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Exploring mean platelet volume and neutrophil-to-albumin ratio as surrogate markers for monitoring tuberculosis treatment: a prospective longitudinal study

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Abstract

Background Tuberculosis (TB) remains a global health challenge, with India bearing a significant burden. Despite advancements in TB diagnosis and treatment, monitoring TB treatment is challenging, particularly in resource-limited settings. This study aimed to explore the mean platelet volume (MPV) as a potential surrogate marker for monitoring TB treatment and assessing if the neutrophil-to-albumin ratio (NAR) enhances treatment monitoring.

Methods Patients diagnosed with TB following NTEP guidelines were recruited. Participants underwent routine blood tests during the six-month Anti-Tubercular therapy course at the start, end of the intensive phase, and end of the continuous phase. Statistical analyses included Spearman correlation, Friedman test, linear mixed effects (LME) models, and multiple linear regression.

Results 150 individuals were included for analysis. Deviations from normality were noted. Significant associations were found between CRP and sputum grade. MPV mediated between CRP and sputum grade. Significant differences were observed across the three-time points. LME models showed changes in MPV and CRP levels over time. Including NAR enhanced predictive capability.

Conclusions MPV may serve as a promising surrogate marker for monitoring ATT. Personalized approaches are crucial in TB treatment monitoring. LME models revealed MPV and CRP level trends. Future research should explore MPV's treatment response mechanisms and cost-effectiveness.

Keywords Surrogate markers, Treatment monitoring, Tuberculosis, Mean platelet volume, Neutrophil-to-albumin ratio, Cost-effectiveness

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Introduction

Tuberculosis (TB) is an infectious disease caused by the bacterium *Mycobacterium tuberculosis* that primarily affects the lungs (pulmonary TB) but capable of infecting other parts of the body. Approximately one-quarter of the global population is estimated to have been infected with TB [1]. According to the Global TB Report 2023, during 2020, India's estimated mortality rate from all forms of TB was 37 per 100,000 people, with an estimated incidence of all forms of TB at 188 per 100,000 people [2].

According to National Tuberculosis Elimination Programme (NTEP) Guidelines [3], pulmonary TB is diagnosed using sputum smear microscopy, chest X-ray, and nucleic acid amplification tests (NAATs). The Programme emphasizes replacing smear microscopy with NAATs and offering upfront NAATs for diagnosis. Microbiologically confirmed TB patients undergo NAATs for rifampicin resistance. Line probe assays (LPA; First Line) are available for rifampicin-sensitive TB. First- and second-line LPAs are used for rifampicin-resistant and isoniazid-resistant TB patients. Liquid culture and drug susceptibility tests assess resistance for drug-resistant TB. All diagnosed TB patients receive a standard first-line anti-TB regimen within three days, after ruling out rifampicin resistance (if possible). Follow-up includes sputum smear microscopy for drug-sensitive TB and liquid culture for drug-resistant TB. In a review conducted by Jan Heyckendorf et al. [4], various treatment monitoring methodologies were outlined. A common feature observed across these methods is their limited availability in primary healthcare centers (PHCs), along with their time-consuming nature and high cost. The methodologies described are summarized in Supplementary Material Table 1.

According to G.D. Sweeney [5], variability in the human drug response is the rule rather than the exception. This variability is a multifaceted phenomenon, encompassing both pharmacodynamic and pharmacokinetic deviations. Pharmacodynamic variations involve abnormal responses of drug receptors despite normal drug levels, while pharmacokinetic variations entail changes in drug concentration due to factors such as formulation, absorption, metabolism, and excretion. These variations can be either genetically inherited or acquired. Consequently, individual responses to drug therapy vary widely, emphasizing the need for personalized approaches. The current treatment protocol for TB advocates for the use of fixed-dose combination (FDC) drugs, aiming to simplify drug prescription and supply management [6]. However, the efficacy of standardizing anti-tuberculosis therapy (ATT) solely through FDCs raises concerns in the absence of directly observed therapy short course (DOTS) and therapeutic drug monitoring [7]. The variability in drug response highlights that a uniform one-size-fits-all treatment approach may lead to inadequate or excessive treatment for certain individuals. Despite these drawbacks, the advantages of FDCs support their continued use. Therefore, there is a pressing need for the development of treatment monitoring biomarkers that can be easily measured, even at PHC, allowing for modifications to ATT if the desired response is not achieved. This approach helps to mitigate the disadvantages associated with FDC-based treatment protocols.

According to the Meeting Report of the WHO Expert Consultation on Drug-Resistant TB Treatment Outcome Definitions [8], the TB community still lacks a reliable, universally applicable biomarker for treatment follow-up and monitoring. The current WHO recommendation for monitoring MDR/RR-TB patients on longer or shorter regimens is to perform sputum culture in addition to sputum smear microscopy, which is ideally repeated monthly. However, sputum culture is time-consuming, and sputum smear lacks sensitivity, unable to indicate bacterial viability. Genotypic or molecular tests may lack specificity and cannot indicate bacterial viability or active disease. Consequently, assessing recurrence in those who complete treatment successfully poses challenges due to the lack of a suitable biomarker for TB disease activity. Several biomarkers have been investigated in the literature to aid in monitoring TB treatment that include cytokines (such as IFN-γ, IL-2, IL-6, IL-8, IL-10, IP-10, MCP-1, and TNF-α), acute phase reactants (CRP, ESR), urine lipoarabinomannan, and anti-TB antibodies. Additionally, new emerging biomarkers like extracellular vesicles and neopterin are currently under investigation. [9]. Studies have explored the role of CRP in monitoring TB progression [10, 11]. However, quantitative CRP measurement is not universally available in PHC setups, nor is it routinely assessed at every visit, as it could strain the healthcare system. Nevertheless, during each visit for FDC drug collection, a complete blood count (CBC) and liver function tests (LFT) are conducted to assess hepatic damage or blood dyscrasias.

In this study, we aimed to investigate whether the mean platelet volume (MPV), can serve as a surrogate marker for TB treatment monitoring. Additionally, our secondary aim was to assess whether the additional use of the neutrophil-to-albumin ratio (NAR) can enhance the predictive capability of treatment monitoring. The rationale behind choosing these biomarkers for investigation is that they can be easily calculated from the routine investigations that are carried out and are available even in PHCs.

Patients & methods

Study Population

We conducted a prospective, longitudinal study at the out-patient department (OPD) of the Department

of Thoracic Medicine, Government Medical College, Omandurar, Government Estate, from April 2023 to August 2023. A sample size of 150 was calculated with a confidence interval of 95%, a 7% margin of error, and a 25% prevalence, and was rounded off to the nearest 10.

Patients presenting with chief complaints such as evening rise of temperature, cough with expectoration, or other symptoms suggestive of pulmonary TB were included in the study after confirming the diagnosis according to NTEP guidelines. Diagnostic tests for all participants included sputum microscopy and chest X-Ray. Additionally, cartridge-based nucleic acid amplification test (CB-NAAT) was performed to assess drug resistance. We excluded individuals with a history of TB infection, familial platelet disorders, chronic infections other than TB, liver disease, chronic inflammatory conditions, and those younger than 18 years of age.

After the study protocol was explained and written informed consent was obtained, participants were recruited by consecutive sampling for a 6-month study period corresponding to the ATT course. A detailed medical history was obtained, followed by a thorough clinical examination. Height and weight were measured for each participant, and body mass index (BMI) was calculated. All findings were documented in a standardized proforma specifically designed for this study. Chest X-Rays were taken at diagnosis to serve as a baseline film and at completion of ATT to check for resolution. Upon the physician's discretion, if there was not complete resolution (for example, seen in slow responders), the physician extended the ATT by 1 month, up to a maximum of 3 months. Additionally, sputum samples were collected from each participant and subjected to Auramine O fluorescence staining. This technique facilitated examination under a fluorescence microscope and subsequent grading of the samples.

Participants were scheduled for visits at the start of the ATT (zero month), end of the intensive phase of ATT (second month), and end of the continuation phase of ATT (sixth month) for routine blood investigations, collection of ATT FDC drugs, and collection of sputum samples. At each visit, 2 mL of venous blood was collected in CB PLUS® Purple Vacutainers (containing K2EDTA) and BIOPRO® Red Vacutainers (containing Clot Activator). Sputum samples were also collected at the end of the intensive phase of ATT (second month) and at the end of the continuation phase of ATT (sixth month). At the end of ATT, the clinical outcome of the participants was assessed using sputum microscopy and chest X-Ray.

A CBC with differential was conducted using the SYSMEX® XN-350 automated hematology analyzer. Serum Albumin levels were estimated using automated photoelectric colorimetry, employing the bromocresol green (BCG) method. The quantitative determination of serum CRP was performed using turbidimetric immunoassay. Both tests were carried out using the ERBA MANNHEIM® XL640 Automated Biochemical Analyzer. Subsequently, we calculated the NAR from the laboratory results.

Statistical analysis

All the data were collected in Microsoft Excel 2020 and later imported into Jamovi Software V.2.3.1 (Syndey, Australia) and R software (V 4.3.2) for statistical analysis. MPV, BMI, CRP, neutrophil count, serum albumin, and NAR were entered as continuous variables. The grading of the smear is recorded as a categorical variable. Numerical suffixes attached to the variable signify specific time points: '0' denotes the initial measurement at the start of ATT, '2' marks the end of an intensive phase of ATT, and '6' indicates the conclusion of a continuous phase of ATT.

The Kolmogorov–Smirnov (KS) test and Anderson–Darling (AD) test were used to assess the normality of the distribution of the data. Continuous variables are expressed as mean ± standard deviation (SD) or median with a 25-75% interquartile range (IQR). Categorical variables are expressed as percentages with 95% confidence intervals. A p-value < 0.001 was considered to indicate statistical significance. To obtain an overall view of the data collected, descriptive analysis was performed. Summary statistics such as the mean, median, SD, and IQR were computed.

We examined the association between CRP0 levels and sputum grade using Spearman correlation analysis. Subsequently, following Baron and Kenny's mediation analysis approach, regression analyses were conducted to investigate the relationships among CRP0 and sputum grade (Step 1), CRP0 and MPV0 (Step 2), and MPV0 and sputum grade while controlling for CRP0 (Step 3). The aim was to ascertain whether the MPV mediates the association between CRP and sputum grade, thereby assessing the potential of the MPV as a surrogate marker for TB progression.

To analyze the changes in MPV, CRP, and NAR values across time points, we employed the Friedman test. Spearman correlation analyses were conducted between MPV, CRP, and NAR at all time points to assess their associations. Two one-sided tests (TOST) were utilized to determine if there were statistically significant differences between MPV and CRP measurements at all points.

We conducted linear mixed effects model (LME) analysis to examine the longitudinal changes in the MPV and CRP over 6 months. This approach allowed us to account for potential confounding factors and individual variations while assessing the utility of the MPV as a surrogate marker for monitoring TB treatment progress compared

Table 1 Descriptive statistics of study variables

Variable	Mean ± SD	Median (IQR 25–75)
Age	40.6 ± 17.3	40.0 (24.3–55.8)
BMI	21.7 ± 2.55	22.0 (19.5–23.7)
C-Reactive Protein		
At Diagnosis	40.6 ± 17.3	40.0 (24.3–55.8)
End of IP (ATT)	22.8 ± 9.32	22.5 (16.0–31.0)
End of CP (ATT)	20.0 ± 6.50	21.0 (13.0–26.0)
Mean Platelet Volume		
At Diagnosis	9.20 ± 0.417	9.10 (8.83–9.57)
End of IP (ATT)	8.86 ± 0.431	8.80 (8.50–9.28)
End of CP (ATT)	10.2 ± 0.945	10.3 (9.50–11.0)
Neutrophil-Albumin Ratio		
At Diagnosis	1852 ± 204	1893 (1853–1938)
End of IP (ATT)	1128 ± 66.7	1143 (1061–1184)
End of CP (ATT)	638 ± 97.8	643 (538–726)
Neutrophil Count		
At Diagnosis	5584 ± 815	5600 (5000–6200)
End of IP (ATT)	4079 ± 517	4100 (3600–4500)
End of CP (ATT)	2662 ± 547	2700 (2100–3175)
Serum Albumin		
At Diagnosis	3.02 ± 0.299	3.00 (2.80–3.20)
End of IP (ATT)	3.60 ± 0.255	3.60 (3.40–3.80)
End of CP (ATT)	4.14 ± 0.231	4.20 (3.90–4.30)

IP – intensive phase; CP – continuous phase

to CRP levels. The LME models included time (0, 2, and 6 months) as a fixed effect predictor variable, capturing the effect of time on MPV and CRP levels. Individual participants were considered random effects to accommodate individual variability. By fitting these models to our data, we were able to estimate the longitudinal changes in the MPV and CRP, assess their significance, and evaluate their associations with TB treatment progress over time. The trends in the MPV and CRP over time were visualized to understand their longitudinal changes.

We used multiple linear regression analysis to compare the predictive power of the combination of the NAR and MPV with the MPV alone for estimating CRP. By examining both models, we determined whether adding NAR significantly enhanced the accuracy of predicting CRP levels compared to MPV alone. This analysis provided insights into the effectiveness of utilizing NAR and MPV together for monitoring ATT.

Results

In our study, between April 2023 and August 2023, we carried out the recruitment process and followed up the patients until their ATT completion. After applying the exclusion criteria, we recruited a group of 162 individuals for 6 months. Due to the loss to follow-up, our cohort decreased to 153 individuals, and for ease of calculation, we rounded this number to 150 individuals for inclusion in our analysis. Out of the 150 participants, 86 (57.33%) were male and 64 (42.67%) were female. At the end of ATT, 135 participants were cured. Among the remaining 15, 8 had their continuation phase of ATT extended by 1 month, 3 by 2 months, and 4 by 3 months. In terms of diagnosis, 113 participants were initially diagnosed based on sputum microscopy, 37 were diagnosed using chest X-ray confirmed by sputum microscopy, and all participants underwent CB-NAAT testing, which confirmed that none had rifampicin resistance. KS and AD tests indicated that our dataset deviated from a normal distribution. Descriptive statistics were calculated for various variables in our study cohort and are presented in Table 1.

Table 2 Changes in sputum grading from diagnosis to the end of the intensive phase (IP) and continuation phase (CP) of ATT

Grade	At Diagnosis	End of IP (ATT)	End of CP (ATT)
0	0 (0%)	132 (88.0%)	144 (96.0%)
1	77 (51.3%)	18 (12.0%)	6 (4.0%)
2	54 (36.0%)	0 (0%)	0 (0%)
3	19 (12.7%)	0 (0%)	0 (0%)

IP – intensive phase; CP – continuous phase

Table 3 Results of regression analyses following baron and Kenny's mediation analysis approach

Step	Variables	Estimate	Std. Error	t value	*p*-value
1	(Intercept)	0.4958	0.1084	4.573	< 0.001
	CRP0	0.0276	0.0025	11.195	< 0.001
2	(Intercept)	8.2261	0.0106	772.70	< 0.001
	CRP0	0.0240	0.0002	99.31	< 0.001
3	(Intercept)	-29.0976	6.4661	-4.500	< 0.001
	MPV0	3.5975	0.7859	4.577	< 0.001
	CRP0	-0.0588	0.0190	-3.093	= 0.002

The changes in sputum grading from diagnosis to the end of the IP and CP of ATT are shown in Table 2.

Spearman correlation analysis revealed a significant correlation between CRP0 levels and sputum grade ($r=0.700$, $p<0.001$), indicating that higher CRP levels were associated with more severe TB. Following Baron and Kenny's mediation analysis approach, a series of regression analyses were conducted to explore the relationships among CRP0, MPV0, and sputum grade. In Step 1, the regression analysis demonstrated a significant relationship between CRP0 and sputum grade. subsequently, Step 2 revealed a significant association between CRP0 and MPV0. in Step 3, after controlling for CRP0, the regression analysis revealed a significant relationship between MPV0 and sputum grade. These findings indicate a potential mediation effect, suggesting that MPV0 may serve as a mediator between CRP0 and sputum grade, thereby highlighting its potential as a surrogate marker for TB severity. The results are tabulated in Table 3.

The Friedman test indicated significant differences in MPV (χ^2=202, $p<0.001$), CRP (χ^2=216, $p<0.001$),

Table 4 Spearman's rho correlation coefficients for CRP, MPV, and NAR at different time points

Variables	Spearman's rho	Variables	Spearman's rho	Variables	Spearman's rho
CRP0		CRP2		CRP6	
MPV0	0.996 ($p<0.001$)	MPV2	0.249 ($p=0.002$)	MPV6	0.176 ($p=0.031$)
NAR0	0.743 ($p<0.001$)	NAR2	0.560 ($p<0.001$)	NAR6	0.492 ($p<0.001$)

Table 5 Summary of TOST test results comparing CRP with MPV and NAR at different time points

Comparison	Equivalence Bounds	Mean Difference	Equivalence Interval	TOST *p*-value	Interpretation
CRP0 vs. MPV0	(29.03, 33.70)	31.36	(29.03, 33.70)	1	No significant difference
CRP0 vs. NAR0	(-1839.51, -1784.11)	1811.81	(-1839.51, -1784.11)	1	No significant difference
CRP2 vs. MPV2	(10.31, 12.07)	11.19	(10.31, 12.07)	1	No significant difference
CRP2 vs. NAR2	(-1116.75, -1098.65)	1107.70	(-1116.75, -1098.65)	1	No significant difference
CRP6 vs. MPV6	(2.91, 4.16)	3.54	(2.91, 4.16)	1	No significant difference
CRP6 vs. NAR6	(-637.13, -610.66)	623.89	(-637.13, -610.66)	1	No significant difference

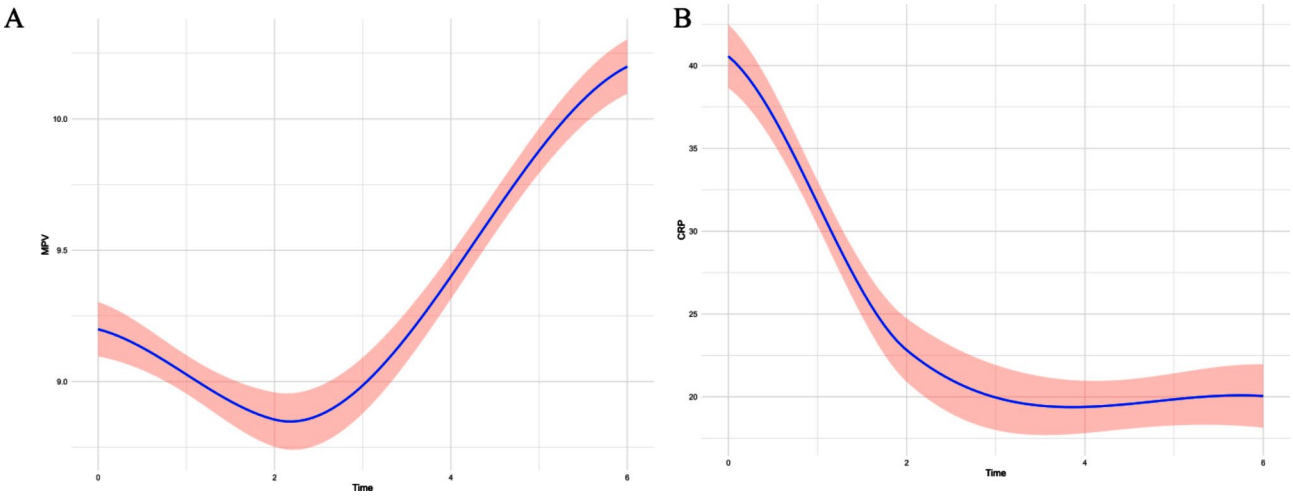

Fig. 1 (**a**) Trend of MPV levels over time smoothed using the LOESS method. (**b**): Trend of CRP levels over time smoothed using the LOESS method

and NAR (χ^2=290, $p<0.001$) across the three-time points during ATT. Spearman correlation analysis demonstrated a significant correlation between MPV, CRP, and NAR at all time points. The results are tabulated in Table 4.

The TOST test indicated no significant differences between the MPV, CRP, and NAR measurements across all time points ($p>0.001$). The results are tabulated in Table 5.

LME assessed the relationship between time and MPV as well as CRP levels in participants undergoing att. For MPV, there was a significant decrease at 2 months (estimate = -0.344, $p<0.001$) followed by a significant increase at 6 months (estimate=1.000, $p<0.001$). CRP levels showed a significant decrease at 2 months (estimate = -20.511, $p<0.001$), followed by another significant decrease at 6 months (estimate = -17.740, $p<0.001$). Random effects analysis indicated variability between participants for both MPV (intercept variance=0.1756) and CRP (intercept variance=85.17).

Figure 1 depicts the trends observed in MPV values over time smoothed using the locally estimated scatterplot smoothing (LOESS) method. This plot depicts and complements the findings derived from the LME model.

Table 6 presents the multiple linear regression results for MPV0, CRP0, and NAR0; MPV2, CRP2, and NAR2; and MPV6, CRP6, and NAR6.

The adjusted R-squared values indicate that including NAR in the models improved their overall fit, suggesting that NAR contributes to explaining a greater proportion of the variance in MPV and CRP levels. Additionally, the F-statistics demonstrate that the enhancement in model fit upon incorporating NAR is statistically significant across all time points. Thus, it can be inferred that the inclusion of NAR significantly enhances the predictive capability of the regression models for MPV and CRP levels throughout various stages of TB treatment.

Table 6 Multiple linear regression results for MPV and NAR across time points

Time Point	Variable	Estimate	Std. Error	t value	*p*-value	Adjusted *R*-squared	F-statistic
MPV0	Intercept	-336.90	3.92	-85.95	< 2e-16	0.985	4901
	MPV0	41.09	0.42	97.37	< 2e-16		
	NAR0	-0.00	0.00	-0.33	0.743		
MPV2	Intercept	-32.60	8.89	-3.67	0.00034	0.3775	46.18
	MPV2	-3.16	1.26	-2.50	0.01341		
	NAR2	0.07	0.01	8.75	4.57e-15		
MPV6	Intercept	3.51	3.58	0.98	0.328	0.2105	20.86
	MPV6	-0.50	0.42	-1.20	0.233		
	NAR6	0.02	0.00	5.96	1.82e-08		

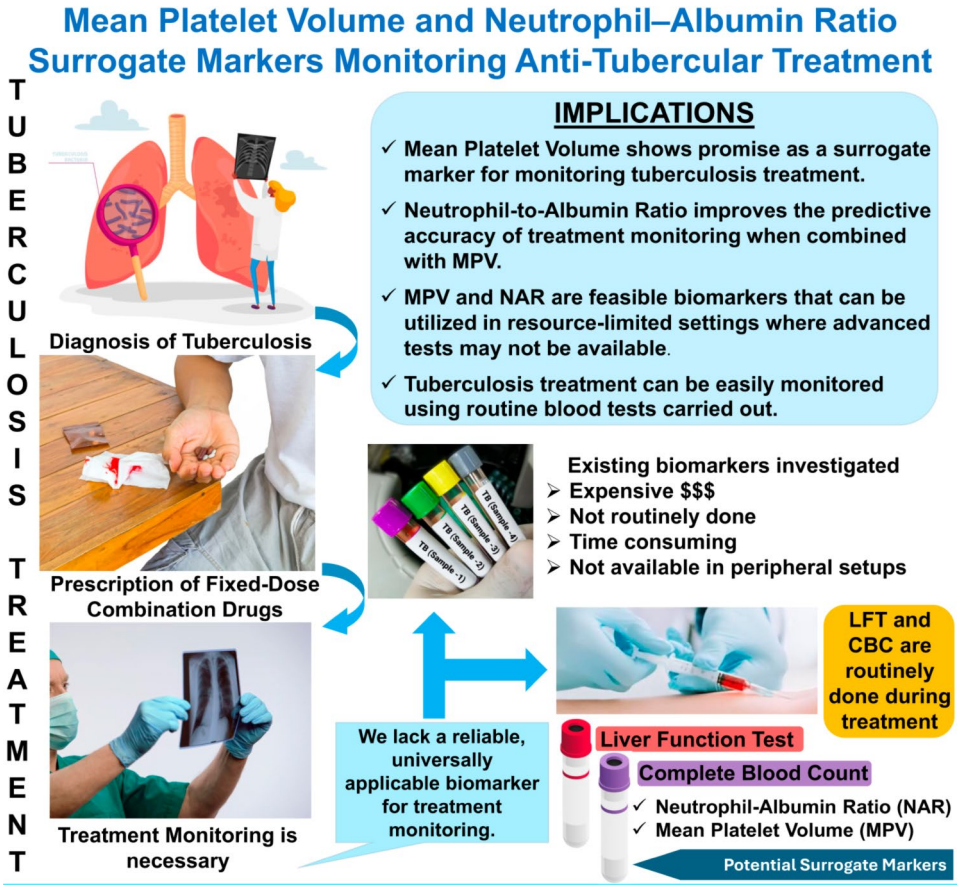

Fig. 2 Graphical abstract illustrating clinical implications of MPV and NAR in TB treatment monitoring

Discussion

We investigated the potential of MPV as a surrogate marker for monitoring TB treatment, as well as the additional use of NAR for enhanced predictive capability. The results suggest that the MPV may serve as a mediator between CRP levels and sputum grade, indicating its potential as a surrogate marker for TB severity. Significant correlations were found between the MPV, CRP, and NAR at different time points during ATT. However, the TOST test indicated no significant differences between CRP and MPV or NAR measurements across all time points. LME models revealed a significant decrease in MPV at 2 months followed by an increase at 6 months, while CRP levels showed a decreasing trend. The inclusion of NAR in multiple linear regression models improved their overall fit, suggesting that NAR contributes to explaining a greater proportion of the variance in MPV and CRP levels, enhancing the models' predictive capability throughout various stages of TB treatment. The clinical implications of this study are illustrated in Fig. 2 as a graphical abstract.

Our study findings align with those of Soedarsono S and Subiantoro MC [12], indicating a reduction in inflammatory conditions following ATT, as evidenced

by a decrease in CRP levels. This suggests that monitoring CRP levels alone could serve as a reliable indicator of treatment response. However, despite its potential utility, several barriers hinder its widespread use. First, the availability of quantitative CRP tests is not uniform across all PHCs. Second, CRP testing is not routinely conducted for all patients undergoing TB treatment. The introduction of additional diagnostic tests such as CRP measurements would impose an added burden on healthcare systems.

The elevated MPV observed at the time of diagnosis can be attributed to the formation of multiple microthromboses around the tuberculous cavities, thereby preventing the dissemination of the infection. This increase in MPV can be explained by the mechanism in which younger, larger platelets are released from the bone marrow into the peripheral blood circulation to compensate for the consumption of platelets during this process [13].

Investigating the pathophysiology behind the observed trend during ATT is essential, and further elucidation is warranted. Initially, during the intensive phase of TB treatment, the MPV decreases, indicating reduced platelet consumption. However, as treatment nears completion, the MPV rises, possibly due to heightened platelet activation and turnover linked to immune reconstitution inflammatory syndrome (IRIS). This hypothesis aligns with findings from Rogelio Hernandez–Pando et al. [14], who suggested that anti-inflammatory mechanisms in TB initially suppress immunity, paving the way for IRIS as treatment concludes.

NAR exhibited a consistent linear decrease as treatment progressed. This trend could be attributed to the initial elevation of neutrophil levels during TB infection [15], which subsequently declined posttreatment [16]. Concurrently, the serum albumin levels increased throughout TB treatment. Conversely, in cases of poor treatment outcomes, serum albumin concentrations showed no significant change relative to baseline levels [17]. The amalgamation of these two parameters into a ratio enhances the accuracy of assessing treatment progression, offering a comprehensive indicator of the disease's response to therapy.

Several studies have provided insights into the relationship between the MPV and CRP in TB patients. Lee et al. [13] reported a positive correlation between CRP and the MPV in TB patients, suggesting that the MPV is a potential inflammatory marker for assessing disease activity. Similarly, Tozkoparan et al. [18] noted elevated MPV levels in active TB patients, which decreased with ATT, supporting the utility of MPV in monitoring treatment response. Gunluoglu et al. [19] reported lower MPV in pulmonary TB patients than in healthy controls but suggested that the MPV may not reliably reflect disease severity. Our findings contrast with Sahin et al. [20], who reported that while platelet count and Plateletcrit were significantly correlated with the radiological extent of TB, MPV, and -platelet distribution width did not exhibit significant correlations.

This study, which was conducted at a single center with a small sample size, may limit the generalizability of findings to a larger population, particularly excluding patients with comorbidities or concurrent HIV infection. The follow-up duration of 6 months, corresponding to standard ATT, may not capture the entirety of treatment, as some patients may require longer regimens. Some patients may have the CP of their ATT extended upon physician's discretion by a maximum of 3 months. We did not account for these extensions in this study. Moreover, the focus on drug-susceptible TB patients may not extend to those with multidrug-resistant (MDR) or extensively drug-resistant (XDR) TB. Additionally, medications with hepatotoxic or bone marrow toxic effects can impact neutrophil and albumin levels, potentially influencing the NAR.

Future directions for research on ATT monitoring encompass several key areas. First, there is a need for exploration of the mechanisms underlying the observed trend between MPV and treatment response. Second, health economics studies should be conducted to evaluate the cost-effectiveness and potential impact of implementing MPV and NAR monitoring strategies on healthcare resource allocation. Finally, correlating MPV, CRP, NAR, and clinical outcomes could provide insights into the prognostic significance of these biomarkers in TB management.

Conclusion

This study highlights promising implications for the monitoring and management of TB treatment. MPV shows potential as a surrogate marker for TB severity during treatment, particularly considering its mediating effect on the relationship between CRP levels and sputum grade. The inclusion of the NAR further enhances the predictive capability of monitoring the TB response. The observed trends in MPV and CRP levels throughout treatment suggest their dynamic nature and potential as indicators of treatment efficacy. Further research exploring the mechanism and clinical implications of these biomarkers in TB management is warranted.

Abbreviations

TB	Tuberculosis
NTEP	National Tuberculosis Elimination Programme
NAATs	Nucleic Acid Amplification Tests
LPA	Line Probe Assay
ATT	Anti-Tuberculosis Therapy
CRP	C-Reactive Protein
MPV	Mean Platelet Volume
NAR	Neutrophil-to-Albumin Ratio
PHC	Primary Healthcare Center
CBC	Complete Blood Count
LFT	Liver Function Tests

CB-NAAT	Cartridge-Based Nucleic Acid Amplification Test
LOESS	Locally Estimated Scatterplot Smoothing
LME	Linear Mixed Effects
MDR	Multidrug-Resistant
XDR	Extensively Drug-Resistant
IRIS	Immune Reconstitution Inflammatory Syndrome

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03236-x.

Supplementary Material 1

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Author contributions

HKR contributed to conceptualization, methodology, software development, formal analysis, investigation, data curation, and writing the original draft, as well as project administration. VCS was involved in conceptualization, methodology, and reviewing and editing the manuscript. AP was involved in methodology, reviewed and edited the manuscript, supervised the project, and handled project administration. DB contributed to conceptualization, methodology, writing review and editing, supervision, and project administration.

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Data availability

The data utilized in this research will be accessible upon request from the first author but will not be publicly accessible to safeguard the confidentiality and privacy of the patients who participated. Requests for data access must specify the purpose for which the data will be utilized. In cases of data reuse, a proposal outlining the purpose, the intended usage of the data, and a letter from the department head or the institution's leadership will be mandatory. Additionally, any subsequent data generation should be communicated to the primary author.

Declarations

Ethical approval and consent to participate

This study was approved by the Institutional Ethics Committee of Government Medical College, Omandurar, Government Estate (Registration Number – ECR/1492/Inst/TN/2021) with approval number 44/IEC/GOMC/2023. All procedures performed in studies involving human patients were in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

Consent for publication

Not applicable.

Conflict of interest

The authors declare no conflicts of interest.

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References

1. Houben RMGJ, Dodd PJ. The global burden of latent tuberculosis infection: A re-estimation using mathematical modelling. PLoS Med [Internet]. 2016;13(10):e1002152. https://doi.org/10.1371/journal.pmed.1002152
2. Global tuberculosis report 2023. Geneva, World Health Organization. : 2023. Licence: CC BY-NC-SA 3.0 IGO [Internet]. https://www.who.int/publications/i/item/9789240083851
3. Central TBD. Ministry of Health and Family Welfare. Government of India. India TB Report 2022. Coming Together to End TB Altogether. New Delhi India; 2022 [Internet]. https://tbcindia.gov.in/WriteReadData/IndiaTBReport2022/TBAnnaulReport2022.pdf
4. Heyckendorf J, Georghiou SB, Frahm N, Heinrich N, Kontsevaya I, Reimann M et al. Tuberculosis treatment monitoring and outcome measures: New interest and new strategies. Clin Microbiol Rev [Internet]. 2022 [cited 2024 Feb 20];35(3). https://doi.org/10.1128/cmr.00227-21
5. Sweeney GD. Variability in the human drug response. Thromb Res [Internet]. 1983;29:3–15. https://doi.org/10.1016/0049-3848(83)90353-5
6. Blomberg B, Spinaci S, Fourie B, Laing R. The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis. Bull World Health Organ [Internet]. 2001 [cited 2024 Feb 20];79(1):61–8. https://pubmed.ncbi.nlm.nih.gov/11217670/
7. Iftikha S, Sarwar MR. Potential disadvantages Associated with treatment of active tuberculosis using fixed-dose combination: a review of literature. J Basic Clin Pharma. 2017;8:S131–136.
8. Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27–29 October 2020. Geneva: World Health Organization. 2021. Licence: CC BY-NC-SA 3.0 IGO [Internet]. https://iris.who.int/bitstream/handle/10665/340284/9789240022195-eng.pdf?sequence=1
9. Yong YK, Tan HY, Saeidi A, Wong WF, Vignesh R, Velu V et al. Immune biomarkers for diagnosis and treatment monitoring of tuberculosis: Current developments and future prospects. Front Microbiol [Internet]. 2019;10. https://doi.org/10.3389/fmicb.2019.02789
10. Rao S, Bernhardt V. Serum C-reactive protein in pulmonary tuberculosis: Correlation with bacteriological load and extent of disease. Infect Dis Clin Pract (Baltim Md) [Internet]. 2009;17(5):314–6. https://doi.org/10.1097/ipc.0b013e3181a4c73d
11. Kumar M, Verma M. Prognostic Value of C - reactive protein in Pediatric Tubercular Patients on ATT [Internet]. https://www.iosrjournals.org/iosr-jdms/papers/Vol15-Issue%206/Version-8/L1506085257.pdf
12. Soedarsono S, Subiantoro MC. Changes of CRP serum levels in pulmonary TB patients with AFB smear-positive sputum before and two months after receiving anti-tuberculosis drug treatment. Indian J Tuberc [Internet]. 2019;66(1):134–8. https://doi.org/10.1016/j.ijtb.2018.07.007
13. Lee MY, Kim YJ, Lee HJ, Cho SY, Park TS. Mean platelet volume inMycobacterium tuberculosisinfection. Biomed Res Int [Internet]. 2016;2016:1–4. https://doi.org/10.1155/2016/7508763
14. Hernandez-Pando R, Orozco H, Aguilar D. Factors that deregulate the protective immune response in tuberculosis. Arch Immunol Ther Exp (Warsz) [Internet]. 2009;57(5):355–67. https://doi.org/10.1007/s00005-009-0042-9
15. Jones TPW, Dabbaj S, Mandal I, Cleverley J, Cash C, Lipman MCI et al. The blood neutrophil count after 1 month of treatment predicts the radiologic severity of lung disease at treatment end. Chest [Internet]. 2021;160(6):2030–41. https://doi.org/10.1016/j.chest.2021.07.041
16. Nwongbouwoh Muefong C, Owolabi O, Donkor S, Charalambous S, Bakuli A, Rachow A et al. Neutrophils contribute to severity of tuberculosis pathology and recovery from lung damage pre- and posttreatment. Clin Infect Dis [Internet]. 2022;74(10):1757–66. https://doi.org/10.1093/cid/ciab729
17. Liu R, Shu W, Song Y-H, Liu Y, Ma L, Gao M. Use of serum albumin level as a predictive marker of clinical outcomes for active tuberculosis. Ann Clin Lab Sci [Internet]. 2020 [cited 2024 Feb 20];50(5):681–6. https://pubmed.ncbi.nlm.nih.gov/33067216/
18. Tozkoparan E, Deniz O, Ucar E, Bilgic H, Ekiz K. Changes in platelet count and indices in pulmonary tuberculosis. Clin Chem Lab Med [Internet]. 2007;45(8). https://doi.org/10.1515/cclm.2007.194
19. Gunluoglu G, Yazar EE, Veske NS, Seyhan EC, Altin S. Mean platelet volume as an inflammation marker in active pulmonary tuberculosis. Multidiscip Respir Med [Internet]. 2014;9(1). https://doi.org/10.1186/2049-6958-9-11

20. Füsun Sahin E, Yazar P, Yildiz. Evaluation of platelet count and indices in pulmonary tuberculosis and pneumonia. Eur Respir J [Internet]. 2011;38(Suppl 55):4387. http://erj.ersjournals.com/content/38/Suppl_55/p4387.abstract

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