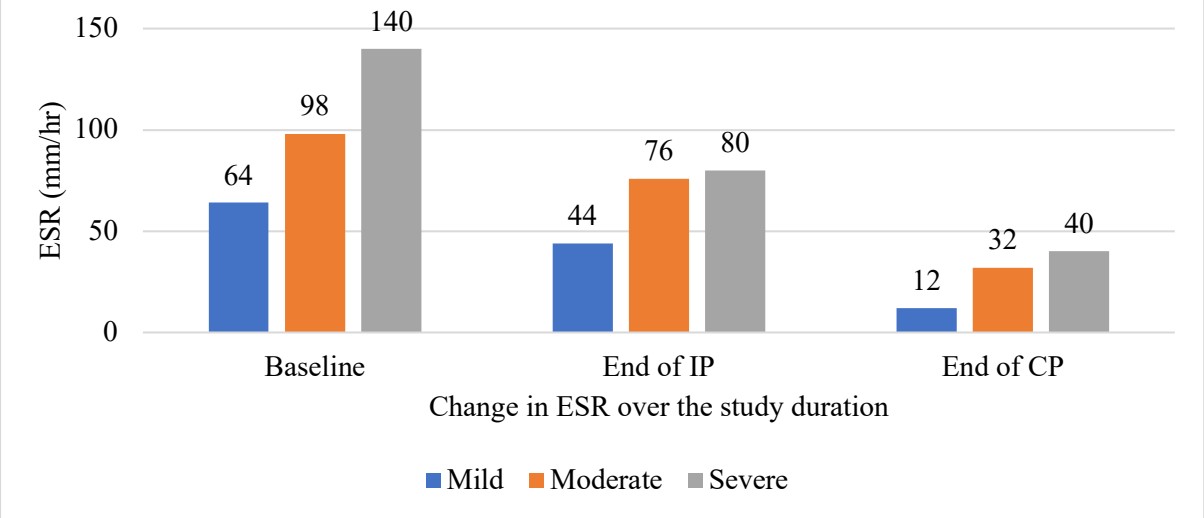

Figure 9C: Association of Disease Severity with Ferritin

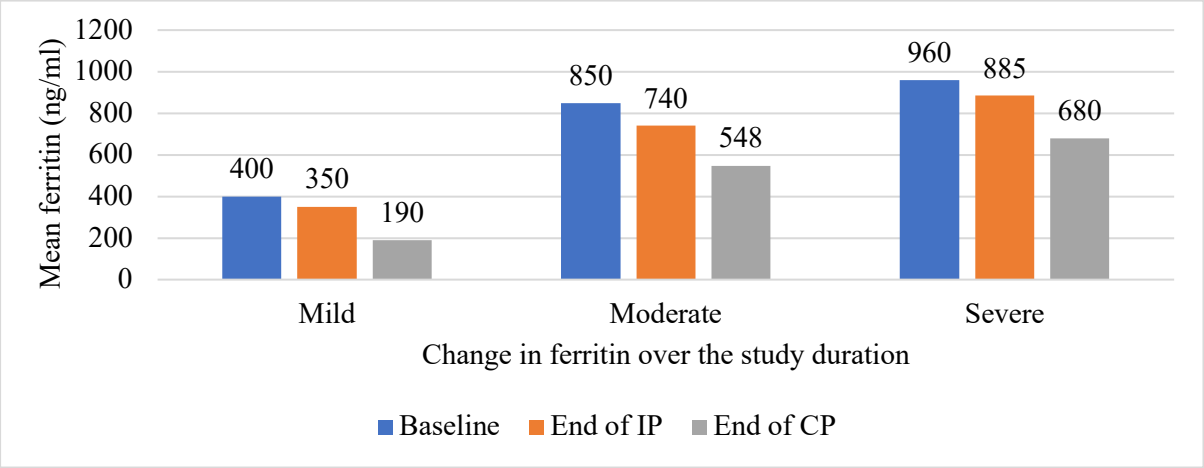

Figure 9D: Change in ferritin over the study duration

Analysis by repeated measure ANOVA revealed significant change in ferritin over the study duration. Post-hoc analysis by 'Bonferroni test' revealed significant decrease in ferritin at the end of CP and IP compared to baseline (both $p<0.0001$), as well as between end of CP and IP ($p<0.0001$) in patients with mild, moderate, and severe PTB.

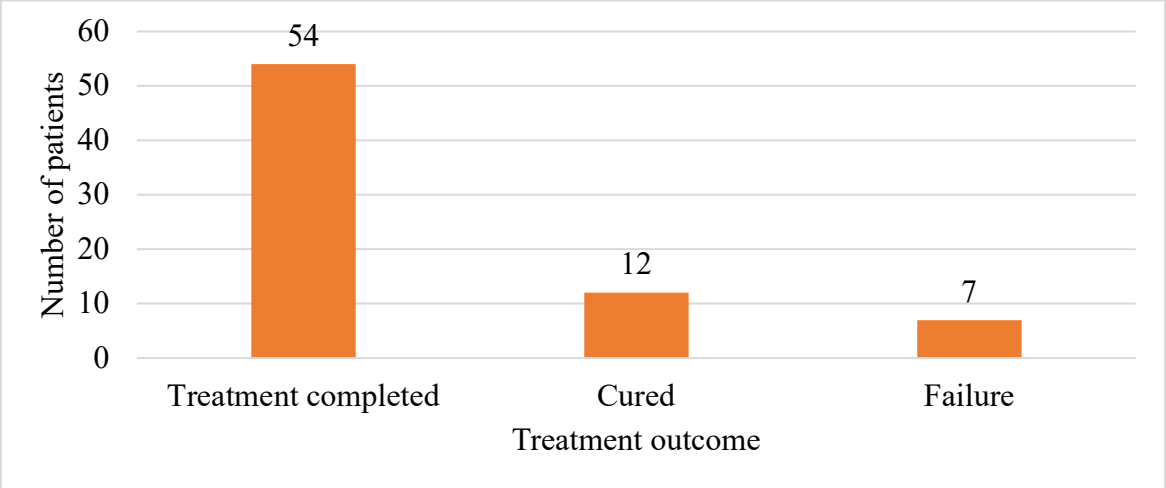

Figure 9E: Association of Disease Severity with Albumin-Globulin Ratio

Analysis by repeated measure ANOVA revealed significant change in AGR over the study duration. Post-hoc analysis by 'Bonferroni test' revealed significant increase in AGR at the end of CP and IP compared to baseline (both $p<0.0001$), as well as between end of CP and IP ($p<0.0001$) in patients with mild, moderate, and severe PTB.

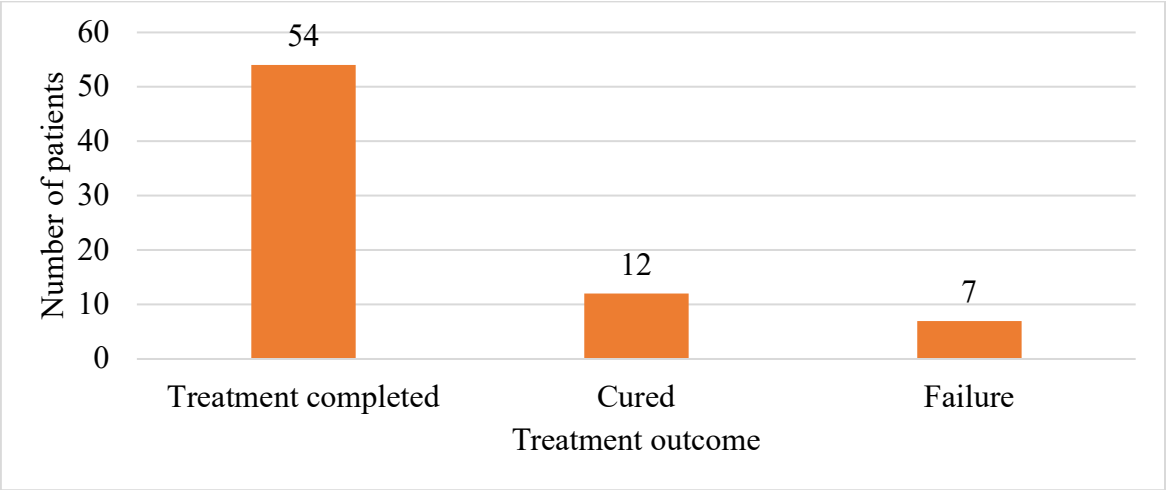

Figure 10: Distribution of Patients Based On Treatment Outcome

Majority of patients had completed the treatment (73.97%) succeeded by 12 (16.40%) patients were cured and 7 (9.59%) patients had failure of treatment. [2]

Discussion

Symptoms: In the present study, chief part of patients had a cough (95.89%). In accordance with the findings of present study, Calderwoodet al. [21] reported that the majority of patients had a cough (99%). Similarly, Mangal et al. [19] and Radović et al. [18] found that most of the patients presented with cough (89.4% and 97.5%, respectively). Additionally, Kumar et al. reported that the most of patients had a cough (96.30%) within cured and failure group. [22] Thus, the high prevalence of cough across these studies underscores its common occurrence in patients, suggesting that cough is a frequent symptom associated with PTB.

Severity of Disease: In the present study, most patients had a moderate disease (49.32%) according to composite TB score. In accordance with my study, Sadek et al. reported that the majority of patients had a moderate advanced disease (37.88%). [23] Similarly, Sahin et al.

observed that PTB was predominantly of moderate severity (2%). [24] However, Rajarajeswari et al. found that the most of patients had a severe disease (43.6%). [25] Thus, the patients mostly have PTB of moderate severity.

Diagnosis: Seventy-three patients were included in my study as study population In the present study, the bulk of the patients were diagnosed microbiologically (50.68%). However, Singanayagam et al. found that themost of patients are radiologically positive (84.51%) succeeded by microbiologically positive (49.11%). [26] Thus, the differences in the proportions of microbiologically and radiologically positive cases highlight varying diagnostic patterns across studies.

Sputum / BAL AFB Positivity: Seventy-three patients were included in my study as study population In the current study, the majority of patients had a 1+ AFB result for Sputum/BAL AFB positivity (41.32s%). In accordance with the findings of present study, Rajarajeswari et al. found that most of patients showed AFB1+ sputum/ BAL AFB positivity (38.6%). [25] On contrary with the findings of present study, Singanayagam et al. [26] reported that most of patients showed AFB3+ sputum/ BAL AFB positivity (48.33% and 19%, respectively). Similarly, Singh et al. reported that most patients showed sputum/BAL AFB positivity of 2+ (35%). [20] Thus, the variations in AFB positivity levels across these studies suggest differences in disease severity.

Change in Erythrocyte Sedimentation Rate (ESR): In the current study, ESR values decreased significantly over the study period ($p < 0.0001$). The decrease in ESR was significant at the end of IP and CP from baseline as well as at the end of CP from IP (both $p<0.0001$). In consensus with the present study, Radović et al. observed significant decrease in ESR at the end of continuation phase of ATT as compared to beginning of treatment ($p < 0.001$).18 Similarly, Martins et al. demonstrated significant decline in ESR values on treatment completion relative to baseline.8 Thus, ATT results in significant decrease in ESR values.

Change in C - reactive protein (CRP): In the present study, CRP decreased significantly over the study duration ($p<0.0001$). This decrease in CRP was significant at the end of IP and CP from baseline as well as at the end of CP from IP (both $p<0.0001$). Consistent with the findings of the present study, Radović et al. observed a significant change in CRP levels from the beginning to the end of treatment ($p<0.001$). [18] Similarly, Mangal et al. found a significant reduction in the levels of high sensitive CRP at 1 month and 2 months after initiation of ATT compared to baseline, in both sputum positive ($p=0.004$ and 0.007, respectively) and negative patients ($p=0.001$ and 0.001, respectively). [19] Additionally, Singh et al. reported that significant decrease in CRP levels at the end of intensive phase of ATT compared that noted before initiating ATT($p<0.001$). [20] Thus, the consistent findings across studies indicate a reliable pattern of CRP level reduction with effective treatment.

Change in Ferritin: In the present study, ferritin values decreased significantly over the study period ($p < 0.0001$). The decrease in ESR was significant at the end of IP and CP from baseline as well as at the end of CP from IP (both $p<0.0001$). In consensus with the findings of the present study, Miranda et al. observed a significant decrease in ferritin levels upon anti-tubercular treatment initiation ($p<0.001$). [17] Similarly, Akpan et al. found that the value of serum ferritin levels lowered notably. Notable decrease in ferritin level were observed from the intensive value to the continuation treatment phase value ($p=0.001$). [27] Likewise, Mangal et al. found a notable decrease in the levels of ferritin at 1 month compared to baseline in smear positive patients ($p=0.016$) and 2 months compared to baseline in sputum negative patients ($p<0.001$). [19] Thus, the consistent decrease in ferritin levels across these studies underscores the effectiveness of treatment in reducing ferritin, indicating a reliable trend of ferritin level reduction with anti-tubercular therapy.

Change in Albumin-Globulin Ratio: In the present study, albumin-globulin ratio increased significantly over the study period ($p<0.0001$). The increase in albumin-globulin ratio was significant at the end of IP and CP from baseline as well as at the end of CP from IP (both $p<0.0001$). Consistent with the present study, Zia et al. reported a significant increase in albumin-globulin ratio before the starting of anti-TB therapy and after completing the treatment ($p < 0.05$) in the TB patients after 15 days, 1 month, 2 months, and 3 months. [28] Likewise, Singh et al. reported an increase in mean albumin-globulin ratio was statistically significant at the end of an intensive phase (p-value<0.001).20 In contrast with the findings of the present study, Stefanescu et al. found that no significant difference in albumin-globulin ratio between before the start of ATT and after end of the intensive phase ($p=0.2336$). [15] Similarly, Shingdang et al. also reported that there was no significant difference in albumin-globulin ratio between intensive phase and continuation phase of ATT ($p=0.612$). [29] Thus, while the majority of studies support a significant increase in the albumin-globulin ratio with treatment, the differences observed highlight that responses may vary and suggest a need for further investigation into factors influencing these outcomes.

Association of PTB Severity with Inflammatory Markers: In the present study, CRP, ESR, and ferritin decreased significantly over the study duration. CRP, ESR, and ferritin decreased significantly at the end of the IP and CP phase compared to baseline (all $p<0.0001$) with significant decrease observed in all the markers between end of CP and end of IP (all $p<0.0001$) across all stages. In contrast, the albumin-globulin ratio significantly increased at the end of CP compared to baseline and the end of IP (both $p<0.0001$), with significant increase observed at the end of CP relative to the end of IP ($p<0.0001$) in all stages. Similar to the findings of the present study, Rajarajeswari et al. found that CRP levels decreased significantly after treatment as compared to their pre-treatment levels in patients with mild ($p=0.047$), moderate ($p=0.013$), and severe PTB ($p=0.001$).

At similar intervals, ESR values declined significantly; however, this decline was significant only in patients with moderate ($p=0.04$) and severe PTB ($p=0.001$). [25] Thus, significant change in inflammatory markers occurs at the completion of treatment across the severity of PTB.

Treatment Outcome

In the present study, most of the patients had completed the treatment (73.97%) succeeded by (16.40%) patients were cured and (9.59%) patients had failure of treatment. Similar to the findings of present study, Kumar et al. found that the most of patients were cured (66.67). [22]

Summary &Conclusion

- The patients were predominantly females (57.53%) and they belonged to the age group of 41–50 years (34.25%).
- The patients mainly presented with cough (95.89%), while only around 13% had history of history of TB.
- The patients mainly had moderate PTB (49.32%).
- More than half of the patients had smoking habit (53.42%) and around 45% patients had diabetes mellitus.
- More than half of the patients were microbiologically positive and exhibited nodular patterns on radiological examination.
- Around a third of patients had a 1+ AFB result for Sputum/BAL AFB positivity.
- ESR, CRP, and ferritin decreased significantly, and albumin-to-globulin ratio increased significantly over the study duration (each $p<0.0001$).
- Around three-fourths of the patients completed the treatment, while only 16.40% patients were cured.

To conclude, treatment in intensive and continuation phase resulted in significant decrease in inflammatory markers, including in ESR, CRP, and ferritin with significant increase in albumin-to-globulin ratio, thereby suggesting positive response with ATT. This positive change was observed across the severity of PTB. Thus, ESR, CRP, ferritin, and albumin-to-globulin ratio are good biochemical markers for the purpose of monitoring of the response to anti-tubercular treatment.

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