v. 5, n. 2, 2025

International Journal of **Biological and Natural Sciences**

Acceptance date: 27/02/2025

TRENDS IN TUBERCULOSIS SEVERITY DISEASE BIOMARKERS

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Abstract: INTRODUCTION: Tuberculosis (TB) is a major global health concern primarily caused by the bacterium *Mycobacterium tuberculosis* (Mtb). The disease exhibits considerable variability in its clinical presentation, pathogenesis, and host response. While some individuals develop effective immune defenses that contain the infection, others fail to do so, resulting in active TB. Even after successful treatment, TB can leave lasting health effects, known as post-TB sequelae, which may include severe lung scarring and cavitation, leading to significant loss of lung function. TB biomarkers play a critical role in enhancing treatment outcomes. Firstly, they enable the stratification of patients into mild, moderate, and severe TB cases. Once severity is determined, additional biomarkers can be used to monitor treatment response, detect early signs of treatment failure, and assess the risk of complications, relapse, or mortality. METHODS: A bibliographic search for this review was conducted using the Google Scholar, PubMed, SciELO, and Virtual Health Library (VHL) databases. Research papers published between 1995 and 2024 were examined, using the following keywords: "Tuberculosis severity," "Tuberculosis severity biomarkers," "Tuberculosis sequelae," and "Tuberculosis post-TB treatment". RESULTS: TB severity biomarkers for preventing post-TB sequelae are still in the early stages, with serum cytokines and inflammatory markers being the primary tools for patient stratification. However, there is a pressing need to identify more specific biomarkers and validate them for clinical use. Ongoing research is focused on validating these biomarkers across diverse populations, developing multiplex diagnostic platforms, and integrating biomarker data into clinical workflows to enable personalized TB care. CONCLUSION: TB disease severity biomarkers are crucial as they can significantly enhance management of the disease in order to avoid post-TB sequelae. TB severity varies widely, from latent infection to active disease with varying levels of organ damage. Biomarkers can help stratify patients based on the severity of their disease, enabling more personalized treatment plans. Biomarkers can identify patients at risk of severe TB complications, such as extensive lung damage or extra-pulmonary spread. Integrating these biomarkers into predictive models could enhance the management of TB by identifying patients at higher risk for severe disease, thereby guiding therapeutic decisions and potentially improving outcomes.
Keywords: Tuberculosis, heterogeneity, Severity, Biomarkers.

TUBERCULOSIS GLOBAL BURDEN

Tuberculosis (TB) is a major global health problem mainly caused by the bacteria *Mycobacterium tuberculosis* (Mtb), which is transmitted from an infected individual through airborne droplets. Mtb infection primarily affects the lungs (active pulmonary TB, APTB) but it is capable of infecting other organs (extra-pulmonary TB). Despite being preventable and treatable, TB remains as the leading human infectious disease killer worldwide (The Lancet 2024). In 2023, there were approximately 10.8 million TB cases globally, an increase from 10.7 million in 2022 (WHO 2024). The burden is unevenly distributed, with the highest incidence rates in low and middle--income countries, particularly in regions of South-East Asia (45%), Africa (24%) and the Western Pacific (17%), with reduced shares in the Eastern Mediterranean (8.6%), the Americas (3.2%) and Europe (2.1%). Among all incident TB cases, 6.1% were among people living with HIV (WHO 2024). TB caused around 1.25 million deaths from which 1.09 million deaths were among HIV-negative people and 161,000 deaths among people with

HIV. Multidrug-resistant TB (MDR/RR-TB) is a significant challenge, with around 400,000 cases reported for the same year 2023 (Goletti et al 2025, WHO 2024). Malnutrition, poor housing, and lack of access to healthcare, increase susceptibility and transmission. This is exacerbated by comorbidities like diabetes and chronic lung diseases. An estimated 25% of the world's population is infected with latent TB, which poses a significant risk for reactivation under immunocompromised conditions.

HETEROGENEITY AND SEVERITY OF TB DISEASE

TB exhibits significant heterogeneity in its clinical presentation, pathogenesis and host response (Cadena et al 2017, Lai et al 2024). The heterogeneity of TB manifests across a spectrum ranging from mild, moderate, to severe active disease. Symptoms variations include persistent cough, with or without hemoptysis (coughing blood), fever, night sweats, and weight loss (Lenaerts et al 2015, Pai et al 2016, Zaidi et al 2023). In addition, Mtb can infect other organs leading to conditions such as TB meningitis, pleuritis, lymphadenitis, and disseminated (miliary) TB (Jain et al 2024, Rindi 2022, Sharma et al 2021). This severity depends upon a complex interplay of factors, including host immune status and genetic predisposition, the genetic variant of Mtb, environmental conditions, and social determinants.

The interactions between Mtb and the host immune system are critical for the disease progression. Mtb infection leads to the formation of granulomas, which can either contain the bacteria or allow its growth and dissemination (Cronan 2022, Ramakrishnan 2012). Some individuals mount effective immune responses that limit disease, while others fail to control the infection, leading to active TB. Different strains of Mtb exhibit diverse characteristics; Some strains, such as the Beijing lineage, are associated with increased virulence, faster progression, and higher transmissibility (Baena et al 2019, Berisio & Ruggiero 2023, Coscolla & Gagneux 2014). Strains with multidrug resistance (MDR-TB) or extensive drug resistance (XDR-TB) present distinct challenges, as they are harder to treat and often lead to worse outcomes.

TB risk and outcomes vary across populations due to social, economic, and environmental factors. High TB burden regions, such as sub-Saharan Africa and Southeast Asia, experience varying predominant Mtb strains, comorbidity profiles (e.g., HIV prevalence), and health infrastructure challenges. Children and older adults have distinct disease presentations and outcomes. Males have higher TB incidence rates, possibly due to behavioral and occupational exposures. Poverty, overcrowding, and malnutrition contribute to increased susceptibility and transmission (Carwile et al 2022, Li et al 2023). Factors such as drug resistance, patient adherence, and coexisting conditions lead to varied treatment outcomes.

SEQUELAE AFTER TB TREATMENT BASED ON DISEASE SEVERITY

Tuberculosis (TB) can leave significant residual health impacts, referred to as post--TB sequelae, even after successful treatment (Menzies et al 2021, Sotgiu et al 2021). The severity of these sequelae is often proportional to the initial disease burden and extent of tissue damage. These complications can affect pulmonary, extra-pulmonary, and systemic health, and they contribute to long-term morbidity, reduced quality of life, and healthcare burden.

The lungs are the primary site of TB infection, and pulmonary sequelae are common, particularly in severe TB (Rachow et al 2019, Tiberi et al 2019). On one end, mild TB may lead to limited fibrosis and scarring in lung tissues, typically asymptomatic with occasional cough or dyspnea, usually non-disabling. But on the other end, a severe TB may lead to long-lasting lung scarring and cavitation, leading to significant loss of functional lung tissue (Akalu et al 2024, Gai et al 2023) (Figure 1). Cavitary lesions predispose patients to fungal infections, often causing hemoptysis and respiratory distress (Urbanowski et al 2020). Persistent hypoxemia and vascular remodeling due to lung damage, can result in elevated pulmonary artery pressures. Advanced lung damage may lead to chronic respiratory insufficiency requiring long-term oxygen therapy or mechanical support. Furthermore, extra-pulmonary TB (EPTB) can result in lasting complications depending on the affected organ system (Niu et al 2024). In the case of TB meningitis, this can cause paralysis, cranial nerve palsies, seizures, and cognitive impairment due to brain tissue damage (Arshad et al 2020) (Figure 1).

Post-TB sequelae are not limited to localized damage but may include systemic effects. Persistent malabsorption or anorexia during TB treatment can leave patients undernourished, impacting recovery (Gupta et al 2009, Phan et al 2016). Muscle loss due to prolonged catabolic states, particularly in severe cases. Post-TB fatigue and reduced physical endurance are common and can persist for months or years, resembling chronic fatigue syndrome. Post-TB mental health disorders such as depression and anxiety due to prolonged illness, social stigma, and financial stress. Post-TB patients have showed immunological alterations due to persistent immune activation that predispose patients to inflammatory diseases or secondary infections (Luo et al 2018) (Figure 1).

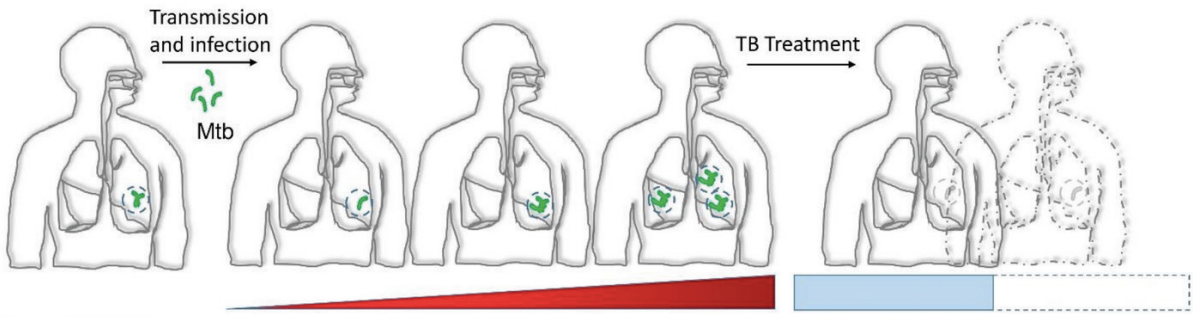
Personalized treatment of TB to avoid sequelae involves tailoring therapeutic strategies to the individual's disease severity, comorbid conditions, and immunological and genetic profile. Personalized approaches aim to optimize outcomes and reduce side effects. Reducing the inflammatory response during TB treatment is important to avoid sequelae after patient curation. However, inflammation must not be suppressed indiscriminately, as it is integral to controlling the infection. Striking a balance between suppressing harmful inflammation and preserving an effective immune response is essential. Corticosteroids (Prednisolone or Dexamethasone) are recommended for severe pulmonary TB to suppress inflammation (Lara-Espinosa et al 2023, Yang et al 2016). The use of biologics like anti-TNF-α or anti-IL-6 therapies are being explored for specific cases of excessive inflammation. By inhibiting IL-6 signaling, drugs like Tocilizumab might mitigate the harmful effects of hyper-inflammation, such as tissue destruction in the lungs and other affected organs (Noh & Dronavalli 2021). While anti-IL-6 therapies hold promise for managing excessive inflammation in TB, their use requires careful consideration of the balance between reducing inflammation and maintaining effective immunity.

It is important to follow up every post-TB patient with imaging studies, to monitor lung healing and detect complications like fibrosis or bronchiectasis. Also, is important to address malnutrition with protein and micronutrient-rich diets. Bronchodilators and steroids for managing obstructive lung disease, and for those with residual lung damage post-treatment. Moreover, it is considered very important to have a psychological support for severe cases requiring prolonged therapy.

BIOMARKERS FOR TB SEVERITY

Due to all the previously described health issues with post-TB sequelae, discovery and implementation of severe TB biomarkers at the initial stages of diagnosis, are then crucial for improving treatment. In first place, some of these biomarkers may allow us to do a patient stratification between mild, moderate, and severe TB. Once we have determined the severity in TB patient we could use other biomarkers to monitor response to anti-TB therapy and early detection of treatment failure, predicting the risk of complications, relapse, or mortality. Moreover, we could also use some of these biomarkers to follow up the inflammatory response during treatment, in order to prescribe tailored treatments to prevent organ and tissue damage in those severe TB patients. The discovery of reliable biomarkers for TB severity has the potential to transform the management of the TB disease in the future. Current research is focused on validating these biomarkers in diverse populations, developing multiplex diagnostic platforms, and integrating biomarker data into clinical workflows for personalized TB care. Here we will describe some of the most notable TB severity biomarkers and discuss their prognostic value (Figure 1).

Some of the proposed host immune response derived biomarkers are originated from immune cells like cytokines or chemokines, signaling pathways, or from systemic inflammatory responses. For cytokines, elevated levels of interferon-gamma (IFN-γ) are associated with active TB, as it plays a central role in the Th1 immune response to Mtb but also of severe TB disease. One of the first studies showed that peripheral blood mononuclear cells (PBMCs) from patients with severe tuberculosis (TB), both HIV-negative and HIV-infected, exhibited significantly diminished production of interferon-gamma (IFN-γ) when stimulated in vitro (Sodhi et al 1997). Moreover, another study showed that IFN-γ/IL10 ratio could provide a useful biomarker of disease severity (Jamil et al 2007). Also, the tumor necrosis factor-alpha (TNF-α) is critical for granuloma formation but may indicate excessive inflammation in severe TB cases. Higher TNF-α levels correlated with more severe clinical manifestations, including extensive pulmonary involvement and weight loss (Beig et al 2023). Contrasting results have also been found, whereas TNF-α production was higher in active-TB patients than in controls, IFN-γ production was strongly depressed during active TB, correlated inversely with TB disease severity, and increased during therapy (Sahiratmadja et al 2007). Elevated levels of interleukin-6 (IL-6) and interleukin-1 beta (IL-1β) are correlated with systemic inflammation and disease severity. Our recent study, followed 108 APTB patients over six months, assessing clinical, immunological, and genetic factors. We found that at diagnosis, patients with severe APTB exhibited significantly higher serum levels of IL-6 compared to those with mild disease (Ocampo et al 2023). This finding validates a previous report that pre-treatment IL-6 is a biomarker for unfavorable TB treatment outcomes in a more severe TB disease (Gupte et al 2022). For chemokines, CXCL10 (IP-10) a chemokine involved in T-cell recruitment, often elevated in active TB and indicative of disease severity and treatment progression (Kumar et al 2019b, Wei et al 2024). Also, the presence of elevated IL-8 levels in various fluids of TB patients suggests a correlation between IL-8 production and disease severity (Ameixa & Friedland 2002). A distinct immune response profile that includes elevated levels of IP-10, IFN-α2 and IL-8, were most effective in separating TB patients with different clinical disease severity could be promising candidates for treatment monitoring (Ashenafi et al 2023).



Severity	Mild	Moderate	Severe	Post-TB
Disease Symptoms	persistent cough, without hemoptysis, fever, night sweats, and weight loss.	Hemoptysis, increased weight loss, cavitation.	Hemoptysis, TB meningitis, pleuritis, lymphadenitis, and both lung lobule affected.	**Sequelae** **Mild:** Mild symptoms. Limited fibrosis and scarring in lung tissues. **Severe:** Significant loss of functional lung tissue, Persistent hypoxemia due to lung damage, anorexia and mental health disorders (depression and anxiety).
Severity predictive Biomarkers	Lower levels IL-6, IFNγ and CHIT-1.	Moderate levels of IL-6, IL-1β, IL-8 and IFNγ.	High levels IL-6, IL-8, IFNγ, IL-1β and CHIT-1. Lower levels of MCP-1.	

Figure 1. Severity symptoms and Long-term sequelae of Tuberculosis.
TB disease severity exists on a dynamic spectrum, ranging from mild to severe symptoms. Following exposure to M. tuberculosis (Mtb), the manifestation of symptoms varies based on the bacterial strain, the host's immune response, and the presence of immune deficiencies or comorbidities. Post-TB treatment sequelae arise as a consequence of the collateral damage caused by these factors.

From the inflammatory biomarkers, the eicosanoids (e.g., prostaglandins, leukotrienes) were associated with TB disease severity. A study observed that disease severity, assessed radiographically and by estimated bacterial burden, was associated with increased systemic levels of certain eicosanoids, notably Lipoxin A4 (LXA4), in TB and TB-diabetes (TB-DM) patients. Altered ratios of LXA4 or 15-epi-LXA4 to leukotriene B4 (LTB4) were also noted, suggesting a role of these eicosanoids in TB pathogenesis (Kumar et al 2019a). Elevated chitotriosidase 1 (CHIT-1) levels were notably associated with severe APTB, suggesting its potential as a biomarker for disease severity (Ocampo et al 2023). Altered levels of metabolites such as tryptophan and its catabolites in the kynurenine pathway reflect immune activation and may correlate with TB severity.

Some acute Phase Reactants, such as the C-reactive protein (CRP), are a non-specific marker of inflammation that correlates with TB severity and disease burden. CRP is an acute-phase reactant produced by the liver in response to inflammation. Elevated CRP levels correlate with TB disease activity and severity and often indicate extensive pulmonary disease or systemic involvement (Kwas et al 2015). Erythrocyte Sedimentation Rate (ESR) is a nonspecific marker of inflammation. Increased ESR levels are commonly observed in active TB and are associated with disease severity. Matrix Metalloproteinases (MMPs) enzymes are involved in tissue remodeling and degradation. Elevated levels of MMP-1, MMP-8, and MMP-9 are associated with lung tissue destruction in severe TB (Kumar et al 2020, Kumar et al 2018). Neopterin is produced by macrophages in response to IFN-γ. Higher levels of Neopterin indicate immune activation and are associated with active TB and disease severity (Soedarsono & Dolli 2020). Serum Amyloid A (SAA) another acute-phase reactant protein (Mishra et al 2022).

SAA was found elevated in active TB and correlates with the severity of inflammation. Hemoglobin and albumin levels are indicators of nutritional and systemic health. Low levels of hemoglobin (anemia) and albumin (hypoalbuminemia) often correlate with severe disease. Notably, gene expression signatures patterns of gene expression in blood samples (e.g., whole-blood RNA profiles), such as the TB-specific "risk signature", can predict disease severity, progression, and treatment outcomes. MicroRNAs (e.g., miR-21, miR-155) small non-coding RNAs that regulate gene expression are associated with TB activity and severity (Abdalla et al 2023). Differential expression of CD4+ and CD8+ T-cell subsets, such as effector and memory phenotypes, can provide insights into disease progression and severity. Overexpression of PD-1 and its ligand PD-L1 on immune cells has been linked to TB severity and immune exhaustion.

Biomarkers directly derived from Mtb or its metabolic products can indicate bacterial burden and disease activity. Lipoarabinomannan (LAM) a component of the Mtb cell wall detected in urine was associated with severe TB, especially in individuals with HIV co-infection (Ricks et al 2020). The Mtb lineaje variants polimorphisms have been used as biomarkers of virulence and are associated with severity of the disease. Mtb evolved to fine-tune the immune response, ultimately modulating the pathogenesis of TB. Therefore, the reason why some individuals develop severe TB, while others do not, may also be explained by the characteristics of the infecting bacteria. Consequently, understanding the underlying bacteria molecular bases will prove important from a clinical standpoint (Sousa et al 2020). Whole-genome sequencing of Mtb isolates have identified specific insertions and deletions (Indels) that could correlate virulence and with severe TB (Baena et al 2023, Worakitchanon et al 2024). Specific genetic mutations in these strains, affecting components such as the ESX-1 secretion system, were associated with their ability to modulate host immune responses and contribute to increased disease severity (Saelens et al 2022). One study, examined how genetic diversity among Mtb strains influences tuberculosis (TB) severity. They found that Mtb strains from patients with mild TB induced stronger cytokine responses, particularly higher levels of IL-1β, in macrophages compared to strains from severe TB cases (Sousa et al 2020). Strains linked to severe TB were found to evade the host's cytosolic surveillance systems, including mechanisms like cGAS and the inflammasome, leading to reduced IL-1β production. Another study did WGS on 88 clinical isolates of Mtb, and revealed a total of 325 genes with insertions and deletions (Indels) within their coding regions when compared to the Mtb H37Rv reference genome. The pattern of association was found between serum levels of CHIT1 and the presence of Indels in Mtb isolates from patients with severe APTB (Ocampo et al 2023). These research highlights the significant role of bacterial genetic diversity in determining TB outcomes and suggests that certain Mtb strains have evolved mechanisms to manipulate host immune responses, leading to more severe forms of the disease.

CONCLUSIONS

TB disease severity biomarkers are crucial as they can significantly enhance management of the disease in order to avoid post-TB sequelae. TB severity varies widely, from latent infection to active disease with varying levels of organ damage. Biomarkers can help stratify patients based on the severity of their disease, enabling more personalized treatment plans. Biomarkers can identify patients at risk of severe TB complications, such as extensive lung damage or extra-pulmonary spread. Early identification allows for timely interventions, reducing

morbidity and mortality. Reliable biomarkers can track the effectiveness of TB therapy. This can help clinicians determine if a patient is responding adequately to treatment or if therapy adjustments are needed. Some biomarkers may predict the likelihood of relapse after treatment completion or the progression from latent TB infection to active disease. There are some challenges in universal TB severity biomarker discovery, like the heterogeneous nature of TB, influenced by host genetics, co-morbidities (e.g., HIV), and environmental factors. Validation of biomarkers in diverse populations and settings is necessary for their clinical utility an in order to become universal. Investing in biomarker research for TB severity can transform the approach to managing the disease, improving outcomes for millions of affected individuals worldwide.

Integrating these type of biomarkers into predictive models could enhance the management of TB by identifying patients at higher risk for severe disease, thereby guiding therapeutic decisions and potentially improving outcomes. Integrative approaches combining omics data (genomics, transcriptomics, proteomics, and metabolomics) could provide robust insights into TB severity biomarkers. For instance, machine learning models integrating multi-omic data have a great potential to identified predictive biomarkers of TB progression. Ongoing research into biomarkers for predicting sequelae risk and advanced therapies holds promise for better management of post-TB outcomes. Finally, all this information on severity biomarkers can guide long-term follow-up and preventive strategies in severe TB.

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