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What the Expert Says

Platelets: The unsung heroes in the battle against tuberculosis – A comprehensive review of platelet indices as diagnostic beacons and pathophysiological players

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ABSTRACT

This review explores the emerging role of platelet indices in tuberculosis (TB) as potential biomarkers for diagnosis, disease monitoring, and understanding pathogenesis. Platelet count, mean platelet volume, platelet distribution width, and plateletcrit have shown significant alterations in TB patients compared to healthy controls and those with other respiratory conditions. These changes are attributed to the inflammatory response, direct platelet activation by *Mycobacterium tuberculosis*, and involvement in granuloma formation. Recent studies have investigated the diagnostic and prognostic value of platelet indices in TB, including their potential for differentiating TB from other respiratory infections, monitoring treatment response, and assessing disease severity. However, challenges such as lack of specificity and measurement variability need to be addressed. The review also highlights the multifaceted role of platelets in TB pathogenesis, including immune modulation and antimicrobial functions. Future research directions include large-scale validation studies, exploration of combined biomarker panels, and investigation of platelet indices in pediatric TB and TB-diabetes comorbidity. As our understanding of platelet-TB interactions grows, these indices may contribute to more personalized and effective TB management strategies.

Keywords: Tuberculosis, Platelets, Platelet distribution width, Plateletcrit, Mean platelet volume

INTRODUCTION

Tuberculosis (TB) remains a significant global health challenge, necessitating improved diagnostic and prognostic tools. In recent years, there has been growing interest in the role of platelets in TB pathogenesis and their potential as diagnostic and prognostic markers. This review aims to explore the relationship between platelet indices and TB, focusing on their potential diagnostic and prognostic value, as well as their role in the pathophysiology of the disease.

PLATELET INDICES: AN OVERVIEW

Platelet indices are parameters that provide information about platelet production, destruction, and activation. The main platelet indices discussed in TB research include:

1. Platelet count (PLT): The total number of platelets per unit volume of blood.
2. Mean platelet volume (MPV): The average size of platelets in a blood sample.
3. Platelet distribution width (PDW): A measure of the variation in platelet size.
4. Plateletcrit (PCT): The volume percentage of platelets in blood.

ALTERATIONS IN PLATELET INDICES IN TB

Numerous studies have reported significant changes in platelet indices in TB patients compared to healthy controls and patients with other respiratory conditions:

1. PLT: Thrombocytosis (elevated PLT) is frequently observed in active TB. Sahin *et al*. found thrombocytosis in 44% of pulmonary TB (PTB) patients, with a mean PLT of 384.5 ± 122 × 10^3/μL in TB patients, compared to 304.4 ± 88.3 × 10^3/μL in pneumonia patients and 253.78 ± 55 × 10^3/μL in healthy controls,[1,2] as shown in Table 1. Renshaw and Gould also reported an association between thrombocytosis and *Mycobacterium tuberculosis* infection.[3]
2. MPV: Findings on MPV have been inconsistent across studies. Sahin *et al*. found no significant difference in MPV between TB patients, pneumonia patients, and healthy controls.[1] However, Tozkoparan *et al*. reported higher MPV values in active TB patients compared to those with inactive TB and healthy controls[4] [Table 1]. A recent study by Xu *et al*. suggested that MPV could be a potential diagnostic marker for comorbidity of TB and diabetes mellitus.[5]
3. PDW: PDW has been found to be significantly higher in PTB patients compared to healthy controls. Sahin *et al*. reported PDW values of 14.7 ± 2.0% in TB patients [Table 1 and Figure 1], higher than pneumonia patients, and healthy controls.[1,2]
4. PCT: PCT has been reported to be significantly higher in TB patients compared to controls and patients with pneumonia. Sahin *et al*. found PCT values of 0.33 ± 0.09% in TB patients [Table 1 and Figure 1], higher than pneumonia patients, and healthy controls.[1,2]

These indices were measured by ABX Pentra 120 (Impedance and Optical, Minnesota, USA) device by Sahin *et al*.[1,2] and Coulter Model-S-Plus automatic counter (Coulter Electronics, Hialeah, FL, USA) with standard calibration and quality control procedures by Tozkoparan *et al*.[4]

DIAGNOSING TB AND DIFFERENTIATING IT FROM PNEUMONIA AND OTHER INFECTIONS

For diagnosing TB, Sahin *et al*.[1,2] and Tozkoparan *et al*.[4] used chest radiography and sputum examination. Sputum smears for acid fast bacilli were prepared by ZN stain and mycobacterial cultures were carried out using Lowenstein–Jensen media and a radiometric BACTEC TB 460 system. When sputum smears were negative or insufficient, bronchoalveolar lavage through fiberoptic bronchoscopy was carried out for smear preparation and *Mycobacterium* culture. Diagnosis of active PTB was confirmed by positive *M. tuberculosis* culture. Patients who exhibited no culture growth were excluded, even if they had clinical and

Table 1: Platelet indices in TB.

Author (year)	Sample size	Platelet count (×1000/μL)		MPV (fL)		PDW (%)		Plateletcrit (%)	
		Before ATT	After ATT	Before ATT	After ATT	Before ATT	After ATT	Before ATT	After ATT
Tozkoparan *et al*. (2007)[4]	TB group (*n*=82)	329±120	221±140	10.05±2.36	9.35±1.08	40.9±23.5	24.2±14.4	0.330±0.166	0.206±0.403
	Non-TB group (*n*=87)	282±99		8.83±1.47		27.0±14.5		0.266±0.128	
	Pneumonia group (*n*=33)	291±126		8.74±1.42		30.0±15.1		0.265±0.085	
Sahin et al. (2012)[1,2]	TB group (*n*=100)	384.5±122	-	8.54±1.39	-	14.7±2.0	-	0.33±0.09	-
	Non-TB group (*n*=28)	253.78±55		8.65±0.52		13.5±1.8		0.21±0.04	
	Pneumonia group (*n*=50)	304.4±88.3		8.74±0.71		14.5±2.3		0.27±0.05	

TB: Tuberculosis, MPV: Mean platelet volume, PDW: Platelet distribution width, ATT: Antitubercular treatment

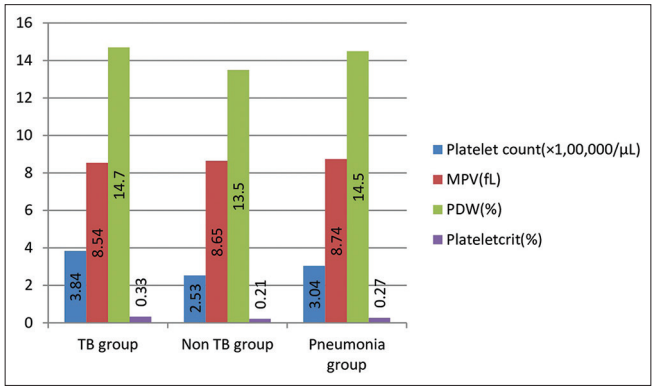

Figure 1: Comparison of platelet indices in various patient groups (Sahin *et al*., 2012) TB: Tuberculosis, MPV: Mean platelet volume, PDW: Platelet distribution width.

radiological improvement after anti-tuberculous treatment and were accepted as having active TB. Inactive PTB was diagnosed when patients had a negative culture result, and radiographic lesions attributable to sequel PTB that showed no change during at least a 3-month follow-up period.

Patients other than those with active PTB comprised the non-tuberculous (non-TB) group as controls, including patients with inactive PTB. Patients with pneumonia in the non-TB group formed a subgroup representing non-TB patients with an acute phase response. Diagnostic criteria for pneumonia were as follows: Symptoms and signs of pyrexia, cough (productive or non-productive), dyspnea, pleuritic chest pain, and auscultatory findings (altered breath sounds, crepitations, and/or localized rales) corresponding to an acute infiltrate on a chest radiograph that was cleared by antibiotic therapy.

PATHOPHYSIOLOGICAL MECHANISMS

The alterations in platelet indices observed in TB patients can be attributed to several pathophysiological mechanisms:

Inflammatory response

TB infection triggers a robust inflammatory response, leading to the production of various cytokines and acute-phase reactants. This inflammatory milieu can stimulate thrombopoiesis, resulting in increased platelet production and thrombocytosis. Unsal *et al*. demonstrated a potential role of interleukin-6 in reactive thrombocytosis and acute phase response in PTB.[6]

Platelet activation

Platelets can be directly activated by *M. tuberculosis* and its components, leading to the release of inflammatory mediators and antimicrobial peptides. Kirwan *et al*. reviewed the role of platelet activation in the immune response to TB, highlighting the complex interactions between platelets and the immune system in TB pathogenesis.[7] La Manna *et al*. demonstrated that expression of either CD61 or CD42a was significantly higher in circulating platelets in active TB compared to healthy donor (P = 0.0047 and 0.0012, respectively).[8]

Granuloma formation and immune modulation

La Manna *et al*. demonstrated that platelets accumulate in lung lesions of TB patients, inhibit T-cell responses, and affect *M. tuberculosis* replication in macrophages.[8] Gene ontology analysis showed 53 platelet associated genes highly expressed in caseous human PTB granulomas, compared to normal lung tissue and of note, among these were ITGB3, TGFB1, and PF4 coding for CD61, transforming growth factor-beta, and platelet factor 4 (PF4 and CXCL4), respectively.[8] This involvement in granuloma formation and immune modulation may explain some of the alterations in platelet indices observed in TB patients.

Hemostatic changes

Turken *et al*. reported various hemostatic changes, including thrombocytosis and hypercoagulability, in active PTB.[9] These changes may be adaptive responses to the infection but could also contribute to TB-associated complications.

DIAGNOSTIC AND PROGNOSTIC VALUE OF PLATELET INDICES IN TB

The observed changes in platelet indices in TB patients have led researchers to investigate their potential diagnostic and prognostic value:

Diagnosis of TB

Studies have explored the use of platelet indices as adjunct diagnostic markers for TB. Sahin *et al*. determined cutoff values for PLT (335,000/µL) and PCT (0.275%) for differentiating TB from pneumonia, with moderate sensitivity and specificity.[1] Hilda *et al*. evaluated platelet indices as markers of TB among children in India, finding potential utility in certain indices.[10]

Monitoring treatment response

Akpan *et al*. investigated hemostatic indices, including PLT, as markers for monitoring PTB treatment.[11] They found that these indices could be useful in assessing treatment efficacy. Awodu *et al*. also reported changes in hemorheological variables during TB therapy.[12] Tozkoparan *et al*.[4] reported the changes in platelet indices after antitubercular treatment [Figure 2].

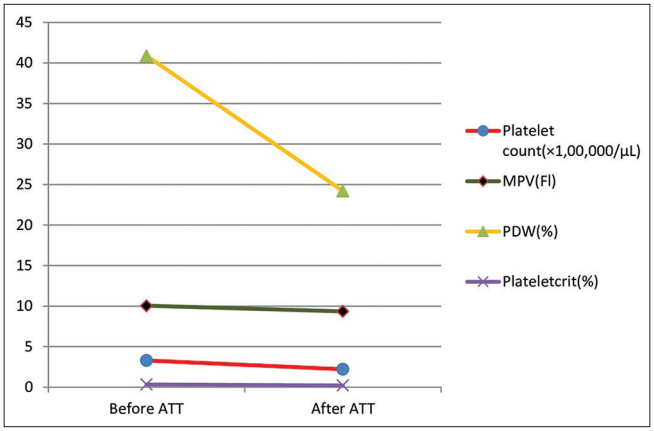

Figure 2: Platelet indices before and after ATT (Tozkoparan *et al.*, 2007) ATT: Antitubercular treatment, MPV: Mean platelet volume, PDW: Platelet distribution width.

Disease severity and prognosis

Higher PLTs and PCT values have been associated with radiologically advanced TB.[1] Chen *et al.* proposed the platelet-lymphocyte ratio as a potential marker for PTB diagnosis in chronic obstructive pulmonary disease patients.[13]

Differential diagnosis

Lee *et al.* investigated the use of MPV in differentiating between *M. tuberculosis* infection and other bacterial infections, suggesting its potential as a rapid and cost-effective marker.[14]

CHALLENGES AND LIMITATIONS

While the evidence supporting the use of platelet indices in TB is growing, several challenges and limitations should be considered:

Lack of specificity

Alterations in platelet indices are not specific to TB and can occur in various inflammatory and infectious conditions.[15]

Variability in measurement

Platelet indices can be affected by various pre-analytical and analytical factors, introducing variability in measurements across different studies and clinical settings.[16,17]

Limited large-scale studies

Many studies investigating platelet indices in TB are limited by small sample sizes or single-center designs.[1,4]

Confounding factors

TB often coexists with other conditions, such as human immunodeficiency virus infection or diabetes mellitus, which can independently affect platelet indices.[5]

FUTURE DIRECTIONS

1. Large-scale, multi-center studies to validate and refine cutoff values for different populations and clinical scenarios.
2. Longitudinal studies to assess the dynamics of platelet indices throughout the course of TB treatment and their correlation with treatment outcomes.
3. Mechanistic studies to further elucidate the role of platelets in TB pathogenesis and immune response.
4. Exploration of combined biomarker panels that incorporate platelet indices with other established and emerging TB biomarkers.
5. Investigation of platelet indices in pediatric TB, as suggested by the recent study by Hilda *et al.*[10]
6. Further research on the potential of MPV as a marker for TB-diabetes comorbidity, as proposed by Xu *et al.*[5]
7. Exploration of the relationship between platelet indices and TB-associated coagulation abnormalities, building on the work of Turken *et al.* and others.[9,18]
8. Investigation of the potential therapeutic implications of modulating platelet function in TB, considering their role in immune modulation and granuloma formation.[8]

CONCLUSION

Platelet indices have emerged as promising diagnostic and prognostic markers for TB, offering potential advantages in terms of cost-effectiveness and rapid results. Significant alterations in PLT, MPV, PDW, and PCT have been observed in TB patients, reflecting the complex interplay between platelets and the immune system during infection. These changes not only contribute to our understanding of TB pathogenesis but also open new avenues for clinical applications.

However, challenges persist, including lack of specificity and measurement variability across different clinical settings. To address these limitations, future research should focus on large-scale, multi-center studies to validate and refine cutoff values for diverse populations. Longitudinal studies exploring the dynamics of platelet indices throughout TB treatment could provide valuable insights into their prognostic value. In addition, investigating combined biomarker panels that incorporate platelet indices with other established TB markers may enhance diagnostic accuracy.

Further exploration of the mechanistic role of platelets in TB immunity and granuloma formation could potentially lead

to novel therapeutic approaches, highlighting the broader implications of this field of study.

Ethical approval

Institutional Review Board approval is not required.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

REFERENCES

1. Sahin F, Yazar E, Yıldız P. Prominent features of platelet count, plateletcrit, mean platelet volume and platelet distribution width in pulmonary tuberculosis. Multidiscip Respir Med 2012;7:38.
2. Sahin F, Yazar E, Yildiz P. Evaluation of platelet count and indices in pulmonary tuberculosis and pneumonia. Eur Respir J 2011;38(Suppl 55):4387.
3. Renshaw AA, Gould EW. Thrombocytosis is associated with *Mycobacterium tuberculosis* infection and positive acid-fast stains in granulomas. Am J Clin Pathol 2013;139:584-6.
4. Tozkoparan E, Deniz O, Ucar E, Bilgic H, Ekiz K. Changes in platelet count and indices in pulmonary tuberculosis. Clin Chem Lab Med 2007;45:1009-13.
5. Xu F, Qu S, Wang L, Qin Y. Mean platelet volume (MPV): New diagnostic indices for co-morbidity of tuberculosis and diabetes mellitus. BMC Infect Dis 2021;21:461.
6. Unsal E, Aksaray S, Köksal D, Sipit T. Potential role of interleukin 6 in reactive thrombocytosis and acute phase response in pulmonary tuberculosis. Postgrad Med J 2005;81:604-7.
7. Kirwan DE, Chong DL, Friedland JS. Platelet activation and the immune response to tuberculosis. Front Immunol 2021;12:631696.
8. La Manna MP, Orlando V, Badami GD, Tamburini B, Azgomi MS, Lo Presti E, *et al*. Platelets accumulate in lung lesions of tuberculosis patients and inhibit T-cell responses and *Mycobacterium tuberculosis* replication in macrophages. Eur J Immunol 2022;52:784-99.
9. Turken O, Kunter E, Sezer M, Solmazgul E, Cerrahoglu K, Bozkanat E, *et al*. Hemostatic changes in active pulmonary tuberculosis. Int J Tuberc Lung Dis 2002;6:927-32.
10. Hilda JN, Venkataraman A, Thiruvengadam K, Brindha B, Karthick M, Subha S, *et al*. Evaluation of platelet indices as markers of tuberculosis among children in India. ERJ Open Res 2024;10:00734-2023.
11. Akpan PA, Akpotuzor JO, Osim EE. Haemostatic indices as markers for monitoring pulmonary tuberculosis treatment. Niger J Physiol Sci 2018;33:31-5.
12. Awodu OA, Ajayi IO, Famodu AA. Haemorheological variables in Nigeria pulmonary tuberculosis patients undergoing therapy. Clin Hemorheol Microcirc 2007;36:267-75.
13. Chen G, Wu C, Luo Z, Teng Y, Mao S. Platelet-lymphocyte ratios: A potential marker for pulmonary tuberculosis diagnosis in COPD patients. Int J Chron Obstruct Pulmon Dis 2016;11:2737-40.
14. Lee MY, Kim YJ, Lee HJ, Cho SY, Park TS. Mean platelet volume in *Mycobacterium tuberculosis* infection. Biomed Res Int 2016;2016:7508763.
15. Zareifar S, Farahmand Far MR, Golfeshan F, Cohan N. Changes in platelet count and mean platelet volume during infectious and inflammatory disease and their correlation with ESR and CRP. J Clin Lab Anal 2014;28:245-8.
16. Korniluk A, Koper-Lenkiewicz OM, Kamińska J, Kemona H, Dymicka-Piekarska V. Mean platelet volume (MPV): New perspectives for an old marker in the course and prognosis of inflammatory conditions. Mediators Inflamm 2019;2019:9213074.
17. Osselaer JC, Jamart J, Scheiff JM. Platelet distribution width for differential diagnosis of thrombocytosis. Clin Chem 1997;43:1072-6.
18. Robson SC, White NW, Aronson I, Woolgar R, Goodman H, Jacops P. Acute-phase response and hypercoagulable state in pulmonary tuberculosis. Br J Haemetol 1996;93:943-9.

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