The Role of miR-29a-3p and miR-223-3p in Latent Tuberculosis Infection during Pregnancy: Implications of Maternal Nutritional Status

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ABSTRACT

Background: *Latent tuberculosis infection (LTBI) during pregnancy poses risks to maternal and neonatal outcomes. Pregnancy-related immunomodulation and maternal malnutrition may influence the risk of LTBI reactivation. MicroRNAs, particularly miRNA-29a-3p and miRNA-223-3p, regulate host immune pathways implicated in Mycobacterium tuberculosis control and may serve as minimally invasive biomarkers.*

Method: *This narrative review synthesized evidence published within the last five years (January 2020-February 2025) to summarize the current understanding of miRNA-29a-3p and miRNA-223-3p expression in latent tuberculosis infection (LTBI) and tuberculosis (TB), particularly in relation to pregnancy and nutritional status. Literature searches were conducted in PubMed, Scopus, Web of Science, and Embase using combinations of keywords related to "microRNA-29a-3p," "microRNA-223-3p," "latent tuberculosis infection," "tuberculosis," "pregnancy," and "nutritional status."*

Result: *Twenty-six eligible studies were included. miRNA-29a-3p and miRNA-223-3p were consistently dysregulated in LTBI/TB compared with controls, reflecting modulation of Th1 responses, IFN-γ signaling, macrophage activation, and autophagy pathways. Nutritional deficits (low BMI, anemia, and micronutrient deficiencies) were associated with aberrant miRNA expression and increased risk of progression from LTBI to active TB. Multi-miRNA panels including these markers demonstrated moderate-to-good discriminatory performance for LTBI/TB.*

Conclusion: *miRNA-29a-3p and miRNA-223-3p show promise as minimally invasive biomarkers for LTBI risk stratification in pregnancy. Nutritional optimization may modulate miRNA-mediated immunity and reduce progression risk. Prospective pregnancy-specific cohorts and assay standardization are required before clinical implementation.*

Keywords: latent tuberculosis infection, pregnancy, microRNA-29a-3p, microRNA-223-3p, nutritional status

How to cite this article: Maidin MA, As'ad S, Massi MN, Husin F, Iskandar H, Setiawati D, Zainuddin AA. The Role of miR-29a-3p and miR-223-3p in Latent Tuberculosis Infection during Pregnancy: Implications of Maternal Nutritional Status. Int J Drug Deliv Technol. 2026;16(21s): 625-638. DOI: 10.25258/ijddt.16.21s.66

INTRODUCTION

Tuberculosis (TB) remains a leading cause of morbidity and mortality worldwide. TB is an infectious

disease caused by the pathogenic bacterium Mycobacterium tuberculosis, which primarily affects the lungs (pulmonary TB) and is transmitted via airborne droplets generated by coughing. The majority of infected individuals develop latent TB infection (LTBI) without clinical symptoms, and approximately one in ten latent infections progress to active disease during their lifetime, with a substantially higher risk (30-50%) among individuals co-infected with HIV. TB continues to represent a major public health and clinical challenge, including in industrialized countries. Within the WHO European Region, eastern countries report markedly higher notification rates than western countries [1].

According to the World Health Organization (WHO), there were 10.6 million new TB cases globally in 2022, with approximately 1.3 million TB-related deaths, including 167,000 deaths among individuals with TB/HIV co-infection. In 2023, the global TB incidence was approximately 134 per 100,000 population, while the prevalence in the WHO South-East Asia Region reached 234 per 100,000 population. TB ranked as the second leading cause of death from infectious diseases worldwide, after COVID-19. In Indonesia, the TB prevalence in 2023 reached approximately 387 per 100,000 population [2].

The Global Tuberculosis Report 2023 showed that the highest TB burden geographically was observed in South-East Asia (45%), Africa (24%), and the Western Pacific (17%), followed by the Eastern Mediterranean (8.6%), the Americas (3.2%), and Europe (2.1%). Approximately 56% of global TB cases were concentrated in five countries, with India (26%) and Indonesia (10%) contributing the largest proportions, followed by China (6.8%), the Philippines (6.8%), Pakistan (6.3%), Nigeria (4.6%), Bangladesh (3.5%), and the Democratic Republic of the Congo (3.1%). Based on these estimates, Indonesia ranks second globally in terms of TB burden [3].

The socioeconomic impact of TB is particularly severe in low- and lower-middle-income countries with limited health system resources. Although the overall global TB burden has declined, substantial disparities persist between regions. High-income countries report lower TB morbidity and mortality due to more robust health systems and effective prevention strategies, whereas low- and lower-middle-income countries continue to face disproportionately high TB burdens. These disparities reflect not only economic and healthcare resource gaps but also the influence of sociodemographic determinants on TB epidemiology [4]. From an epidemiological perspective, TB occurrence results from the interaction between host, agent, and environmental factors, with active pulmonary TB commonly developing during periods of compromised host immunity [5].

According to the Global Tuberculosis Report 2024, an estimated 10.8 million new TB cases occurred globally in 2023, corresponding to an incidence of 134 per 100,000 population. Among these cases, 662,000 (6.1%) were co-infected with HIV, and 400,000 (3.7%) had multidrug-resistant TB (MDR-TB) or rifampicin-resistant TB (RR-TB). The prevalence of MDR/RR-TB was 3.2% among new cases and 16% among previously treated cases. Global TB-related deaths reached 1.25 million in 2023, making TB the leading cause of death from a single infectious disease worldwide, with mortality nearly twice that of HIV/AIDS. These data highlight the persistent and severe nature of the TB epidemic and the urgent need for more effective control strategies [6].

In 2023, most individuals who developed TB resided in the WHO South-East Asia (45%), Africa (24%), and Western Pacific (17%) regions, with smaller proportions in the Eastern Mediterranean (8.6%), the Americas (3.2%), and Europe (2.1%). The ranking of the eight countries with the highest TB burden remained unchanged over the past three years, collectively accounting for more than two-thirds of the global incident TB cases. India and the Philippines were among 39 countries in which TB incidence in 2023 exceeded that in 2015 by more than 5%, indicating stagnation or reversal of progress in TB control [7].

Approximately 90% of TB cases occur in South-East Asia, Africa, and the Western Pacific, with India, China, Indonesia, the Philippines, and Pakistan being the most severely affected countries. Women account for approximately one-third of all TB cases globally, with higher prevalence during the reproductive age. An estimated 216,500 cases of active TB occurred among pregnant women globally in 2011, with a 2.56-fold increased risk among pregnant women living with HIV. TB-HIV co-infection is most prevalent in low- and middle-income countries, where the majority of maternal deaths occur. Pregnancy represents a critical opportunity to integrate screening for TB, HIV, and emerging infectious diseases into antenatal care services. However, up-to-date global and Indonesia-specific prevalence data on TB among pregnant women, distinct from the general population, remain limited, as global reports primarily focus on overall TB incidence and mortality [8].

METHODS

This narrative review synthesized evidence published within the last five years (January 2020-February 2025) to summarize the current understanding of miRNA-29a-3p and miRNA-223-3p expression in latent tuberculosis infection (LTBI) and tuberculosis (TB), particularly in relation to pregnancy and nutritional status. Literature searches were conducted in PubMed, Scopus, Web of Science, and Embase using combinations of keywords related to "microRNA-29a-3p," "microRNA-223-3p," "latent tuberculosis infection," "tuberculosis," "pregnancy," and "nutritional status." Eligible articles included original human studies and high-quality clinical or translational research investigating circulating or cellular miRNA-29a-3p and/or miRNA-223-3p in LTBI or active TB, including studies conducted in pregnant women or women of reproductive age, and studies reporting associations with nutritional indicators such as body mass index, anemia, or micronutrient status. Only articles published in English within the last five years were considered.

Reviews, editorials, case reports, conference abstracts without full text, animal-only studies, and studies lacking extractable outcome data were excluded. Relevant information extracted from each study included study population characteristics, pregnancy status, TB phenotype (LTBI or active TB), biological specimen type, miRNA detection method (e.g., qRT-PCR or next-generation sequencing), direction and magnitude of miRNA expression changes, and reported associations with nutritional parameters. Due to heterogeneity in study designs, populations, and laboratory methodologies, findings were synthesized narratively to provide an integrated overview of current evidence and identify research gaps and future directions.

RESULTS

Overview of TB Pathogenesis: Transition from Exposure to Latent Infection

The pathogenic life cycle of Mycobacterium tuberculosis (M. tb) begins with airborne transmission through aerosolized droplets expelled by individuals with active TB during coughing, sneezing, or speaking. After inhalation, bacilli traverse the respiratory tract and reach the lungs, where the host innate immune system constitutes the first line of defense. At this stage, tubercle bacilli are internalized by alveolar macrophages. When macrophages fail to inhibit or eliminate the bacilli, the bacteria replicate within the intracellular environment, are released, and subsequently phagocytosed by other alveolar macrophages, thereby perpetuating the infection cycle. Subsequently, lymphocytes are recruited to the site of infection, initiating a cell-mediated immune response characterized by the accumulation of immune cells attempting to contain the bacteria and limit further replication. During this phase, individuals typically remain asymptomatic, and M. tuberculosis may be completely eradicated or enter a latent state within granulomas. However, when host immunity is compromised, the infection may progress directly to active TB with overt clinical manifestations [9].

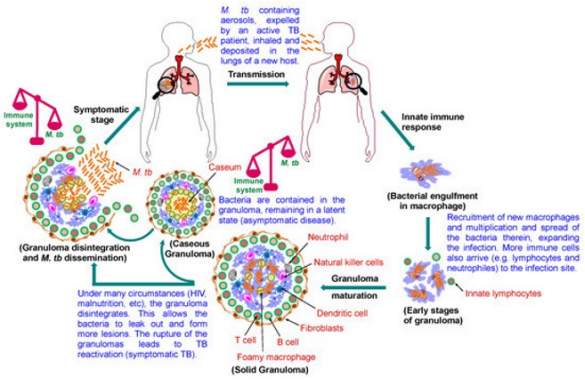

Figure 1. Pathogenesis of Mycobacterium tuberculosis Infection: From Transmission to Latent Infection and Reactivation [9]

Following transmission to a new host, M. tuberculosis enters the lungs and is phagocytosed by macrophages. Additional immune cells are recruited to contain infected macrophages, leading to granuloma formation, the hallmark of TB. In immunocompetent individuals, infection remains latent and may be controlled at this stage, although reactivation risk persists (**Figure 1**.). Foamy macrophages undergo necrosis and release lipid contents, resulting in caseation necrosis within the granuloma core. Progressive granuloma remodeling allows bacilli to leak from macrophages into the caseous layer. Upon reactivation, M. tuberculosis proliferates extensively, bacterial burden increases, granulomas rupture, and bacilli disseminate into the airways. These bacilli are expelled as infectious aerosol droplets, restarting the transmission cycle [9].

Immunological Changes During Pregnancy and Their Impact on TB Latency and Reactivation

During pregnancy, elevated levels of estrogen, progesterone, and human chorionic gonadotropin (hCG) directly suppress $CD4^+$ T lymphocytes, disrupting immune homeostasis and facilitating reactivation or progression of latent M. tuberculosis infection. This provides a mechanistic

basis for the observation that high estrogen levels may accelerate TB relapse. $CD4^+$ T lymphocytes, including T helper and regulatory T cells, play a central role in host immunity against M. tuberculosis. Pregnancy-associated surges in estrogen, progesterone, and hCG impair $CD4^+$ T-cell function and disturb the balance between T helper and regulatory T cells. These immunomodulatory effects facilitate mycobacterial dissemination, promote reactivation of latent infection, and accelerate disease progression [10]. Consequently, strategies aimed at mitigating excessive estrogen exposure such as careful hormonal modulation during ovarian stimulation in women with a history of TB and avoidance of multiple pregnancies may help reduce the risk of TB recurrence [11]. Studies by Orazulike and Sharma et al. demonstrated that active TB during pregnancy is associated with markedly adverse maternal and fetal outcomes through disruption of maternal fetal immune tolerance. This immune suppression compromises timely recognition and effective control of TB infection, leading to delayed diagnosis and treatment. Such delays are associated with preterm birth, fetal growth restriction, and stillbirth [12].

Table 1. Summary of Tuberculosis Pathophysiology and Immunological Changes During Pregnancy Relevant to Latent Infection and Reactivation

Aspect	Key Process	Main Cellular/Molecular Events	Clinical Implication	Reference (IEEE)
Transmission of *M. tuberculosis*	Inhalation of aerosol droplets from active TB cases	Bacilli deposited in alveoli; uptake by alveolar macrophages	Initial establishment of pulmonary infection	[7]
Early innate immune response	Phagocytosis by macrophages	Intracellular survival and replication of *M. tuberculosis* when macrophage killing is insufficient	Persistence of bacilli and initiation of infection cycle	[8]
Granuloma formation	Recruitment of immune cells	Aggregation of macrophages, T cells, B cells, NK cells, dendritic cells; containment of bacilli	Development of latent TB infection (asymptomatic state)	[10]
Latent TB infection (LTBI)	Containment within granuloma	Bacilli persist in hypoxic, nutrient-limited granuloma core	Long-term asymptomatic infection with reactivation risk	[13]
Caseation and granuloma disintegration	Foamy macrophage necrosis	Lipid release leads to caseous necrosis; weakening of granuloma structure	Increased risk of bacillary escape and disease progression	[15]
Reactivation and transmission	Granuloma rupture and airway dissemination	High bacillary burden; release into airways and aerosolization	Progression to active TB and transmission to new hosts	[19]
Pregnancy-related hormonal changes	Increased estrogen, progesterone, hCG	Suppression of $CD4^+$ T-cell function; altered Th/Treg balance	Increased susceptibility to LTBI reactivation	[21]
Immune tolerance during pregnancy	Maternal–fetal immune modulation	Reduced cell-mediated immunity against *M. tuberculosis*	Delayed TB diagnosis and disease progression	[22], [30]
Maternal and fetal	TB during	Impaired immune	Preterm birth, fetal	[31]

Aspect	Key Process	Main Cellular/Molecular Events	Clinical Implication	Reference (IEEE)
outcomes	pregnancy	response to TB	growth restriction, stillbirth	

Noted: M. tuberculosis = Mycobacterium tuberculosis; LTBI = latent tuberculosis infection; NK cells = natural killer cells; hCG = human chorionic gonadotropin; Th = T helper cells; Treg = regulatory T cells.

Table 1. This table summarizes the key biological processes involved in the pathogenesis of Mycobacterium tuberculosis infection, from airborne transmission and early innate immune responses to granuloma formation, latent tuberculosis infection (LTBI), caseation, and reactivation leading to active disease and onward transmission. It also highlights pregnancy-related immunological and hormonal changes, including increased estrogen, progesterone, and human chorionic gonadotropin (hCG), which modulate $CD4^+$ T-cell–mediated immunity and the balance between T helper and regulatory T cells. These immunomodulatory effects may facilitate reactivation of latent TB and contribute to adverse maternal and fetal outcomes, underscoring the heightened vulnerability to TB during pregnancy.

Role of microRNAs in Immune Modulation During Mycobacterium tuberculosis Infection

During the interaction between Mycobacterium tuberculosis (Mtb) and host cells, miRNA expression profiles are dynamically altered, leading to changes in host cellular metabolism, inflammatory responses, apoptosis, and miRNA-mediated autophagy. Differential miRNA expression patterns can discriminate healthy individuals, patients with active TB, and individuals with latent TB infection. This review highlights the roles of miRNAs in immune regulation and their potential application as biomarkers in TB [13]. Differentially expressed miRNAs have been further investigated to delineate their roles in innate immune responses during Mtb infection. In vitro and in vivo studies have confirmed the involvement of miRNAs in modulating gene expression in the primary target cells of Mtb, including macrophages, dendritic cells (DCs), natural killer (NK) cells, and T lymphocytes. M. tuberculosis can induce or suppress specific host miRNAs to evade immune responses. Activation of apoptotic pathways, induction of autophagy, and stimulation of interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) secretion are among the defense mechanisms employed by host cells during bacterial infection [14].

Among miRNAs upregulated in TB patients, miR-146a-5p, miR-21-5p, miR-99b-5p, and miR-132-5p negatively regulate host inflammatory pathways triggered by Toll-like receptor (TLR) signaling in myeloid cells, thereby enhancing Mtb survival. Other miRNAs upregulated in Mtb-infected macrophages, such as miR-27a-5p, miR-33, miR-125-5p, and miR-144-5p, inhibit autophagosome formation and macrophage-mediated killing of Mtb. Notably, miR-223-3p and miR-125-5p, both increased in infected macrophages, directly target IFN-γ and TNF-α, suppressing immune responses against intracellular Mtb [15]. Apoptosis and inflammasome activation represent additional host defense mechanisms against intracellular pathogens and are regulated by host miRNAs modulated by Mtb, including miR-325-3p and miR-20b-5p. Conversely, certain miRNAs, such as miR-155-5p and let-7f, which are modulated during Mtb infection, play pivotal roles in activating innate and adaptive immunity and promoting bacterial clearance [16].

Innate immune responses that contribute to the control of Mtb infection are initiated by pathogen recognition and uptake by resident pulmonary macrophages, resulting in cytokine and chemokine production, upregulation of immune receptors, and activation of host defense mechanisms, including antimicrobial molecule production and reactive oxygen species generation [17]. Recognition of Mtb occurs through multiple pattern recognition receptors and associated molecules, including TLR2, TLR9, the adaptor molecule MYD88, DC-SIGN, and NLRP3. Stimulation of these receptors induces the expression of pro-inflammatory cytokines, chemokines, and cell adhesion receptors, promoting immune cell recruitment and activation. In addition to pulmonary macrophages, DCs, NK cells, neutrophils, and other immune cells contribute to the early innate response to Mtb and may initially limit infection [18]. However, in most cases, Mtb survives and proliferates within infected macrophages, necessitating antigen-specific T-cell activation for effective pathogen clearance. The primary role of innate immunity during early Mtb infection is therefore to establish conditions conducive to the induction of adaptive T-cell responses. Adaptive immunity against Mtb is characterized by IFN-γ and chemokine production by antigen-specific T cells, facilitating further T-cell recruitment and enhancing macrophage phagocytic activity against intracellular bacteria [19].

Figure 2. Present the active tuberculosis (TB), miR-191 levels are increased in exosomes and decreased in neutrophils. Compared with unaffected healthy controls, the levels of miR-3179 and miR-147 in sputum, miR-589-5p and miR-199b-5p in peripheral blood mononuclear cells (PBMCs), miR-331 and miR-204 in neutrophils, and miR-132 and miR-26a in monocyte-derived macrophages (MDMs) are all increased. miR-582-5p is upregulated in monocytes and PBMCs from patients with active TB. miR-320 exhibits a unique expression pattern in patients with TB: miR-320a is increased in neutrophils but decreased in plasma, whereas miR-320b is decreased in serum [20], [21].

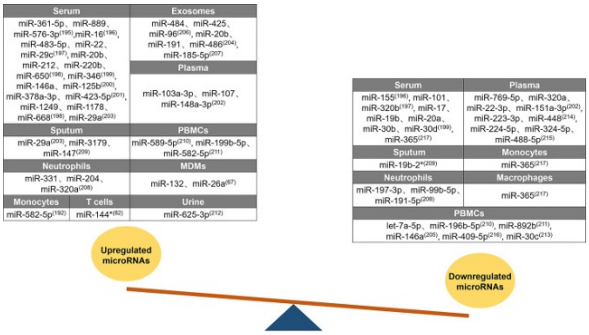

Figure 2. Differentially Expressed microRNAs in Tuberculosis Across Clinical Specimens and Immune Cell Types [21]

The expression levels of miR-144* and miR-625-3p are increased in T cells and urine from patients with active TB, respectively. Three miRNAs (miR-155, miR-101, and miR-17) are downregulated only in the serum of patients with active TB. Members of the miR-30 family are also downregulated in patients with active TB; for example, miR-30b and miR-30d are decreased in serum, and miR-30c is decreased in PBMCs. In patients with active TB, seven miRNAs (miR-769-5p, miR-151a-3p, miR-223-3p, miR-448, miR-224-5p, miR-324-5p, and miR-488-5p) are downregulated exclusively in plasma, four miRNAs (let-7a-5p, miR-196b-5p, miR-892b, and miR-409-5p) are downregulated only in PBMCs, and two miRNAs (miR-197-3p and miR-99b-5p) are downregulated only in neutrophils. miR-365 is downregulated in serum, monocytes, and macrophages from patients with active TB. Among the miRNAs summarized above, five miRNAs (miR-22, miR-20, miR-146a, miR-191, and miR-320) show distinct expression patterns across different tissue and biofluid samples, suggesting their potential utility as biomarkers to distinguish patients with active TB from healthy individuals [21].

The expression levels of several miRNAs (miR-29a-3p, miR-361-5p, miR-196b, miR-451a, miR-340-5p, miR-199b-3p, miR-6856-3p, miR-16-5p, miR-374c-5p, miR-6886-3p, and miR-378) were increased in patients with tuberculosis and latent tuberculosis infection (LTBI). Using qRT-PCR, the overexpression of miR-29a-3p was confirmed as a valuable biomarker candidate for distinguishing active tuberculosis from LTBI in a cohort from Cameroon [22].

Active Mycobacterium tuberculosis infection induces neutrophil and macrophage infiltration in the lungs, driving local inflammation. miR-223-3p, a myeloid-enriched miRNA highly expressed in neutrophils and macrophages, is abundantly detected in blood and lung parenchyma in human and murine tuberculosis. In myeloid cells, miR-223-3p modulates NF-κB activity and negatively regulates pro-inflammatory cytokine release by directly targeting CXCL2, CCL3, and IL-6. Experimental evidence shows that miR-223-3p knockout mice fail to control pulmonary tuberculosis due to excessive neutrophil recruitment and aggravated inflammation, indicating a protective role in restraining immunopathology through regulation of leukocyte chemotaxis and NF-κB signaling. Beyond tuberculosis, miR-223 participates broadly in inflammatory lung diseases such as pulmonary sarcoidosis and fibrosis. In patients with active pulmonary TB, miR-223 is abundant in blood, while TB-resistant mice lacking miR-223 exhibit heightened susceptibility to acute lung infection. miR-223 limits neutrophil-driven pathology by targeting CXCL2, CCL3, and IL-6, thereby modulating CXCR2-mediated chemotaxis; however, circulating miR-223 levels are reported to be significantly reduced in plasma of some TB patients, potentially reflecting strain-dependent host pathogen interactions. Given the central role of STAT1 in anti-mycobacterial immunity, STAT1-associated miR-223 has been proposed as a potential biomarker for progression to active TB [23].

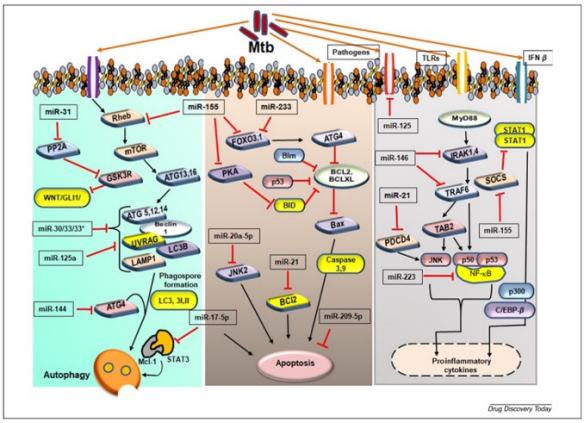

Figure 3. microRNA-Mediated Regulation of Autophagy, Apoptosis, and Inflammatory Signaling During Mycobacterium tuberculosis Infection[20]

Figure 3. present the schematic illustrates the regulatory roles of host microRNAs in key intracellular pathways that determine the outcome of Mycobacterium tuberculosis (Mtb) infection, including autophagy, apoptosis, and proinflammatory signaling. Mtb modulates the expression of multiple miRNAs to subvert host antimicrobial mechanisms. In the autophagy pathway, miRNAs such as miR-31, miR-33/33*, miR-125a, and miR-144 target components of the mTOR-ATG-LC3 axis, UVRAG, and LAMP1, thereby impairing phagophore formation and autophagosome maturation. Concurrently, Mtb-induced miRNAs (e.g., miR-155) regulate FOXO3, ATG4, and BIM, further suppressing autophagy and facilitating intracellular survival of the pathogen [20].

In parallel, miRNAs regulate apoptosis and inflammatory signaling to promote immune evasion. miRNAs such as miR-20a-5p, miR-21, miR-209-5p, and miR-17-5p modulate the balance between pro-apoptotic (BID, BAX, caspases) and anti-apoptotic (BCL2, BCL-XL) factors, thereby limiting apoptosis of infected macrophages. Inflammatory pathways downstream of Toll-like receptors (TLRs) and the MyD88–IRAK–TRAF6 axis are further fine-tuned by miRNAs including miR-125, miR-146a, miR-21, miR-223, and miR-155, which collectively dampen NF-κB and STAT1/STAT3 signaling and reduce proinflammatory cytokine production. These coordinated miRNA-mediated mechanisms enable Mtb persistence by attenuating host innate and adaptive immune responses, highlighting miRNAs as potential biomarkers and therapeutic targets in TB [23].

Current Diagnostic Modalities for Latent Tuberculosis Infection

The diagnosis of latent tuberculosis infection (LTBI) is indirect and relies on detecting host immune responses to Mycobacterium tuberculosis (Mtb) antigens, assuming that immunological sensitization has occurred following exposure. The tuberculin skin test (TST, Mantoux) and interferon-gamma release assays (IGRAs) are the two principal diagnostic tools for LTBI; both are immunological assays that do not directly assess the presence or viability of Mtb bacilli [24]. The Mantoux TST involves intradermal injection of purified protein derivative (PPD) and measurement of induration after 48-72 h, reflecting a T-cell mediated type IV hypersensitivity response. The test is inexpensive, widely available, and feasible in resource-limited settings; however, its specificity is limited because PPD contains multiple antigens shared with M. bovis, Bacillus Calmette Guérin (BCG), and environmental mycobacteria, leading to false-positive results, particularly in BCG-vaccinated populations. Moreover, technical and interpretative variability, the booster phenomenon with repeat testing, and reduced reactivity in immunosuppressed individuals or at extremes of age further compromise test performance [25], [26].

Importantly, TST has limited predictive value for progression to active TB, as most individuals with positive results do not develop disease, which may lead to overtreatment when preventive therapy is broadly applied. False-negative results commonly occur in the early weeks after infection and in immunocompromised populations, including people living with HIV and those receiving immunosuppressive therapies, as well as due to improper intradermal administration or subjective reading of induration [27]. False-positive results may result from prior BCG vaccination or exposure to non-tuberculous mycobacteria, posing particular challenges in high-burden settings with widespread BCG coverage. Despite these limitations, rapid TST conversion following recent exposure to an infectious case remains an important indication for preventive therapy. Collectively, these shortcomings highlight the need for more accurate biomarkers capable of stratifying LTBI by progression risk, particularly in vulnerable populations such as pregnant women [28],[29].

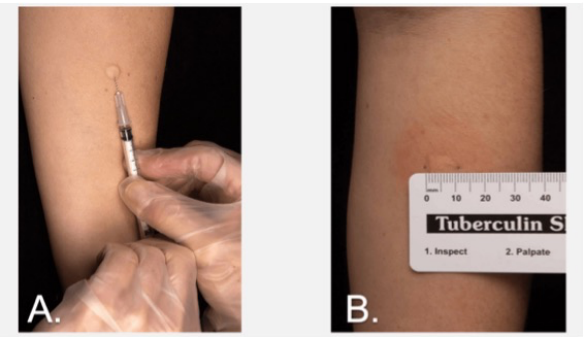

Figure 4. Tuberculin Skin Test (Mantoux Test) Procedure and Induration Measurement [29]

Figure 4. present the intradermal administration of purified protein derivative (PPD) for the tuberculin skin test (TST) (panel A) and the subsequent measurement of induration 48–72 h after injection using a standardized ruler (panel B). The diameter of palpable induration, rather than erythema, is measured in millimeters to determine test positivity, reflecting a delayed-type (type IV) hypersensitivity response mediated by antigen-specific T lymphocytes sensitized to Mycobacterium tuberculosis antigens. Although TST is widely used for screening latent tuberculosis infection due to its low cost and feasibility in resource-limited settings, its diagnostic performance is limited by false-positive results related to prior Bacillus Calmette Guérin vaccination and exposure to non-tuberculous mycobacteria, as well as false-negative results in early infection and immunocompromised states, underscoring the need for more specific biomarkers for LTBI risk stratification [29].

Mechanisms and Methodological Challenges in microRNA Detection as Tuberculosis Biomarkers

The first step in establishing microRNAs (miRNAs) as effective biomarkers for tuberculosis (TB) diagnosis is the identification of consistent differential miRNA expression signatures in samples from patients with active TB compared with healthy controls. Over the past decade, multiple discovery studies have profiled miRNAs in serum/plasma and blood cells, including peripheral blood mononuclear cells (PBMCs) [30]. Although serum and plasma are generally preferred for diagnostic screening, cellular sources are often used in discovery phases. Broad, unbiased profiling approaches such as miRNA microarrays and next-generation small RNA sequencing tend to provide more comprehensive candidate signatures than targeted panels, but these methods are frequently applied to small cohorts, with subsequent validation by quantitative reverse transcription PCR (qRT-PCR) in larger populations [31]. This workflow may limit robustness and reproducibility. Poor consensus across studies has been reported, likely due to differences in analytical platforms, cohort heterogeneity, ethnicity, and RNA isolation protocols. Exosome-focused approaches are of particular interest given the enrichment of miRNAs in extracellular vesicles, although findings across exosome-based studies remain inconsistent [32], [33].

Despite heterogeneity in reported signatures, several miRNAs have been repeatedly identified as promising TB biomarkers, including miR-26a-5p and miR-223-3p, which are significantly dysregulated in active TB and modulate host immune responses by targeting IFN-γ signaling. Anti-inflammatory miRNAs such as miR-21-5p and miR-146a-5p show potential to discriminate active TB from latent infection or healthy states, while miR-155-5p plays a central role in host defense against Mycobacterium tuberculosis and is consistently overexpressed in active disease [34],[35]. Evidence from broader biomarker research demonstrates that circulating miRNAs are stable in blood due to their association with protein complexes such as Argonaute2 and their packaging in extracellular vesicles, supporting their feasibility as non-invasive diagnostic biomarkers. Given their abundance, accessibility, and tissue-specific regulatory roles, miRNAs represent promising tools for early TB detection and risk stratification, with future RNA-based diagnostics and therapeutics becoming increasingly plausible as technologies mature [36], [37].

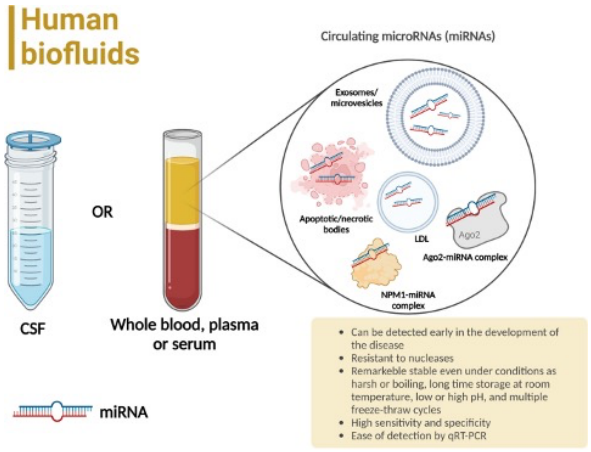

Figure 5. Circulating microRNAs in Human Biofluids as Stable Diagnostic Biomarkers [38]

Figure 5. present the sources and carriers of circulating microRNAs (miRNAs) in human biofluids, including cerebrospinal fluid (CSF) and peripheral blood (whole blood, plasma, or serum), highlighting their potential as non-invasive biomarkers for tuberculosis and other diseases. Circulating miRNAs are released into biofluids within extracellular vesicles (exosomes and microvesicles), apoptotic or necrotic bodies, and lipoproteins (e.g., LDL), or bound to protein complexes such as Argonaute 2 (Ago2) and nucleophosmin 1 (NPM1), which protect them from nuclease degradation. These carrier mechanisms explain the remarkable stability of miRNAs under harsh conditions (e.g., boiling, prolonged room-temperature storage, and repeated freeze–thaw cycles) and support their high sensitivity and specificity for

early disease detection using minimally invasive methods such as quantitative real-time PCR (qRT-PCR), making circulating miRNAs promising candidates for biomarker development in tuberculosis [38].

Table 2. Differential Expression Profiles of Circulating microRNAs in Infectious Diseases

microRNA (miRNA)	Expression Profile	Disease
miR-19a-3p, miR-19b-3p, miR-92a-3p	Upregulated	COVID-19
miR-150, miR-146b-5p	Downregulated	Human Immunodeficiency Virus (HIV)
miR-150	Downregulated	Human Immunodeficiency Virus (HIV)
miR-122, miR-21, miR-34a	Upregulated	Hepatitis C
miR-149, miR-638, miR-491	Upregulated	Hepatitis C
miR-122	Upregulated	Hepatitis C
miR-361-5p, miR-889, miR-576-3p	Downregulated	Tuberculosis
miR-144	Upregulated	Tuberculosis
miR-378, miR-483-5p, miR-22, miR-29c	Upregulated	Tuberculosis
miR-101, miR-320b	Downregulated	Tuberculosis
miR-16, miR-451	Downregulated	Malaria

Note: Upregulated indicates increased miRNA expression levels in patients compared with healthy controls, while downregulated indicates decreased expression levels. The listed miRNAs were identified from different clinical studies using various biological samples, including whole blood, plasma, serum, and peripheral blood mononuclear cells (PBMCs). Variations in miRNA expression profiles may be influenced by differences in study design, patient characteristics, sample types, and analytical methods.

Table 2. present the differential expression profiles of selected circulating microRNAs (miRNAs) reported in various infectious diseases, including COVID-19, HIV infection, hepatitis C, tuberculosis, and malaria. Specific miRNAs are shown to be either upregulated or downregulated in disease states compared to healthy controls, reflecting their involvement in host immune regulation, inflammatory responses, and pathogen–host interactions. The consistent alteration of miRNA expression patterns across different infectious diseases highlights their potential utility as non-invasive biomarkers for disease detection, prognosis, and therapeutic monitoring. In particular, tuberculosis-associated miRNAs demonstrate distinct expression signatures, supporting the role of circulating miRNAs as promising molecular biomarkers in the development of novel diagnostic approaches for infectious diseases [39].

miRNA Detection in TB and LTBI Using qRT-PCR

Quantitative reverse transcription PCR (qRT-PCR) is currently the most widely used method for validating microRNA (miRNA) biomarkers in tuberculosis (TB) and latent tuberculosis infection (LTBI) [40]. This technique combines reverse transcription of small RNAs into complementary DNA (cDNA) with quantitative PCR amplification, enabling sensitive and specific quantification of target miRNAs in clinical specimens. In TB research, qRT-PCR is commonly applied to serum, plasma, whole blood, peripheral blood mononuclear cells (PBMCs), sputum, pleural fluid, and exosome-enriched fractions. Compared with high-throughput discovery platforms (microarray and next-generation sequencing), qRT-PCR offers superior analytical sensitivity, lower cost, faster turnaround time, and better suitability for clinical translation [41].

The typical workflow for miRNA qRT-PCR in TB/LTBI includes: (1) sample collection and processing (serum/plasma/PBMCs), (2) RNA extraction using miRNA-optimized kits, (3) reverse transcription using stem-loop or poly(A)-tailing primers, (4) quantitative PCR amplification using miRNA-specific primers or probes, and (5) data normalization using endogenous controls (e.g., U6 snRNA, miR-16) or exogenous spike-in controls (e.g., cel-miR-39) [42]. Several studies have consistently reported differential expression of miRNAs such as miR-29a-3p and miR-223-3p in TB/LTBI compared with healthy controls, supporting their potential as minimally invasive biomarkers. However, inter-study heterogeneity remains substantial due to differences in sample types, RNA isolation protocols, normalization

strategies, and cohort characteristics. Standardization of pre-analytical and analytical procedures is therefore essential before clinical implementation (**Table 3**.) [43].

Table 3. Overview of qRT-PCR–Based miRNA Detection in TB and LTBI Studies

Aspect	Description
Sample types	Serum, plasma, whole blood, PBMCs, sputum, pleural fluid, exosomes
RNA isolation	miRNA-enriched extraction kits; optional exosome isolation prior to RNA extraction
Reverse transcription	Stem-loop RT primers or poly(A) tailing followed by universal RT
Quantification platform	qRT-PCR (SYBR Green or TaqMan probe-based assays)
Common normalization controls	U6 snRNA, miR-16; exogenous spike-in (cel-miR-39)
Key miRNAs reported in TB/LTBI	miR-29a-3p, miR-223-3p, miR-21-5p, miR-146a-5p, miR-155-5p
Diagnostic purpose	Differentiation of active TB vs LTBI vs healthy controls; monitoring treatment response
Advantages	High sensitivity and specificity, low cost, rapid turnaround, clinically feasible
Limitations	Inter-laboratory variability, lack of standardized normalization, pre-analytical bias

Note: the key methodological components and commonly reported miRNA targets in qRT-PCR based studies for tuberculosis and latent tuberculosis infection, highlighting both technical advantages and current limitations for clinical translation.

Figure 6. present depicts the standard workflow for microRNA (miRNA) detection in tuberculosis (TB) and latent tuberculosis infection (LTBI) using quantitative reverse transcription polymerase chain reaction (qRT-PCR). The process begins with the collection of clinical specimens, including serum, plasma, or peripheral blood mononuclear cells (PBMCs), followed by the isolation of total RNA enriched for small RNAs. In some protocols, extracellular vesicles (exosomes) are isolated prior to RNA extraction to enhance analytical sensitivity, as miRNAs are highly enriched and stabilized within vesicular compartments. Extracted miRNAs are subsequently reverse-transcribed into complementary DNA (cDNA) using stem-loop primers or poly(A)-tailing methods, enabling specific amplification of mature miRNA sequences [44].

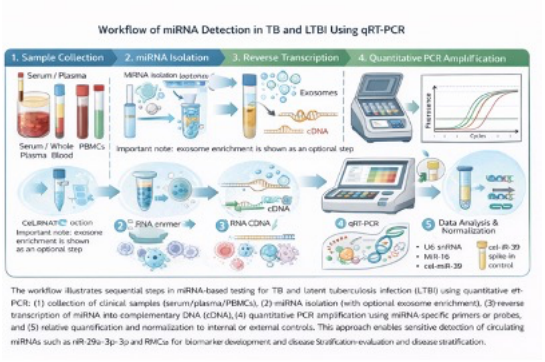

Figure 6. Schematic Workflow of microRNA Detection in Tuberculosis and Latent Tuberculosis Infection Using qRT-PCR [44]

The generated cDNA is quantified by real-time PCR using sequence-specific primers or probe-based assays, and relative expression levels are calculated after normalization to endogenous controls (e.g., U6 snRNA or miR-16) or exogenous spike-in controls (e.g., cel-miR-39). This workflow allows sensitive and reproducible quantification of TB-associated miRNAs, such as miR-29a-3p and miR-223-3p, which have been implicated in host immune regulation and disease progression. The figure highlights the feasibility of translating miRNA-based assays into clinical practice for TB/LTBI screening and risk stratification, while also underscoring the importance of standardized pre-analytical and analytical procedures to ensure reproducibility and inter-laboratory comparability **(Figure 6.)** [45],[46].

Maternal Nutritional Status and Tuberculosis During Pregnancy

Maternal nutritional status is a critical determinant of health during pregnancy, and in Indonesia it is commonly assessed using mid–upper arm circumference (MUAC) and body mass index (BMI). Pregnant women are considered nutritionally normal if their BMI during pregnancy is 18.5–24.9 kg/m² or MUAC ≥ 23.5 cm, whereas MUAC < 23.5 cm indicates risk of chronic energy deficiency (CED) due to insufficient energy and protein intake. National data indicate that the prevalence of CED risk among pregnant women remains substantial, although recent routine reports show improvements compared with national targets. Across several developing countries in

South and Southeast Asia, the prevalence of maternal undernutrition (based on BMI) remains high, underscoring persistent structural and dietary vulnerabilities [47]. Poor maternal nutrition is significantly associated with tuberculosis (TB) at the population level. Ecological and observational studies in Indonesia demonstrate a significant association between undernutrition and TB incidence, with undernourished individuals showing higher odds of TB. The bidirectional relationship between TB and nutrition is well recognized: TB increases resting energy expenditure, causes nutrient malabsorption, and disrupts protein and lipid metabolism, leading to wasting and malnutrition; conversely, undernutrition compromises immune defenses and increases the likelihood that latent TB infection progresses to active disease. Globally, undernutrition is estimated to account for a substantial proportion of incident TB, and individuals with low BMI have a markedly higher risk of active TB compared with well-nourished controls [48],[49].

In pregnancy, the consequences of CED extend to both mother and fetus. Women with CED have higher risks of maternal morbidity, difficult or prolonged labor, preterm birth, postpartum hemorrhage, and operative delivery, while infants face increased risks of low birth weight and stunting. WHO classifies CED as BMI < 18.5 kg/m² (mild, moderate, and severe at 18.5, 17.0, and 16.0 kg/m², respectively), reflecting chronic deficits in energy and protein often rooted in long-standing undernutrition. Integrating nutritional screening (MUAC/BMI), targeted supplementation, and TB prevention/treatment during antenatal care is therefore essential to reduce adverse maternal–fetal outcomes and to mitigate TB risk and progression in pregnant populations [50],[51].

Table 4. Maternal nutritional factors, immune pathways, and expected modulation of miR-29a-3p and miR-223-3p in LTBI during pregnancy

Nutritional factor	Immune pathway affected	Expected impact on miR-29a-3p	Expected impact on miR-223-3p	Clinical implication
Vitamin D insufficiency	Macrophage activation, autophag	↑ (damp ens IFN-γ	— / context-dependent	Reduced intracellular killing; higher
	y, IFN-γ responsiveness	signaling)		reactivation risk
Iron deficiency (with inflammation)	Myeloid function, oxidative burst	—	↑ (modulates neutrophil/monocyte activation)	Impaired pathogen clearance; anemia of inflammation
Zinc deficiency	Neutrophil chemotaxis, cytokine balance	—	↑ (alters inflammatory tone)	Dysregulated inflammation; susceptibility to infection
Protein–energy malnutrition	T-cell function, cytokine production	↑	↑	Weakened cellular immunity; LTBI instability
Folate/B12 insufficiency	Epigenetic regulation, cell turnover	Possible ↑	Possible ↑	Altered miRNA biogenesis; immune dysregulation

Note: Arrows denote hypothesized direction of modulation based on reported immune miRNA interactions in TB and pregnancy contexts.

Table 4. present the maternal nutritional determinants such as energy protein adequacy, micronutrient status (vitamin D, iron, zinc), and overall inflammatory balance shape immune pathways relevant to latent tuberculosis infection (LTBI) during pregnancy and are expected to modulate miRNA expression profiles. Adequate nutrition supports effective innate and adaptive immunity (macrophage activation, Th1 cytokine responses, and granuloma stability), which is hypothesized to normalize or downregulate pathogenic

overexpression of miR-29a-3p (linked to impaired IFN-γ signaling) while maintaining balanced miR-223-3p levels involved in neutrophil regulation and inflammation control. In contrast, chronic energy deficiency and micronutrient deficiencies may promote immune dysregulation, higher inflammatory tone, and impaired mycobacterial containment, potentially driving aberrant upregulation of miR-29a-3p and dysregulated miR-223-3p expression, thereby increasing the risk of LTBI reactivation and adverse pregnancy outcomes [51].

CONCLUSION

MicroRNAs play crucial roles in modulating host immune responses during Mycobacterium tuberculosis infection and pregnancy by regulating inflammation, apoptosis, autophagy, and cytokine signaling, with consistent dysregulation of key miRNAs such as miR-223-3p, miR-21-5p, miR-146a-5p, and miR-155-5p in tuberculosis. Their stability in biofluids and detectability using established platforms support their potential as minimally invasive biomarkers for latent and active TB, particularly in pregnant women. However, substantial heterogeneity across studies due to differences in cohorts, sample types, RNA isolation methods, and analytical platforms limits reproducibility, underscoring the need for standardized methodologies and large, multicenter longitudinal validation studies to enable clinical translation of miRNA-based diagnostics and risk stratification in TB.

ACKNOWLEDGMENTS

The authors would like to express their sincere gratitude to the Faculty of Medicine, Hasanuddin University, for institutional support and the academic environment that facilitated the completion of this narrative review. We also thank colleagues and staff who provided valuable input during the manuscript preparation. No specific external funding was received for this work.

AUTHOR CONTRIBUTIONS

Conceptualization: M, SA, MNM. Study Design and Methodology: M, SA, MNM. Data Collection: M. Data Analysis and Interpretation: M, SA, MNM. Supervision: SA, MNM.

Academic and Methodological Examination: FH, HI, DS, AAZ. Manuscript Drafting: M. Critical Revision of the Manuscript: SA, MNM, FH, HI, DS, AAZ. Final Approval of the Manuscript: All authors. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST

The authors declare no financial or non-financial conflicts of interest that could have influenced the conduct of the study or interpretation of its results.

FUNDING

This study did not receive funding from any public, commercial, or non-profit funding agencies. All research costs were self-funded by the principal investigator.

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