Exploring Tuberculosis Through the Lens of Post-Infection Mortality

I. Introduction

Tuberculosis (TB) continues to represent a significant global health burden and remains one of the leading causes of infectious disease–related mortality worldwide, with an estimated 1.6 million deaths occurring annually during or prior to treatment according to the World Health Organization (WHO) data. In 2023, over 10.8 million cases of tuberculosis were reported (Global Tuberculosis Report, 2024). Tuberculosis is highly pathogenic because *Mycobacterium tuberculosis* evades macrophage killing, establishing persistent infection. TB's variable incubation period for primary infection of 3-8 weeks further complicates timely diagnosis (Behr et al., 2018), particularly in resource-limited settings, highlighting the urgent need for affordable, rapid, and scalable diagnostic tools to improve detection and outcomes. This literature review aims to explore and examine the key biological and non-biological endpoints that complicate the prevention, diagnosis and management of tuberculosis. The goal of this review would also be to highlight the importance of systematically integrating long-term patient-centered care along with successful clinical outcomes in tuberculosis management. This review compares key categories, including pharmacological treatment strategies, contributors to TB-related mortality such as immune dysregulation, and the social and environmental determinants that underscore the need for patient-centered care in complex, multifactorial diseases.

II. Summary

DiNardo et al. (2025) conducted a narrative comparative literature review to examine non-microbiological, patient-centered outcomes and associated host biomarkers in tuberculosis. Drawing on clinical, epidemiological, and mechanistic studies, the authors demonstrate that microbiological cure alone is a poor predictor of long-term outcomes, as TB survivors face substantially increased risks of all-cause mortality, relapse, chronic lung dysfunction, cardiovascular disease (CVD), cancer, and impaired quality of life. Persistent immune dysregulation and systemic and lung-specific inflammation commonly persist despite effective antibiotic therapy and appear to be key drivers of post-treatment morbidity. Although several nonspecific host biomarkers (e.g., CRP, IL-6, albumin, hemoglobin, and markers of immune anergy) stratify risk for mortality, lung damage, and relapse, no validated biomarkers exist for TB-associated CVD or cancer underscoring major gaps in current TB clinical trial endpoints and the need for broader, patient-centered outcome measures.

Romanowski et al. (2019) conducted meta-analysis of observational cohort studies (1997–2018) evaluated long-term mortality among individuals with bacteriologically or clinically confirmed tuberculosis compared with population controls. Using Embase, MEDLINE,

and Cochrane databases, ten eligible studies comprising 40,781 individuals and 6,922 deaths were included, with pooled standardized mortality ratios (SMRs) estimated via random-effects models. Standardized mortality ratios (SMRs) were extracted or calculated by dividing observed deaths by expected deaths. Studies that reported mortality hazard ratios or rate ratios instead, these were converted or pooled with SMRs. Pooled estimates were obtained using random-effects meta-analysis, which accounts for variability between studies by assuming that each study estimates a slightly different underlying effect and incorporating this heterogeneity into the overall estimate.Tuberculosis survivors experienced nearly a threefold higher all-cause mortality than the general population (SMR 2.91), which increased to 3.76 among those who completed treatment or were cured, indicating that excess mortality persists beyond microbiological resolution. Post-treatment deaths were largely attributable to CVD, while substantial proportions of survivors suffered chronic respiratory impairment. These findings illuminate that post-TB sequelae, rather than reinfection, drive excess mortality and highlight critical gaps in outcome assessment and long-term follow-up in TB care and research.

Dangisso et al. (2018) conducted a ten-year retrospective cohort study to evaluate long-term mortality and recurrence among smear-positive tuberculosis patients in southern Ethiopia following treatment initiation and completion. Among 2,727 smear-positive TB cases followed for 8,780 person-years, 10.5% of patients died, with nearly 92% of deaths occurring during treatment or within five years of initiation. Mortality risk was highest among older adults, males, urban residents, economically disadvantaged patients, and those with poor or repeated treatment outcomes, while TB recurrence occurred predominantly within the first five post-treatment years and was strongly associated with prior re-treatment. Although the overall standardized mortality ratio was modest (SMR 1.2), substantial excess mortality and recurrence early after treatment illuminates the persistence of TB-related vulnerability beyond microbiological cure and highlight the need for sustained post-treatment monitoring and targeted interventions for high-risk groups. Children under 15 years old had an elevated mortality risk (SMR 8.0), followed by males (SMR 2.8) and urban residents (SMR 6.3)

III. Outcomes

Within all three of the studies, the consistent finding is that tuberculosis has persistent consequences that extend far beyond the biological or clinical resolution. As it stands the disease continues to exert chronic effects long after antimicrobial therapy ends. Both the meta-analysis of observational cohort studies and the Ethiopian retrospective cohort study explicitly demonstrate an excess of all-cause mortality among TB survivors compared with the general population even with individuals who have successfully completed treatment. The meta-analysis reports a three to fourfold increase in mortality with CVD emerging as a leading cause of post-treatment death, while Dangisso et al. (2018) indicated that mortality appears to be

concentrated in the first five years following treatment initiation and is strongly patterned by age, sex, socioeconomic status, and treatment history. However, as noted previously, Dangisso et al (2018) does primarily focus on a region with a higher TB incidence. At a conceptual level, Dinardo et al. (2025) reinforces these epidemiologic findings by presenting the argument that microbiological cure is a poor metric as a sole measure to adequately reflect long-term prognosis. Persistent immune dysregulation and inflammation are primary drivers of post-TB morbidity including CVD, chronic lung dysfunction, cancer, recurrent TB, and reduced quality of life.

All three studies are in agreement in identifying post-TB sequelae, rather than reinfection, as the primary determinant of excess mortality and morbidity. However, they vary in their emphasis; in the meta-analysis, Romanowski et al (2019) quantifies the magnitude of mortality risk across diverse settings, Dangisso et al. (2018) provided granular, environment-specific insights into recurrence and early post-treatment deaths in the high-burden, resource-limited setting of Northwest Ethiopia, and Dinardo et al. (2025) synthesized mechanistic and clinical evidence to further explain why these poor outcomes are persisting. Cumulatively, they present a structured account of linking epidemiologic patterns with underlying biological mechanisms.

The three studies identify substantial barriers that exist preventing the adequate measuring and addressing of long-term TB outcomes. These studies share the challenge of addressing how the historical focus of TB programs and trials has solely been on microbiological endpoints, which obfuscates non-fatal but clinically meaningful outcomes such as CVD, lung impairment, and diminished quality of life. Romanowski et al's meta-analysis highlights underdiagnosis, misclassification, and incomplete notification of TB cases particularly with regards to resource-limited settings. This likely significantly contributes to the underestimation of true mortality and obscures cause-specific outcomes. Dangisso et al. similarly acknowledges the loss to follow-up with concerns to migration and limited post-treatment surveillance, a reflection of structural barriers to long-term patient tracking.

VI. Limitations and Gaps

There are study-specific limitations that further contribute to shifting interpretations. Romanowski et al's (2019) even given its robust estimates, showcases extreme heterogeneity (I^2 >95%), which reflects variability in study design, follow-up duration shorter than 12 months, diagnostic cohort, and population characteristics. Dangisso et al.'s retrospective cohort study was conducted in a high-burden Ethiopian setting, which provided insight into early post-treatment mortality and recurrence but is constrained by its reliance on smear-positive cases, limited cause of death ascertainment due to resource availability, and potential underestimation of late outcomes. Conversely, Dinardo et al.'s narrative review puts an emphasis on mechanistic

pathways particularly those associated with persistent inflammation and immune dysregulation. However, it is limited by non-systemic synthesis and the lack of data on TB-associated CVD and cancer as there are no current studies that have identified quantifiable biomarkers.

Across the articles reviewed, the limitations are largely reflective of the broader challenges in TB research: significant financial constraints coupled with the complexity of generating data that links biomarkers with long-term clinical outcomes. The lack of infrastructure and comprehensive TB databases currently prevents systematic investigation of the multifactorial drivers of morbidity and mortality and restricts broader access for researchers. Latent tuberculosis infection (LTBI) remains underexplored as a public health issue, particularly due to its asymptomatic nature, which complicates surveillance and early intervention efforts. Critical gaps also remain regarding the biomarkers linking TB to cancer and CVD, as well as effective management of LTBI at the population level.

V. Conclusion

A prevailing concern in TB is the elevated mortality observed even among patients who have completed treatment, with rates 3–4 times higher than the local population (Romanowski et al., 2018). This underscores that current therapeutic regimens alone are insufficient to fully mitigate TB-related mortality. Understanding these outcomes highlights the importance of patient-centered care approaches, improved immunodiagnostic tools to prevent delayed diagnosis, investigation of treatment failures, evaluation of comorbid conditions, and addressing structural barriers to care, all of which contribute to mortality despite available pharmacological therapies. Future TB research should focus on emerging drug-resistant strains, TB-associated immune reconstitution inflammatory syndrome (TB-IRIS), and community-based management and screening programs. Additionally, investigating comorbid conditions such as HIV/AIDS that affect immune regulation is essential to optimize treatment protocols. Shorter, accessible, and reliable diagnostic strategies are critical to improving early detection and treatment success. Finally, research of TB must have a call to action dedicated toward integrating the social determinants of health and comorbidities into post-TB care models. Interventions should be targeting modifiable risk factors, such as smoking, malnutrition, diabetes and poverty which should be integrated within the framework of TB programs in order to mitigate long-term morbidity and excess mortality. The ultimate objective would be shifting research focus towards holistic, long-term outcomes in order to bridge the existing gaps in TB care, improving survivorship, informing policy, and clinical practice.

References

Behr, M. A., Edelstein, P. H., & Ramakrishnan, L. (2018). Revisiting the timetable of tuberculosis. *BMJ (Clinical research ed.)*, *362,* k2738. https://doi.org/10.1136/bmj.k2738

Romanowski, K., Baumann, B., Basham, C. A., Ahmad Khan, F., Fox, G. J., & Johnston, J. C. (2019). Long-term all-cause mortality in people treated for tuberculosis: a systematic review and meta-analysis. *The Lancet. Infectious diseases*, *19*(10), 1129–1137. https://doi.org/10.1016/S1473-3099(19)30309-3

Dangisso, M. H., Woldesemayat, E. M., Datiko, D. G., & Lindtjørn, B. (2018). Long-term outcome of smear-positive tuberculosis patients after initiation and completion of treatment: A ten-year retrospective cohort study. *PloS one*, *13*(3), e0193396. https://doi.org/10.1371/journal.pone.0193396

DiNardo, A. R., Sabiiti, W., Gillespie, S. H., Georghiou, S. B., Heinrich, N., Hittel, N., Taghlabi, S., Carrero Longlax, D., Kohli, M., Panzner, U., Musia, C., Lange, C., Vasiliu, A., Arts, R. J. W., Mandalakas, A. M., Ruhwald, M., Stuyver, L. J., & van Crevel, R. (2025). Inclusion of patient-centered, non-microbiological endpoints and biomarkers in tuberculosis drug trials. *Frontiers in antibiotics*, *4*, 1570989. https://doi.org/10.3389/frabi.2025.1570989

World Health Organization (2024). *Global tuberculosis report 2024*. World Health Organization. https://iris.who.int/handle/10665/379339. License: CC BY-NC-SA 3.0 IGO