Profiles of Erythrocytes, Thrombocytes, Leukocytes, Macrophages, and Interleukin-6 for Evaluating Molecular Rapid Test Results in Patients with Suspected Pulmonary Tuberculosis

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ABSTRACT
Pulmonary tuberculosis (TB) causes changes in hematologic profiles and increased proinflammatory cytokines. Molecular Rapid Testing (MRT) is the standard for TB diagnosis, but the access remains limited in some healthcare facilities. This systematic review aims to evaluate changes in hematological and immunological profiles in patients diagnosed with TB using RMT. A systematic review of the literature was conducted following the Preferred Reference Guidelines for Systematic Reviews and Meta-Analysis (PRISMA). A literature search was conducted on PubMed, ScienceDirect, and Google Scholar for publications from 2020–2025, using the keywords "Hematological Parameters in Tuberculosis," "IL-6 in Tuberculosis," "Hematological Parameters in Pulmonary TB," and "IL-6 Tuberculosis Hematology GeneXpert". The initial search identified 1,152 articles, which subsequently underwent a screening process based on the predefined inclusion and exclusion criteria. Included studies were clinical research articles written in English or Indonesian, measuring hematological parameters and/or IL-6 in pulmonary TB patients, available in full-text form, and having a Digital Object Identifier (DOI). A multi-step screening of titles, abstracts, and full-text articles was conducted, resulting in 15 articles for analysis through narrative synthesis. Most studies reported a consistent pattern of pulmonary TB causing anemia, leukocytosis with neutrophilia and lymphopenia, thrombocytosis, and an elevated Erythrocyte Sedimentation Rate (ESR) as signs of systemic inflammation. Nearly all studies reported a significant increase in IL-6 in active TB, which plays a role in fever, tissue inflammation, elevated hepcidin, and hematologic changes. The findings also indicate that macrophages, the primary target cells for TB infection, produce high levels of IL-6, triggering an inflammatory response reflected in hematological parameters. In conclusion, hematological parameters and IL-6 levels consistently exhibit changes in pulmonary TB and have potential as diagnostic biomarkers, particularly in healthcare settings with limited rapid diagnostic tools. Integrating hematological and IL-6 examinations with RMT may provide a more comprehensive understanding of inflammation and disease progression in patients with suspected pulmonary TB.
Keywords: Hematological parameters; Interleukin-6; macrophage response; pulmonary tuberculosis; rapid molecular testing

INTRODUCTION
Tuberculosis (TB) is an infectious disease that continues to pose a major global health challenge. The World Health Organization (WHO) reported that in 2021 there were approximately 10.6 million TB cases worldwide, an increase of 600,000 cases compared to the previous year [1]. TB is caused by *Mycobacterium tuberculosis*, a pathogenic bacterium that primarily infects the lungs but may disseminate to other organs and tissues [2]. Transmission occurs mainly through respiratory droplets expelled when an infected individual coughs or sneezes [3], enabling TB bacilli to be inhaled by others and initiate primary infection [4].

TB exerts broad effects on the hematopoietic system and immune response. Infection with *M. tuberculosis* can disrupt the production and function of various blood cells, including erythrocytes, leukocytes, and platelets [5]. These hematological changes are clinically relevant because they reflect the degree of inflammation and disease severity. Anemia of chronic disease is one of the most common hematological complications in TB, driven by inflammation-induced hepcidin expression mediated by IL-6, which restricts iron release and utilization [6].

Leukocytes, particularly neutrophils and lymphocytes, play essential roles in the immune response to TB. Neutrophils act as the first line of defense through phagocytosis and secretion of inflammatory mediators [7]. Increased neutrophil counts or elevated neutrophil-to-lymphocyte ratios (NLR) indicate active systemic inflammation in pulmonary TB [8]. Conversely, lymphopenia is frequently observed in active TB and reflects impaired adaptive immunity [9]. Sihombing et al. [10] reported that patients with pulmonary TB exhibit significantly increased neutrophils and decreased lymphocytes, correlating with disease severity. Active TB is also commonly accompanied by thrombocytosis as a response to chronic inflammation [11]. Manna et al. [12] demonstrated that patients with active TB have elevated platelet-to-lymphocyte ratios (PLR), with IL-6 contributing to megakaryocyte activation. These findings reinforce the value of hematological profiles as early indicators of inflammatory status in TB.

Macrophages are also central to the immune response against *M. tuberculosis*, serving as the primary site of bacterial replication. After entering the alveoli, *M. tuberculosis* is phagocytosed by alveolar macrophages, which constitute the first line of defense. These macrophages migrate into the lung interstitium and aggregate to form granulomas, the hallmark structure of TB infection that helps contain bacterial spread [13]. Activated macrophages produce pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which recruit additional immune cells to the infection site [14]. Shifts in macrophage polarization (M1 pro-inflammatory versus M2 anti-inflammatory) play a critical role in determining TB disease progression [15]. These findings highlight the importance of macrophage–cytokine interactions, particularly IL-6, in the pathogenesis of pulmonary TB.

Interleukin-6 is a key cytokine in the acute inflammatory phase, released by macrophages, epithelial cells, and lymphocytes in response to infection. In pulmonary TB, IL-6 induces fever, increases acute-phase protein production, and suppresses erythropoiesis, contributing to anemia [16]. Multiple studies have reported significantly elevated IL-6 levels in active TB, correlating with lesion extent, bacterial burden, and symptom severity [17,18]. IL-6 is also closely associated with thrombocytosis through stimulation of thrombopoietin production, thereby increasing platelet counts [19]. When combined with hematological parameters such as hemoglobin, neutrophils, lymphocytes, and platelets, IL-6 enhances the ability to identify active TB cases. Djody and Musdalifah [20] found that TB patients with extensive lung lesions exhibited reduced T-lymphocyte counts, elevated IL-6 levels, and decreased erythrocyte counts, reinforcing IL-6 as a pro-inflammatory biomarker and indicator of disease activity.

The current gold standard for pulmonary TB detection is the Molecular Rapid Test (TCM) or GeneXpert MTB/RIF, which can detect *M. tuberculosis* and rifampicin resistance [21]. This tool has high sensitivity, capable of detecting bacterial loads as low as 131 CFU/mL [22]. However, its use is limited by cost, specialized equipment requirements, and availability constraints in many health facilities [23,24]. These limitations underscore the need for additional diagnostic methods that are rapid, affordable, and accessible.

Although TCM is the primary diagnostic method, it only detects *M. tuberculosis* DNA and does not provide information on inflammatory status or patient physiology. Therefore, integrating molecular testing with hematological parameters and IL-6 may offer a more comprehensive clinical assessment [25,26]. This approach is particularly valuable in resource-limited settings, as hematological tests and IL-6 measurements are relatively inexpensive, widely available, and rapid. Beyond improving diagnostic accuracy, these combined biomarkers have potential as an initial screening system for suspected pulmonary TB cases [27]. Accordingly, this study conducted a systematic review to evaluate biomarker changes in complete blood profiles (erythrocytes, leukocytes, platelets), macrophages, and IL-6 in pulmonary TB patients. These biomarker changes may be combined or correlated with TCM or GeneXpert results as a screening system for diagnosing suspected pulmonary TB.

METHODS

Study design

This study is a systematic review aimed at evaluating changes in hematological profiles, Interleukin-6 (IL-6) levels, and the role of macrophages in patients with pulmonary tuberculosis (TB), as well as their relationship with the results of the Molecular Rapid Test (TCM) or GeneXpert. The conduct and reporting of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Figure 1).

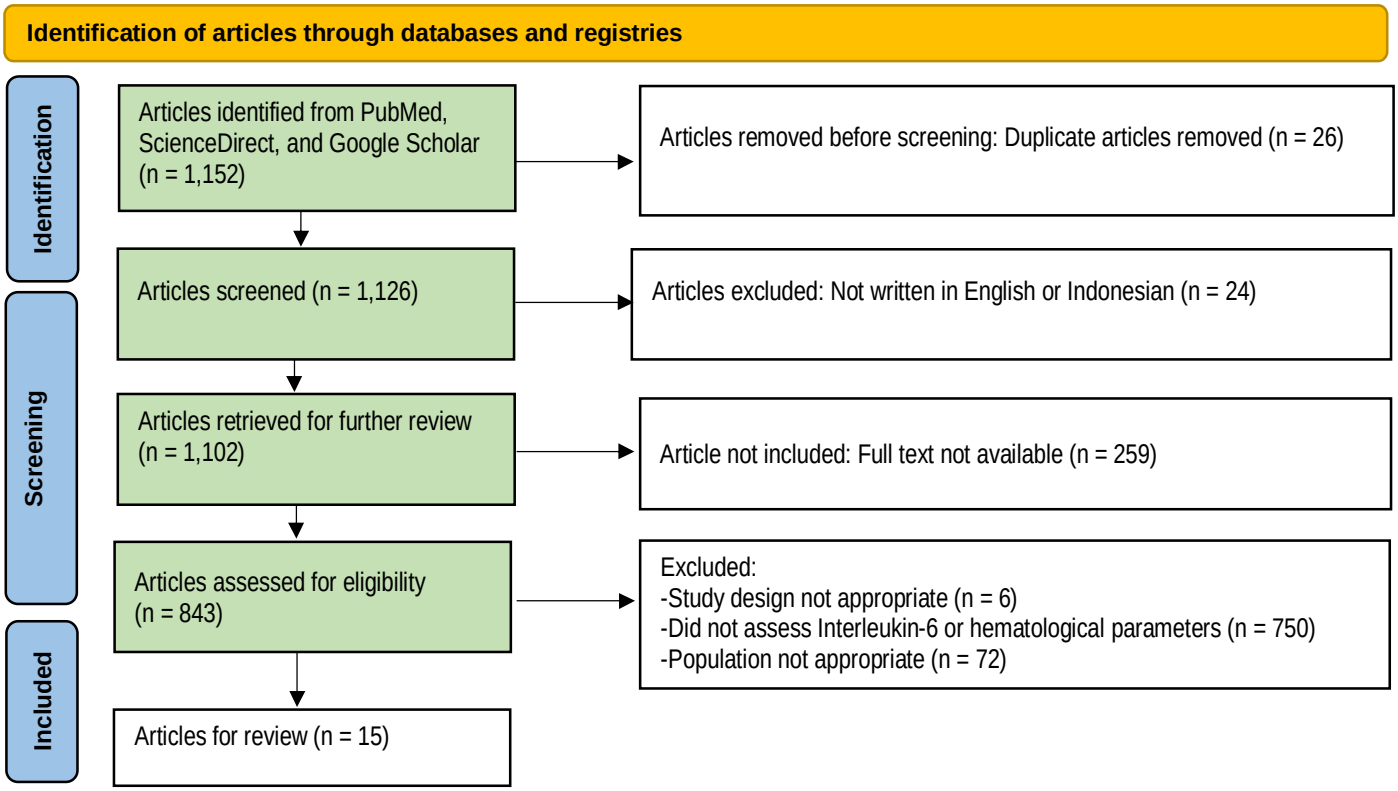


Figure 1. PRISMA flow diagram for article selection in the review

Study question

The research question addressed in this systematic review is: "How do hematological profiles, IL-6 levels, and macrophage activity change in patients with pulmonary TB, and how are these changes associated with TCM or GeneXpert results?"

Literature search strategy

The literature search was conducted using three databases: PubMed, ScienceDirect, and Google Scholar. The search was limited to articles published between 2020 and 2025. Keywords included "Hematological Parameters in Tuberculosis," "IL-6 in Tuberculosis," "Hematological Parameters in Pulmonary TB," and "IL-6 Tuberculosis Hematology GeneXpert." All retrieved records were compiled and screened according to predefined criteria.

Inclusion and exclusion criteria

Inclusion criteria consisted of clinical research articles involving patients with pulmonary TB, written in Indonesian or English, available in full text, possessing a DOI, and evaluating hematological parameters and/or IL-6. Accepted study designs included cross-sectional, case-control, cohort, and other relevant clinical studies. Exclusion criteria included review articles, editorials, case reports, animal or in vitro studies unrelated to the research objective, studies involving extrapulmonary TB without pulmonary TB data, and studies that did not assess hematological parameters or IL-6.

Article selection

Based on Figure 1, article selection was conducted in several stages: identification, removal of duplicates, screening of titles and abstracts, assessment of full-text availability, and evaluation of eligibility based on inclusion and exclusion criteria. A total of 1,152 articles were initially identified across the three databases. After removing duplicates and excluding articles based on language, full-text availability, study design, assessed parameters, and population relevance, 15 articles met all inclusion criteria and were included in the systematic review.

Data extraction

Data from eligible articles were systematically extracted, including author names and publication year, study title, study design, research location, sample size and characteristics, evaluated parameters, examination methods, and main findings. Extracted data were presented in tabular form and served as the basis for narrative synthesis across all included studies.

Quality assessment and risk of bias

Methodological quality and risk of bias were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools, adapted to the specific study design of each article. Assessment covered relevant methodological aspects such as appropriateness of inclusion criteria, subject characteristics, variable measurement, identification and control of confounding factors, and adequacy of statistical analysis.

Data synthesis and analysis

Findings from the 15 included studies were synthesized narratively according to parameter groups, including erythrocytes and anemia, leukocytes and leukocyte differentials, platelets, IL-6, and macrophage activity, while considering their relationship with TCM or GeneXpert results. Data analysis was conducted descriptively and narratively by identifying patterns of similarities and differences across studies. Variations in subject characteristics, study design, examination methods, treatment status, and evaluated parameters were considered in interpreting the findings.

RESULTS

Most studies have found that hematological profiles and the cytokine IL-6 play an important role in the progression of tuberculosis. TB patients commonly experience anemia, reflected by decreased hemoglobin (Hb) levels and reduced red blood cell (erythrocyte) counts. In addition, the majority of TB patients present with leukocytosis due to bacterial inflammation, neutrophilia indicating an acute inflammatory phase, lymphocytopenia, thrombocytosis, and a marked increase in erythrocyte sedimentation rate (ESR) as a consequence of systemic inflammation. Most research also reports that IL-6 levels increase significantly in patients with active TB because IL-6 contributes to fever, inflammation, and anemia. As treatment progresses, IL-6 concentrations gradually decline. Meanwhile, macrophages play a crucial role in pulmonary TB and are closely associated with hematological profiles and IL-6 dynamics. Several studies show that patients with positive GeneXpert MTB/RIF (TCM) results have higher leukocyte counts, neutrophil levels, and IL-6 concentrations compared with suspected TB patients who test negative (Table 1).

Table 1. The summary of articles

No	Author(s)	Title	Object	Methods	Results
1.	Shah et al., 2022 [28]	Evaluation of hematological parameters in pulmonary tuberculosis patients	Hemoglobin (Hb), erythrocytes, leukocytes, platelets, and Erythrocyte Sedimentation Rate (ESR).	This study employed an observational comparative research design. The sample consisted of 70 patients with pulmonary tuberculosis (TB) confirmed by a positive sputum smear and 70 healthy individuals as controls, totaling 140 participants. The study was conducted in the Department of Pathology at a tertiary care hospital in India.	White blood cell counts, absolute neutrophil counts, platelet counts, and ESR were significantly higher in patients with tuberculosis (TB) compared to the control group ($p<0.05$). Conversely, Hb levels, erythrocyte counts, and platelet counts were significantly lower in TB patients.
2.	Hartono et al., 2024 [29]	Hasil pemeriksaan GeneXpert terhadap jumlah dan jenis sel leukosit pada pasien suspek tuberkulosis	Total leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, and basophils.	This study employed a correlational research design with a cross-sectional approach, involving 36 subjects who met the study's inclusion criteria. Sample collection and analysis were conducted at the Clinical Pathology Laboratory of the Bumi Panua Regional General Hospital in Pohuwato, Gorontalo.	The results indicate that patients with a positive GeneXpert test result had higher total leukocyte counts ($p=0.000$) compared to those with a negative GeneXpert result. Furthermore, neutrophil counts were also elevated in the GeneXpert-positive group ($p=0.004$), while lymphocyte counts tended to be lower in patients with a positive GeneXpert result ($p=0.032$). Regarding monocytes, the GeneXpert-positive group exhibited higher levels ($p=0.010$). Conversely, no significant differences were observed in eosinophil or basophil levels between the GeneXpert-positive and GeneXpert-negative groups.

No	Author(s)	Title	Object	Methods	Results
3.	Obeagu et al., 2020 [30]	Studies on some cytokines, hepcidin, iron status and hematological parameters of patients with pulmonary tuberculosis in Southeast Nigeria	Interleukin (IL)-6, IL-10, Interferon (IFN)-γ, hepcidin, erythrocytes, leukocytes, and monocytes.	This study is an analytical comparative study with a control group (observational design) that assesses the profiles of cytokines, hepcidin, iron status, and hematological parameters in patients with pulmonary tuberculosis compared to healthy subjects. The sample consisted of 200 individuals—100 patients with pulmonary tuberculosis and 100 healthy controls—selected using a purposive sampling technique. The study was conducted at the TB-DOTS Centre, Federal Medical Centre, Umuahia, Southeast Nigeria, with laboratory analyses performed using ELISA, GeneXpert, and full blood count.	IL-6 levels were significantly higher in TB patients compared to healthy individuals (12.46 ± 3.29 pg/mL vs. 7.98 ± 0.22 pg/mL). Interleukin-10, IFN-γ, and monocyte counts were elevated, while erythrocyte counts were significantly lower in TB patients.
4.	Okeke et al., 2023 [31]	Assessment of gender differences in some inflammatory cytokines of tuberculosis patients before and during treatment	IL-6, IL-2, IL-10, Tumor Necrosis Factor (TNF)-α.	This study employed a comparative follow-up study design, comparing inflammatory cytokine levels in male and female tuberculosis (TB) patients before treatment, after two months of intensive-phase treatment, and after six months of the continuation phase. A total of 60 pulmonary TB patients—comprising 35 men and 25 women—were enrolled via consecutive sampling from an initial pool of 80 patients. The study was conducted at Mile Four Hospital in Abakaliki, Ebonyi State, Nigeria.	Prior to the initiation of TB treatment, IL-6 levels were higher in men (p=0.046). After two months of therapy, IL-6 levels were higher in women (p=0.042). TNF-α and IL-10 levels were higher in men; however, no significant differences between men and women were observed after six months of treatment.
5.	Yu et al., 2023 [32]	Development of a new cellular immunological detection method for tuberculosis based on HupB protein induced IL-6 release test	IL-6 (HupB antigen assay) and Interferon-Gamma Release Assay (IGRA) comparison.	This study employed a cross-sectional design with a diagnostic test approach, involving 190 patients with pulmonary TB, 33 patients with non-TB pulmonary diseases, and 273 healthy controls in a multi-center study, supplemented by samples from the exploration and initial validation phases. Data collection was conducted at referral hospitals and specialized pulmonary hospitals across several locations in China, including Wuhan Jinyintan Hospital, Wuhan Polytechnic University Hospital, the General Hospital of the Yangtze River Shipping, Henan Provincial Chest Hospital, Xiangyang City Hospital for Tuberculosis, and Xiangyang Central Hospital.	The HupB antigen specifically stimulates the release of IL-6 in the peripheral blood mononuclear cells of TB patients. Combining the HupB test with an IGRA improves the accuracy of TB diagnosis.
6.	Kumar et al., 2024 [33]	Hematological parameters in patients with pulmonary tuberculosis and its presentation among favorable and unfavorable treatment outcomes	Hb, leukocytes, neutrophils, monocytes, lymphocytes, eosinophils, platelets, monocyte/lymphocyte (M/L) ratio, neutrophil/lymphocyte (N/L) ratio, and platelet/lymphocyte (P/L) ratio.	This study employed a randomized clinical trial design (an open-label, parallel-arm randomized clinical trial). The sample size analyzed for hematological parameters consisted of 1,059 sputum-positive pulmonary tuberculosis patients, out of a total of 1,371 patients recruited. The study was conducted at referral hospitals—specifically the ICMR-National Institute for Research in Tuberculosis (NIRT) in Chennai and Madurai, India.	Hb levels increased, while leukocytes and the M/L, N/L, and P/L ratios decreased following treatment. These changes did not differ significantly between favorable and unfavorable treatment outcomes.
7.	Sanogo et al., 2023 [34]	Hematological profiles of patients with tuberculosis and nontuberculous *Mycobacteria* infections in Bamako, Mali	Hb, hematocrit (Hct), leukocytes, platelets, basophils, eosinophils, lymphocytes, monocytes, and neutrophils.	This research was a cross-sectional study with a sample size of 90 patients, conducted at the Point G referral hospital and a district referral health center in Bamako, Mali; laboratory analyses were performed at the UCRC Laboratory (USTTB).	TB patients exhibited higher platelet and basophil counts compared to non-TB patients. Eosinophil counts were lower in TB patients than in non-TB patients, while both Hb and Hct levels were low in both groups.

No	Author(s)	Title	Object	Methods	Results
8.	Kahase et al., 2020 [35]	Evaluation of peripheral blood parameters of pulmonary tuberculosis patients at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia: Comparative study	Hb, Hct, Mean Corpuscular Hemoglobin Concentration (MCHC), leukocytes, platelets, ESR (erythrocyte sedimentation rate), lymphocytes, and neutrophils.	This study employed a comparative cross-sectional design with a sample size of 80 individuals (40 patients with culture-confirmed pulmonary tuberculosis and 40 healthy controls, matched for age and sex). The study was conducted at St. Paul's Hospital Millennium Medical College in Addis Ababa, Ethiopia.	Hb, Hct, MCHC, and lymphocyte counts were lower in TB patients, while leukocyte counts, platelet counts, ESR, and neutrophil counts were higher. Furthermore, anemia and thrombocytosis were observed in the majority of the TB patients.
9.	Nyamagoud et al., 2025 [36]	Evaluating hematological and inflammatory biomarkers in tuberculosis management	Hb, leukocytes, Serum Amyloid A (SAA), C-Reactive Protein (CRP), and ESR.	This study employed an observational cross-sectional design with a sample of 80 tuberculosis patients. It was conducted in the TB inpatient ward of the Tuberculosis Department at Vivekananda General Hospital, Hubballi, Karnataka, India.	Hb levels were found to be decreased, while leukocyte, SAA, CRP, and ESR levels were elevated in TB patients. Hb values showed a negative correlation with leukocyte, SAA, and ESR levels.
10.	Odeyemi et al., 2023 [37]	Assessment of hematological parameters in pulmonary tuberculosis patients in Ondo State	Hb, Hct, MCHC, leukocytes, platelets, ESR, lymphocytes, and neutrophils.	This study employed a comparative cross-sectional design, with a sample size of 623 patients with pulmonary tuberculosis—diagnosed using GeneXpert/RIF—and 20 healthy individuals as controls. The study was conducted at healthcare facilities in Ondo State, Nigeria, with hematological analyses performed at the Hematology Laboratory of the University of Medical Sciences Teaching Hospital, Akure.	Hb, Hct, MCHC, and lymphocyte levels were lower in TB patients, whereas leukocyte, platelet, ESR, and neutrophil values were higher.
11.	Nancy Pandiarajan et al. 2025 [38]	Association of altered baseline hematological parameters with adverse tuberculosis treatment outcomes	Hb, erythrocytes, Hct, leukocytes, neutrophils, lymphocytes, monocytes, N/L ratio, and M/L ratio.	This study employed a nested case–control design (with a 1:2 ratio of cases to controls), involving 201 patients with pulmonary tuberculosis (68 cases with poor treatment outcomes and 133 controls with favorable treatment outcomes). The study was conducted at the ICMR–National Institute for Research in Tuberculosis (NIRT), Chennai, India.	High N/L and M/L ratios were found to correlate with poor outcomes. Conversely, lower levels of Hb, erythrocytes, Hct, and lymphocytes were associated with poor treatment outcomes.
12.	Batool et al., 2022 [39]	Hematological manifestations in patients newly diagnosed with pulmonary tuberculosis	Hb, leukocytes, platelets, ESR, lymphocytes.	This study employed a retrospective cross-sectional design, with a sample size of 500 patients newly diagnosed with pulmonary tuberculosis. The study was conducted at the Department of Hematology, Nishtar Medical University & Hospital, Multan, Pakistan, using data extracted from the electronic medical records of both outpatients and inpatients.	Anemia was observed in 82.6% of the newly diagnosed TB patients, leukocytosis in 46.2%, and thrombocytosis in 26.2%, while 99% of patients exhibited an elevated ESR.
13.	Adewole et al., 2022 [40]	Platelet indices in drug resistant tuberculosis patients in Ibadan	Platelets, plateletcrit (PCT), mean platelet volume (MPV), and erythrocyte sedimentation rate (ESR).	This study employed a prospective case–control design with a sample size of 90 individuals (30 patients with drug-resistant TB, 30 patients with drug-sensitive TB, and 30 healthy individuals as controls). The study was conducted at the Government Chest Hospital in Jericho, Ibadan, Nigeria, with laboratory analyses performed at Clina-Lancet Laboratories, Ibadan.	In patients with drug-resistant TB, platelet counts and PCT values were elevated, while MPV was decreased. In patients with drug-sensitive TB, platelet counts, PCT, and ESR were all elevated.
14.	Ifeanyi et al., 2021 [41]	Studies on some cytokines, CD4, iron status, hepcidin and some hematological parameters in pulmonary tuberculosis patients based on duration of treatment in Southeast, Nigeria	IFN-γ, IL-6, IL-10, CD4, hepcidin, iron, total iron-binding capacity (TIBC), percentage of transferrin saturation (TSA), Hb, erythrocytes, leukocytes, erythrocyte sedimentation rate (ESR), and platelets.	This study employed an analytical cross-sectional design based on the duration of tuberculosis (TB) treatment, involving 200 subjects (comprising 50 pulmonary TB patients each at the following stages: pre-treatment, 2 months of treatment, 4 months of treatment, and 6 months of treatment). The study was conducted at the TB DOTS Center, Federal Medical Centre, Umuahia, Nigeria, with laboratory analyses performed at Links Laboratory, Owerri, and the Diagnostic Laboratory Unit of Michael Okpara University of Agriculture, Umudike.	Hb, erythrocytes, and CD4 counts increased over the course of treatment, while levels of IL-6, IL-10, hepcidin, ESR, and monocytes decreased. Total iron-binding capacity (TIBC) increased significantly with the duration of pulmonary TB treatment (p=0.000). Transferrin saturation also showed a significant increase in relation to the duration of treatment (p=0.000).

No	Author(s)	Title	Object	Methods	Results
15.	Sa'ad et al., 2024 [42]	Assessment of Interleukin 6 (IL-6) as a marker of inflammation among adult patients with pulmonary tuberculosis in Zaria, Nigeria	IL-6 levels.	This study employed a cross-sectional design with a sample size of 90 individuals (30 newly diagnosed pulmonary TB patients, 30 pulmonary TB patients currently undergoing treatment, and 30 healthy individuals as controls). The study was conducted at the National Tuberculosis and Leprosy Training Center (NTBLTC) in Saye, Zaria, Nigeria.	IL-6 levels were significantly elevated in patients with active TB compared to healthy controls.

DISCUSSION

The systematic review of 15 studies demonstrates a consistent pattern indicating that pulmonary tuberculosis (TB) infection induces significant alterations in hematological parameters, particularly marked reductions in erythrocyte indices leading to the development of Anemia of Chronic Disease (ACD). Nearly all studies, including those by Shah et al. (2022), Kahase et al. (2020), and Batool et al. (2022), reported anemia characterized by decreased erythrocyte count, hemoglobin (Hb), and hematocrit (Hct). These findings support the established theory of ACD, in which inflammation mediated by interleukin-6 (IL-6) stimulates hepcidin production, thereby restricting iron availability and impairing erythropoiesis in TB patients [28,35,39]. In contrast, leukocyte levels were consistently elevated, with a characteristic pattern of neutrophilia among TB patients. Most studies documented increases in total leukocyte count accompanied by elevated neutrophils, lymphopenia, and monocytosis. Increased neutrophil and monocyte counts reflect an active innate immune response, whereas lymphopenia indicates impairment of adaptive immunity [35,37].

Pulmonary TB was also found to induce thrombocytosis, a finding reported across nearly all hematological studies. Chronic inflammation in TB stimulates thrombopoietin production through IL-6–mediated pathways, resulting in elevated platelet counts [43]. Derived hematological biomarkers such as the Platelet-to-Lymphocyte Ratio (PLR), Neutrophil-to-Lymphocyte Ratio (NLR), and Monocyte-to-Lymphocyte Ratio (MLR) have demonstrated diagnostic value in TB [44]. Collectively, hematological changes involving erythrocytes, leukocytes, and platelets serve as indicators of inflammatory status and disease progression, thereby supporting the objectives of this systematic review.

The review further shows that IL-6 levels are significantly elevated in active TB compared to healthy controls [30]. Increased IL-6 in TB patients is associated with the degree of pulmonary inflammation, anemia via hepcidin induction, thrombocytosis, and bacterial burden [45–48]. Although some studies, such as Okeke et al. (2023), reported sex-based variations, the overall trend consistently demonstrates elevated IL-6 across all demographic groups [31]. These findings reinforce the notion that IL-6 is not merely an inflammatory marker but is also closely linked to hematological alterations observed in TB.

In addition to IL-6, macrophages play a central role in TB pathogenesis. Macrophages are the first cells infected by *Mycobacterium tuberculosis* upon entry into the alveoli [15]. Although macrophages phagocytose *M. tuberculosis*, the bacteria can survive within the phagolysosome [49]. Alveolar macrophages serve as the primary site of bacterial replication and the core of granuloma formation. Activated macrophages stimulate the production of cytokines such as IL-1β, tumor necrosis factor-α (TNF-α), and IL-6 [50]. Elevated IL-6 levels largely originate from activated macrophages, explaining the concurrent rise in IL-6 and neutrophils [51], as well as the emergence of anemia and thrombocytosis [46,52].

Macrophage polarization (M1 and M2) further contributes to cytokine dynamics. M1 macrophages promote pro-inflammatory cytokines through NF-κB pathways, resulting in high IL-6 levels [53,54], whereas M2 macrophages promote anti-inflammatory cytokines, particularly in chronic or progressive TB [55]. Increased IL-6 released by macrophages stimulates neutrophil production [56], induces hepatocytes to produce C-reactive protein (CRP), elevates erythrocyte sedimentation rate (ESR) [57,58], suppresses erythropoiesis leading to inflammatory anemia, and activates platelet production [59,60]. Thus, macrophages serve as key cells linking *M. tuberculosis* infection, IL-6 release, and hematological alterations. The combination of these changes may support prediction of GeneXpert (TCM) results.

Currently, TCM functions solely as a molecular test for detecting *M. tuberculosis* DNA. However, Hartono et al. (2024) reported that TCM-positive patients generally exhibit higher leukocyte, neutrophil, monocyte counts, and elevated NLR. Conversely, TCM-negative patients tend to have lower leukocyte counts and higher lymphocyte levels [29]. Active TB patients with positive TCM results also show higher IL-6 levels compared to non-TB individuals [42]. As macrophages activate inflammatory pathways that increase IL-6, subsequent effects on the bone marrow lead to hematological changes in TB patients. These hematological alterations may serve as indicators of infection activity detectable through TCM. Therefore, although hematological biomarkers and IL-6 cannot replace TCM, they may serve as supportive indicators for TB diagnosis, particularly for early screening, predicting TCM results, and estimating the degree of inflammation in TB patients.

The findings of this systematic review align with previous literature demonstrating consistent hematological changes, elevated IL-6 levels, and the central role of macrophages in TB pathogenesis. Studies by Shah et al. (2022), Kahase et al. (2020), and Batool et al. (2022) corroborate the observed reductions in erythrocytes and increases in leukocytes and platelets among TB patients, consistent with chronic inflammatory patterns described in earlier research [28,35,39]. The elevated IL-6 levels identified in this review are also in agreement with studies by Obeagu (2020), Yu et al. (2023), and Sa'ad et al. (2024), which highlight IL-6 as a major pro-inflammatory cytokine in active TB [30,32,42]. The relationship between IL-6, hepcidin, and chronic anemia reported in immunological studies further supports this biological mechanism. Nonetheless, two studies reported divergent findings. Anisyah et al. (2024) found no significant association between hematological parameters and TCM results, differing from most literature [61]. Such discrepancies may be attributed to small sample sizes, variations in laboratory techniques, or differences in patient categories. Patient characteristics; including disease severity, treatment status (newly diagnosed vs. undergoing therapy), TB type (drug-sensitive vs. drug-resistant), comorbidities such as anemia or diabetes, and demographic factors such as age, nutrition, or sex may influence hematological and cytokine responses. Sex-based variations in IL-6 reported by Okeke (2023) further suggest that demographic factors may modulate inflammatory responses [31].

Overall, this systematic review reinforces that hematological biomarkers and IL-6 levels can serve as early indicators of inflammatory status in suspected pulmonary TB patients, even before TCM testing is performed. These findings are particularly relevant for healthcare facilities with limited access to molecular diagnostics, as hematological and IL-6 assessments are more accessible, rapid, and cost-effective. Hematological parameters (erythrocytes, leukocytes, platelets) may be utilized as early indicators of inflammation in patients with suspected TB. Changes such as leukocytosis, thrombocytosis, or inflammatory anemia can assist clinicians in estimating active infection when TCM results are pending or

unavailable. IL-6 levels may serve as an additional biomarker for assessing inflammatory severity, aiding in disease stratification and treatment monitoring. Elevated IL-6 is consistent with macrophage activation and granulomatous inflammation characteristic of pulmonary TB. Therefore, combining complete blood count profiles with IL-6 measurements may provide early insights into immune activity prior to molecular confirmation, supporting triage and early clinical decision-making (e.g., isolation, referral, or further testing).

Further research is needed to deepen understanding of hematological parameters and IL-6 in TB. Longitudinal studies are essential to evaluate IL-6 changes before and after therapy, determining whether this biomarker accurately reflects treatment response. Additionally, studies comparing IL-6 levels across varying disease severities are needed to clarify the relationship between IL-6 elevation and TB progression. Future research should also aim to establish standardized IL-6 cutoff values, as differences in laboratory methods and population characteristics currently lead to variability in results. Variations in IL-6 across studies may arise from differences in ELISA kits, analytical platforms, sample types (serum vs. plasma), and pre-analytical procedures. Population-related factors; including TB severity, treatment status, comorbidities such as HIV or diabetes, age, sex, nutritional status, and genetic background also significantly influence IL-6 production. Therefore, normalization and standardization of IL-6 thresholds are necessary before IL-6 can be widely adopted as a clinical biomarker for pulmonary TB.

This systematic review has several limitations. Most included studies employed cross-sectional designs, limiting the ability to assess temporal changes in IL-6 or hematological parameters. Additionally, variations in IL-6 measurement methods; including differences in assay kits, instrument sensitivity, and cutoff values limit direct comparability across studies. Another limitation is that not all studies directly assessed macrophage activity; some inferred macrophage involvement solely from inflammatory biomarkers, which may not fully represent actual pulmonary tissue conditions.

CONCLUSION

Based on a systematic review of various research articles, it can be concluded that patients with pulmonary tuberculosis (TB) exhibit consistent patterns of change in several complete blood count parameters; most notably inflammatory anemia, leukocytosis, and thrombocytosis. IL-6 levels are also almost invariably elevated in pulmonary TB patients, reflecting an active inflammatory response. Findings from several studies support the view that macrophages play a crucial role in shaping the initial immune response, including by triggering the production of IL-6 as part of the inflammatory process and infection control. While these hematological profiles and IL-6 levels cannot replace molecular testing (such as the rapid molecular test, or TCM), they do provide an early indication of an inflammatory process relevant to TB. Consequently, these parameters; hematological markers, IL-6, and the role of macrophages can help strengthen clinical suspicion, either while awaiting the results of molecular testing or in settings where such molecular diagnostics are not yet accessible.

Ethical consideration, competing interest and source of funding

-This systematic review was conducted in accordance with established ethical principles, ensuring transparency and accuracy.
-There is no conflict of interest related to this publication.
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