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Evaluating hematological and inflammatory biomarkers in tuberculosis management

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Abstract

Tuberculosis (TB) remains a significant public health concern, particularly in resource-limited settings. Accurate and timely diagnosis and effective monitoring of disease progression and treatment response remain a challenge. This research aims to evaluate the function of hematological and inflammatory biomarkers, including hemoglobin (HB), serum amyloid A (SAA), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell (WBC) count, in TB patients. Overall, 80 TB patients were analyzed to evaluate the association of these biomarkers with disease status and demographic characteristics. The findings revealed significant alterations in inflammatory markers, with elevated WBC, SAA, CRP, and ESR levels, indicating an ongoing inflammatory response. Additionally, decreased HB levels were observed, suggesting the presence of anemia, which is commonly associated with chronic infections such as TB. Pearson's correlation analysis revealed a significant negative connection between HB and inflammatory markers, reinforcing the link between anemia and TB-associated inflammation. However, no noteworthy associations were found between biomarker levels and demographic parameters, including age and gender, residence, or treatment duration. These findings emphasize the potential utility of these biomarkers in TB diagnosis, prognosis, and treatment monitoring, especially in regions where advanced diagnostic tools are not readily available. The study suggests that routine hematological and inflammatory markers can serve as cost-effective adjunctive tools in TB administration. Additional investigation is needed to confirm these results and determine their role in predicting treatment outcomes and disease severity.

Key words: tuberculosis, inflammatory biomarkers, C-reactive protein, anemia in TB, hematological markers.

Introduction

Tuberculosis (TB) is a severe infectious disease mainly caused by *Mycobacterium tuberculosis*. This infection mainly impacts the lungs and can be transmitted to other organs. It remains a serious worldwide health issue, with an estimated 10 million new cases and 1.5 million fatalities per year [1]. Tuberculosis is highly widespread in countries with low to middle incomes and insufficient healthcare resources. High-risk groups include individuals with malnutrition, HIV/AIDS, diabetes, and immunosuppression. India bears the highest TB burden, contributing nearly 27% of global cases [2]. Despite advances in diagnostics and treatment, TB control remains challenging, highlighting the need for improved disease monitoring and management tools.

Biomarkers play a crucial role in TB diagnosis, severity assessment, and treatment monitoring by providing insights into host-pathogen interactions and immune responses [3]. Various biomarkers, including inflammatory markers, acute-phase proteins, and hematological parameters, have been studied for their clinical relevance in TB. This study focuses on HB, SAA, CRP, ESR, and WBC count due to their strong association with TB-related inflammation and immune activation [4].

Each of these biomarkers has clinical significance in TB. HB levels are often reduced in TB patients due to anemia, reflecting disease severity and nutritional status [5]. SAA, an acute-phase protein, rises in TB and may be a marker for active infection and treatment response [5]. CRP is widely used to assess systemic inflammation and correlates with TB severity [6]. ESR is an indirect measure of chronic inflammation, often elevated in TB cases [7]. WBC count variations, particularly lymphopenia and neutrophilia, indicate immune response alterations in TB [8]. Current tuberculosis (TB) diagnostic methods in developing countries face significant challenges, particularly in smear-negative and extrapulmonary TB cases, leading to delayed or missed diagnoses due to low sensitivity. Traditional approaches like sputum smear microscopy, culture, and GeneXpert have limitations in terms of sensitivity, accessibility, and turnaround time, particularly in resource-limited settings. As a result, there is a growing need for cost-effective and easily accessible biomarkers for effective disease monitoring [9].

The biomarkers studied here are readily available, cost-effective, and require minimal infrastructure, making them valuable tools for TB management. In the context of TB, a decline in SAA levels over time may indicate a favorable treatment response. Therefore, persistently elevated SAA could potentially correlate with poorer treatment outcomes. This study assesses the role of biomarkers in TB diagnosis, severity evaluation, and treatment monitoring, contributing to improved clinical outcomes and TB control tactics. Moreover, the negative correlation between hemoglobin (HB) and various inflammatory markers, such as CRP and WBC, underscores the potential of anemia as an indirect marker of inflammation in TB patients.

Materials and Methods

Study design

An observational cross-sectional study was conducted from August 2024 to January 2025. Pilot research was initially performed to ascertain the optimal sample size. The final study included 80 Patients with tuberculosis who were hospitalized in the TB ward at Vivekananda General Hospital, Hubballi, India.

Study setting

The study was conducted at the TB Department of Vivekananda Hospital, a tertiary care center in Hubli, Karnataka. All participants were enrolled from this single facility, which ensured uniformity in sample handling and diagnostic criteria. However, this may restrict the generalizability of the findings to broader or more diverse populations.

Study population

The research comprised 80 TB patients receiving treatment at VGH Hospital.

Inclusion criteria: the study included patients diagnosed with TB and admitted to the inpatient TB ward. Eligibility requires a confirmed TB diagnosis, first-line anti-TB therapy, and control of comorbidities like diabetes or hypertension. Patients with a history of TB who completed treatment but experienced a relapse were also included.

Exclusion criteria: the study excluded patients in the outpatient department, those without informed consent, pregnant and lactating women, those with severe immunosuppressive conditions, and those with active malignancies or end-stage organ failure.

Data collection

Data was gathered from patients admitted to the hospital after a detailed history was taken, with all participants providing informed consent. This process ensured the accuracy and completeness of the study data. Blood samples for biomarker analysis were collected at the time of TB diagnosis, before the initiation of anti-tubercular therapy. No follow-up samples were included in this study.

Statistical analysis

For statistical studies, SPSS version 27.0 was used. The relationships between biomarkers (HB, SAA, CRP, ESR, WBC) have been assessed using Pearson's correlation. Independent t-tests were applied to examine the relationship between biomarkers and factors such as age, gender, residency, and treatment duration. Statistical significance was defined as a p-value of less than 0.05 and a p-value of less than 0.001.

Sample size calculation

Based on pilot research, the following formula was used to establish the study's sample size.

$$n = \frac{[Z_{1-\alpha/2}]^2 p(1-p)}{d^2}$$

Where:

n = Required sample size

Z = Critical value

p = Proportionality

d = Precision

α = Confidence Level

Results

Clinical profile of study participants

A total of 80 patients were enrolled in the study. The majority of the participants were female, comprising 58.75% (47), while males accounted for 41.25% (33). The most common age group was 61–70 years, representing 18.75% (15) of the participants, followed by the age groups 21–30, 41–50, and 51–60, each contributing 17.5% (14). Patients aged 31–40 made up 15% (12), those aged 20 accounted for 7.5% (6), and the least represented group was patients aged 71 years, comprising 6.25% (5).

Regarding the residence, 75% (60) of patients were from rural areas, while 25% (20) were from urban areas. In terms of income, the majority were from the Below Poverty Line (BPL) category, accounting for 58.75% (47), followed by 26.25% (21) from the Above Poverty Line (APL) group. The remaining 15% (12) had an annual income above 19,000.

The most common diagnosis among the patients was Pulmonary Tuberculosis (PTB), which affected 42.5% (34) of them. Old Pulmonary Tuberculosis (Old PTB), referring to past TB infections with signs like scarring, calcifications, or a history of previous treatment, was found in 26.25% (21) of patients. Miliary Tuberculosis was seen in 12.5% (10) of patients, while Meningeal Tuberculosis was found in 8.75% (7). Multidrug-Resistant Tuberculosis (MDR TB) was diagnosed in 10% (8) of patients. Active TB was diagnosed through positive sputum tests, GeneXpert results, and clinical symptoms. Relapse cases, where patients who had been treated before showed reactivation of the disease, were seen in 10% (8) of patients.

Regarding comorbidities, hypertension was the most prevalent, seen in 20% (16) of patients, followed by anemia in 16.25% (13), pneumonia in 12.5% (10), and lower respiratory tract infections (LRTI) and Type 2 Diabetes Mellitus (Type 2 DM), each affecting 11.25% (9). Secondary infections were present in 10% (8) of patients. Additionally, 8.75% (7) had no

comorbidities, while upper respiratory tract infections (URTI) were observed in 6.25% (5). Anemia combined with Type 2 DM was the least common comorbidity, occurring in 3.75% (3) of patients.

Regarding treatment duration, most patients underwent treatment for 12–24 months, comprising 50% (40). Treatment durations of 24 months and above accounted for 18.75% (15), while 17.5% (14) were treated for 6–12 months, 7.5% (6) for 3–6 months, and 6.25% (5) for less than 3 months (Table 1).

Hematological and inflammatory biomarker profiles in TB patients

The profiles of hematological and inflammatory biomarkers in TB patients exhibit unique patterns, indicating the immune and inflammatory responses linked to the condition. Among the categories of White Blood Cell (WBC) counts, mild leucocytosis (12,000 - 15,000 cells/microlitre) was the most common, noted in 45% of patients, followed by moderate leucocytosis (15,001 - 18,000 cells/microlitre) at 38.75%, and severe leucocytosis (over 18,000 cells/microlitre) at 16.25%. The levels of SAA were mostly moderately raised (81-100 mg/L), observed in 52.5% of patients, while 36.25% exhibited severe elevation (>101 mg/L). In terms of CRP, most patients (73.75%) showed elevated levels (>60 mg/L), signifying considerable inflammation, whereas 20% presented moderate levels (10-60 mg/L) and merely 6.25% had normal levels (<10 mg/L). The ESR was mainly elevated (60-120 mm/hr), noted in 46.25% of individuals, while 32.5% exhibited extremely high ESR (>120 mm/hr), and 15% showed moderate values (20-60 mm/hr). Concerning Hb, 38.75% of patients displayed low levels (6.5 g/dL), which suggests anemia, while 32.5% had moderate levels (6.6 - 8.9 g/dL) and 28.75% presented high levels (9.0 g/dL). These results emphasize the notable hematological and inflammatory reactions in TB patients, with increased markers reflecting the disease's systemic impacts. TB patients show considerable inflammatory and hematological changes, characterized by increased WBC, SAA, CRP, and ESR levels, along with pervasive anemia. These biomarkers can assist in monitoring diseases and assessing treatment effectiveness (Table 2).

Correlation among biomarkers

Pearson's correlation analysis showed strong negative relationships between Hb and WBC ($r = -0.807$, $p < 0.001$), SAA ($r = -0.710$, $p < 0.001$), and ESR ($r = -0.470$, $p < 0.001$), indicating that lower Hb levels correspond with higher inflammatory markers. Decreased Hb levels are strongly associated with increased inflammation, suggesting its potential role as an indirect indicator of inflammation in TB patients.

WBC showed a highly significant positive association with SAA ($r = 0.910$, $p < 0.001$), indicating that when WBC count increases, SAA levels also rise. WBC also correlated positively with ESR ($r = 0.469$, $p < 0.001$), reinforcing its link to systemic inflammation. Similarly, SAA has shown favourable associations with CRP ($r = 0.222$, $p = 0.047$) and ESR ($r = 0.467$, $p < 0.001$), highlighting their roles as reactive proteins in inflammation. Additionally, CRP and ESR were strongly correlated ($r = 0.666$, $p < 0.001$), supporting CRP's role as a key marker of acute inflammation.

In this study, Hb showed a weak and non-significant correlation with CRP ($r = -0.047$, $p = 0.680$), indicating that Hb levels did not have a meaningful influence on CRP levels. However, strong positive correlations were observed among other inflammatory markers, specifically WBC, SAA, CRP, and ESR, highlighting their close association in the context of TB-related inflammation. While Hb was negatively correlated with these markers, the lack of a significant relationship with CRP suggests it may not directly reflect acute-phase inflammatory activity. The strong associations between SAA, CRP, and ESR support their shared role in the acute-phase response and reinforce their potential use as surrogate indicators of inflammation in TB. The negative relationship between Hb and these inflammatory markers also points to the presence of anemia of chronic disease as part of the overall TB inflammatory profile (Table 3).

Comparison of biomarkers and demographic characteristics among study participants

Association of biomarkers with gender and residency status

An independent t-test was used to determine variations in biomarker levels depending on gender and residence. The p-values for all biomarkers were greater than 0.05 (e.g., $p = 0.445$ for HB, $p = 0.937$ for WBC, $p = 0.792$ for SAA), indicating no significant differences between males and females. Similarly, urban and rural comparisons showed no significant variation in biomarker levels (e.g., $p = 0.891$ for HB, $p = 0.091$ for WBC, $p = 0.246$ for SAA). These findings suggest that gender and residency do not significantly influence the biomarker levels in this study (Table 4).

Association of biomarkers with age and treatment duration

An independent t-test was employed to evaluate the connection between biomarker levels and both age and treatment duration. The p-values for all biomarkers were greater than 0.05 (e.g., $p = 0.378$ for HB, $p = 0.695$ for WBC, $p = 0.959$ for SAA), indicating that age does not significantly influence biomarker levels. Similarly, treatment duration (<6 months vs. >6 months) showed no significant impact on biomarkers (e.g., $p = 0.504$ for HB, $p = 0.500$ for WBC, $p = 0.498$ for SAA). These findings suggest that neither age nor treatment duration plays a critical role in altering biomarker levels in this study (Table 5).

Discussion

This study highlights the significant role of hematological and inflammatory biomarkers in TB patients, emphasizing their potential utility in disease monitoring and management. The observed alterations in HB, SAA, CRP, ESR, and WBC count provide valuable insights into TB-associated inflammation and immune responses. The study results revealed substantial variations in hematological and inflammatory markers among TB patients. The significant positive correlations among SAA, CRP, and ESR suggest a collective acute-phase response, while strong inverse relationships between HB and these markers highlight the contribution of chronic inflammation to anemia.

A high proportion of patients exhibited elevated WBC counts, with 45% experiencing mild leucocytosis, 38.75% moderate leucocytosis, and 16.25% severe leucocytosis. The increased WBC count suggests heightened immune activation in response to Mycobacterium tuberculosis infection, consistent with previous studies indicating leucocytosis as a common feature of TB-related inflammation [10]. SAA, an acute-phase protein associated with inflammation, was found to be moderately elevated in 52.5% of patients and severely elevated in 36.25%. This finding aligns with research demonstrating the function of SAA as a biomarker for treatment response and TB activity [11]. Similarly, CRP levels were markedly elevated in 73.75% of patients, reflecting significant systemic inflammation. CRP has been extensively studied as a marker of TB severity, with elevated levels correlating with disease progression and treatment response [12]. ESR, another widely used inflammatory marker, was found to be elevated (>60 mm/hr) in 46.25% of patients, while 32.5% exhibited extremely high ESR levels (>120 mm/hr). ESR is known to rise in chronic inflammatory conditions, including TB, making it a valuable marker for disease monitoring [13]. Furthermore, anemia was prevalent among TB patients, with 38.75% having low Hb levels (6.5 g/dL). The strong association between TB and anemia has been well-documented, with chronic inflammation, iron sequestration, and malnutrition contributing to reduced Hb levels in infected individuals [14].

The correlation analysis provided key insights into the relationships between biomarkers. There was a significant inverse connection found between HB and inflammatory markers like WBC ($r = -0.807$, $p < 0.001$), SAA ($r = -0.710$, $p < 0.001$), and ESR ($r = -0.470$, $p < 0.001$). This suggests that lower Hb levels indicate higher inflammation, reinforcing the role of anemia as a secondary consequence of chronic TB infection. Similar results have been shown in earlier research, emphasizing the impact of inflammatory cytokines on erythropoiesis [15]. Additionally, WBC had a significant positive association with SAA ($r = 0.910$, $p < 0.001$) and ESR ($r = 0.469$, $p < 0.001$), indicating that immune activation in TB leads to increased production of acute-phase proteins and inflammatory mediators. The observed correlation between SAA and CRP ($r = 0.222$, $p = 0.047$) further highlights the interrelated nature of these

inflammatory markers in TB pathophysiology [16]. Interestingly, while HB showed strong negative correlations with most inflammatory markers, its correlation with CRP was weak and statistically insignificant ($r = -0.047$, $p = 0.680$). This suggests that while anemia is closely linked to chronic inflammation in TB, it may not be directly associated with acute-phase responses captured by CRP levels.

The study found no significant differences in biomarker levels based on gender, residency, age, or treatment duration ($p > 0.05$), suggesting that TB-related inflammatory and hematological responses are largely independent of these factors. This aligns with previous research indicating that TB-associated immune responses are not significantly influenced by demographics [17,18]. These findings have important clinical implications, highlighting the potential of HB, SAA, CRP, ESR, and WBC count as cost-effective tools for TB monitoring, especially in resource-limited settings where traditional diagnostics like sputum microscopy and GeneXpert pose challenges [19].

Elevated WBC counts, SAA, CRP, and ESR levels can serve as reliable indicators of active TB and ongoing inflammation. The strong negative correlation between HB and inflammatory markers further suggests that anemia assessment could provide additional insights into disease severity. Moreover, the strong interrelationships among these biomarkers highlight their collective utility in TB management. A key strength of this study is the focus on accessible and cost-effective markers.

Limitations

Despite the promising findings, this study has a few limitations. One limitation is the small sample size (80 participants), which may affect how widely the results can be applied. Larger studies with more participants from different centers would be needed to confirm these results in different populations. Also, since the study was conducted at a single center, the results might not be representative of all regions.

Another limitation is that the biomarkers studied, such as SAA, CRP, and ESR, are not specific to TB. These markers can also be raised in other conditions with inflammation. So, while they are helpful for monitoring TB, they cannot be used alone to diagnose it. The study also didn't measure biomarkers over time to see how they change during treatment, which could have provided more information about how these markers relate to treatment progress.

Finally, while the study found important connections between biomarkers and disease outcomes, it didn't explore the exact biological processes behind these relationships. Future research looking into how these biomarkers affect TB could provide a better understanding of their role in the disease and treatment response.

Conclusions

This study highlights the importance of hematological and inflammatory biomarkers in TB management. Elevated WBC, SAA, CRP, and ESR levels, and reduced HB reflect the systemic inflammatory response in TB. The negative correlation between HB and inflammatory markers suggests that anemia may indicate disease severity. These biomarkers provide a cost-effective tool for monitoring TB, especially in resource-limited settings. More investigation is required to validate their function in directing therapy and enhancing results.

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Table 1. Study participants' clinical and demographic features.

Sl. No	Categories	Frequency (N)	Percentage (%)
1	**Gender**		
	Male	33	41.25
	Female	47	58.75
2	**Age**		
	20	6	7.5
	21-30	14	17.5
	31-40	12	15
	41-50	14	17.5
	51-60	14	17.5
	61-70	15	18.75
	71	5	6.25
3	**Residence**		
	Rural	60	75
	Urban	20	25
4	**Income**		
	APL	21	26.25
	Others	12	15
	BPL	47	58.75
5	**Diagnosis**		
	MDR TB	8	10
	Meningeal TB	7	8.75
	Miliary TB	10	12.5
	Old PTB	21	26.25
	PTB	34	42.5
6	**Comorbidities**		
	2° infection	8	10
	Anemia	13	16.25
	Anemia with type 2 DM	3	3.75
	HTN	16	20
	LRTI	9	11.25
	No comorbidities	7	8.75
	Pneumonia	10	12.5
	Type 2 DM	9	11.25
	URTI	5	6.25
7	**Treatment duration**		
	Less than 3 months	5	6.25
	3-6 months	6	7.5
	6-12 months	14	17.5
	12-24 months	40	50
	24 months and above	15	18.75

Table 2. Hematological and inflammatory biomarker profiles in TB patients.

Sl. No	Biomarkers	Frequency	Percentage (%)
1	**WBC Range (cells/microlitre)**		
	Mild Leucocytosis (12000-15000)	36	45
	Moderate Leucocytosis (15001-18000)	31	38.75
	Severe Leucocytosis (>18000)	13	16.25
2	**SAA (mg/L)**		
	Mild Elevation (65-80)	9	11.25
	Moderate Elevation (81-100)	42	52.5
	Severe Elevation (> 101)	29	36.25
3	**CRP (mg/L)**		
	Normal (< 10)	5	6.25
	Moderate (10-60)	16	20
	High (> 60)	59	73.75
4	**ESR (mm/hr)**		
	Normal (< 20)	5	6.25
	moderate (20-60)	12	15.00
	High (60-120)	37	46.25
	Very High (> 120)	26	32.50
5	**Hb (g/dL)**		
	Low (6.5)	31	38.75
	Moderate (6.6 - 8.9)	26	32.5
	High (9.0)	23	28.75

Table 3. Correlation analysis of hematological and inflammatory biomarkers in TB patients.

Biomarkers		HB	WBC	SAA	CRP	ESR
HB	**R-value**	1	-.807**	-.710**	-.047	-.470**
	p-value		**<0.001**	**<0.001**	.680	**<0.001**
WBC	**R-value**	-.807**	1	.910**	.179	.469**
	p-value	**<0.001**		**<0.001**	.112	**<0.001**
SAA	**R-value**	-.710**	.910**	1	.222*	.467**
	p-value	**<0.001**	**<0.001**		**.047**	**<0.001**
CRP	**R-value**	-.047	.179	.222*	1	.666**
	p-value	.680	.112	**.047**		**<0.001**
ESR	**R-value**	-.470**	.469**	.467**	.666**	1
	p-value	**<0.001**	**<0.001**	**<0.001**	**<0.001**	

**The correlation is significant at >0.001and <0.05 level.

Table 4. Comparison of biomarkers with gender and residency.

Biomarkers	Gender	p-value
HB	Male	0.445
	Female	0.431
WBC	Male	0.937
	Female	0.936
SAA	Male	0.792
	Female	0.789
CRP	Male	0.968
	Female	0.969
ESR	Male	0.433
	Female	0.436
	Residency	**p-value**
HB	Urban	0.891
	Rural	0.906
WBC	Urban	0.091
	Rural	0.084
SAA	Urban	0.246
	Rural	0.285
CRP	Urban	0.167
	Rural	0.164
ESR	Urban	0.159
	Rural	0.128

Table 5. Comparison of biomarkers with age and duration of treatment.

Biomarkers	Duration of treatment	p-value
HB	Less than 6 months	0.504
	More than 6 months	0.479
WBC	Less than 6 months	0.500
	More than 6 months	0.493
SAA	Less than 6 months	0.498
	More than 6 months	0.466
CRP	Less than 6 months	0.545
	More than 6 months	0.622
ESR	Less than 6 months	0.320
	More than 6 months	0.366
	Age	**p-value**
HB	Less than 40 years	0.378
	More than 40 years	0.373
WBC	Less than 40 years	0.695
	More than 40 years	0.707
SAA	Less than 40 years	0.959
	More than 40 years	0.961
CRP	Less than 40 years	0.571
	More than 40 years	0.582
ESR	Less than 40 years	0.336
	More than 40 years	0.366