Association Between Body Mass Index and Mortality in Patients With Tuberculosis-HIV Co-Infection in Asia and Africa: A Systematic Review and Meta-Analysis Protocol

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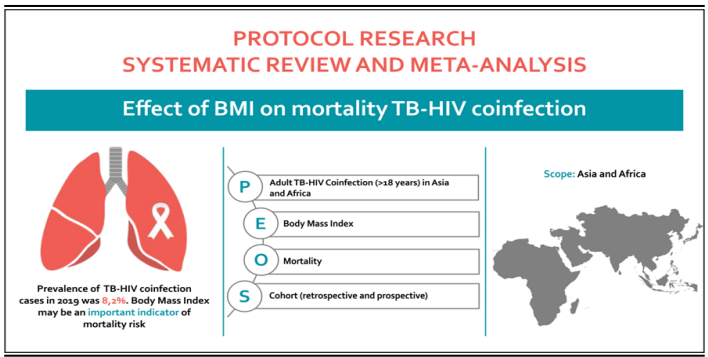
ABSTRACT

Globally, the prevalence of tuberculosis (TB) and human immunodeficiency virus (HIV) co-infection in 2019 was 8.2%. In 2020, TB-related deaths among individuals with HIV totaled 214,000, representing an increase from the previous year. Previous studies suggest that body mass index (BMI) is a significant predictor of mortality risk in individuals with TB and HIV co-infection, as malnutrition and low BMI are frequently linked to poorer clinical outcomes. This protocol has been developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines. A systematic review and meta-analysis will be conducted by searching three databases: MEDLINE/PubMed, Scopus, and ProQuest. This protocol aims to outline the stages and procedures of the forthcoming systematic review and meta-analysis, including the justification of the research question; the definition of Population, Exposure, Outcome, and Study design (PEOS); the inclusion and exclusion criteria; the search strategy; study screening and data extraction; and the planned data analysis. Identifying BMI as a prognostic factor through this study may inform nutrition-based interventions and treatment protocols aimed at reducing mortality among individuals co-infected with TB and HIV in Asia and Africa.

ABSTRAK

Secara global, prevalensi kasus koinfeksi TB dan HIV pada tahun 2019 adalah 8,2%. Pada tahun 2020, jumlah kematian akibat TB pada orang dengan HIV adalah 214.000 orang, yang mencerminkan peningkatan dari tahun sebelumnya. Penelitian sebelumnya menunjukkan bahwa Indeks Massa Tubuh (IMT) dapat menjadi indikator penting risiko kematian pada pasien koinfeksi TB dan HIV, karena malnutrisi dan IMT yang rendah sering dikaitkan dengan hasil klinis yang lebih buruk. Protokol ini ditulis berdasarkan pedoman Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P). Tinjauan sistematis dan meta-analisis akan dilakukan dengan mencari secara sistematis di tiga basis data: Medline/Pubmed, Scopus, dan ProQuest. Hasil dari protokol ini diharapkan dapat memberikan gambaran mengenai tahapan dan prosedur tinjauan sistematis dan meta-analisis yang akan dilakukan, mulai dari justifikasi pertanyaan penelitian, penentuan Populasi, Eksposure, Outcome, dan Studi (PEOS), kriteria inklusi-eksklusi, strategi penelusuran, skrining, ekstraksi, hingga analisis yang akan dilakukan. Identifikasi IMT sebagai faktor prognostik melalui penelitian ini dapat memandu intervensi berbasis nutrisi dan protokol pengobatan untuk menurunkan angka kematian pada pasien koinfeksi TB dan HIV di Asia dan Afrika

GRAPHICAL ABSTRACT



Keyword
body mass index
coinfection
hiv infections
medline
tuberculosis

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INTRODUCTION

TB/HIV co-infection remains a global epidemic despite widespread access to antiretroviral therapy aimed at reducing the burden of the disease. Individuals living with HIV are approximately 18 times more likely to develop active TB compared to those who are HIV-negative. As HIV compromises the immune system and weakens the body's defenses (World Health Organization, 2020), this dual burden has emerged as a leading cause of mortality, particularly in low- and middle-income countries. Globally, as of 2021, there were 7.5 million newly reported TB cases, of which 630,000 were co-infected with HIV (Zhang et al., 2024). Sub-Saharan Africa, Southeast Asia, and South Asia accounted for a significant proportion of the global TB/HIV burden (World Health Organization, 2021). The high prevalence of TB/HIV co-infection in low- and middle-income countries is primarily attributed to limited healthcare access and adverse socioeconomic conditions (Okhovat-Isfahani et al., 2019; Jiamsakul et al., 2018).

Studies from Ethiopia and the Democratic Republic of the Congo (DRC) reported that the mortality rate among adult patients with TB/HIV co-infection was approximately twice as high as that among patients with HIV infection alone (Vos et al., 2020; Shah et al., 2021). In cases of TB/HIV co-infection, the progression of HIV to AIDS is more rapid, and the risk of latent TB infection progressing to active disease is significantly higher than in individuals with a single infection (Bell & Noursadeghi, 2018; Nigam et al., 2022). This synergistic interaction exacerbates disease severity, increasing susceptibility to opportunistic fungal, bacterial, and viral infections (Mehrian et al., 2019; Peña Donati & Laufer, 2020). The financial burden imposed on patients significantly affects their families and further complicates healthcare delivery (Assebe et al., 2020; Nigam et al., 2022).

Several factors have been identified as contributors to poorer health outcomes in individuals with TB/HIV co-infection. Meta-analyses from Ethiopia reported that individuals older than 44 years faced an 82% higher risk of mortality (Moges & Lajore, 2024). Extrapulmonary tuberculosis was also associated with a higher mortality rate compared to pulmonary tuberculosis. Patients with reduced functional status, such as those who were bedridden or ambulatory, exhibited higher mortality rates compared to those who were physically active or working (Moges & Lajore, 2024; Yang et al., 2023). Adherence to treatment regimens for HIV and TB has been shown to reduce mortality by minimizing the risk of opportunistic infections (Moges & Lajore, 2024; Kegne et al., 2024; Yang et al., 2023).

Nutritional status is a key predictor of mortality among individuals with TB/HIV co-infection, as it significantly contributes to disease progression (Shasho et al., 2024; Moges & Lajore, 2024). Immunological deterioration caused by co-infection redirects the body's energy toward eradicating pathogens, resulting in immune and metabolic imbalance. Although the body requires increased energy to combat pathogens, hypothalamic dysregulation often induces anorexia in patients. Consequently, a negative energy balance ensues, prompting the utilization of fat and protein reserves, ultimately resulting in malnutrition. This condition leads to increased mortality due to the body's diminished capacity to control infection (Liebenberg et al., 2021).

Given the substantial burden of TB/HIV co-infection and high rates of undernutrition, Africa and Asia remain the most vulnerable regions, where these conditions mutually exacerbate one another. Sub-Saharan Africa and Asia together bear a significant proportion of the global TB/HIV co-infection burden. In sub-Saharan Africa, TB/HIV co-infection rates are estimated at 72%, with high incidences of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) (Naidoo & Naicker, 2019). Asia accounts for approximately 60% of global TB incidence, with countries such as India, Indonesia, and China contributing sub-

Table 1
Search Terms Used in Literature Search

Population	Exposure	Outcome	Studies
"Coinfection"[Mesh]	"Body Mass Index"[Mesh]	"Mortality"[Mesh]	"Cohort Studies"[Mesh]
"Tuberculosis"[Mesh]	BMI	Fatal*	Cohort study
"HIV Infections"[Mesh]		Death	Cohort
"Adult"[Mesh]		Case fatality rate	
Co-infection		Mortality rate	
Multiple infections			
TB			
HIV			
Human immunodeficiency virus			
TB/HIV			
Mature			
Person over 18			

Note: Fatal* captures "fatality" "fatalities", etc.

stantially to the global burden (Basnyat et al., 2018; Okada et al., 2012). The prevalence of undernutrition is notably higher in Africa and Asia than in other regions (Ayenew et al., 2024). Undernutrition and HIV compromise immune function, increasing the risk of TB reactivation and progression to active disease. Malnutrition significantly elevates mortality among patients with TB and HIV/AIDS (Alebel et al., 2021). However, the relationship between TB/HIV co-infection, BMI, and mortality remains underexplored in the contexts of Africa and Asia. This study aims to summarize the association between BMI and mortality among patients with TB/HIV co-infection in Asia and Africa.

METHODS

This protocol is written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) (Haddaway et al., 2022). The PRISMA-P checklist is attached as a supporting document. This protocol has been registered in the Open Science Framework (Irsal et al., 2024).

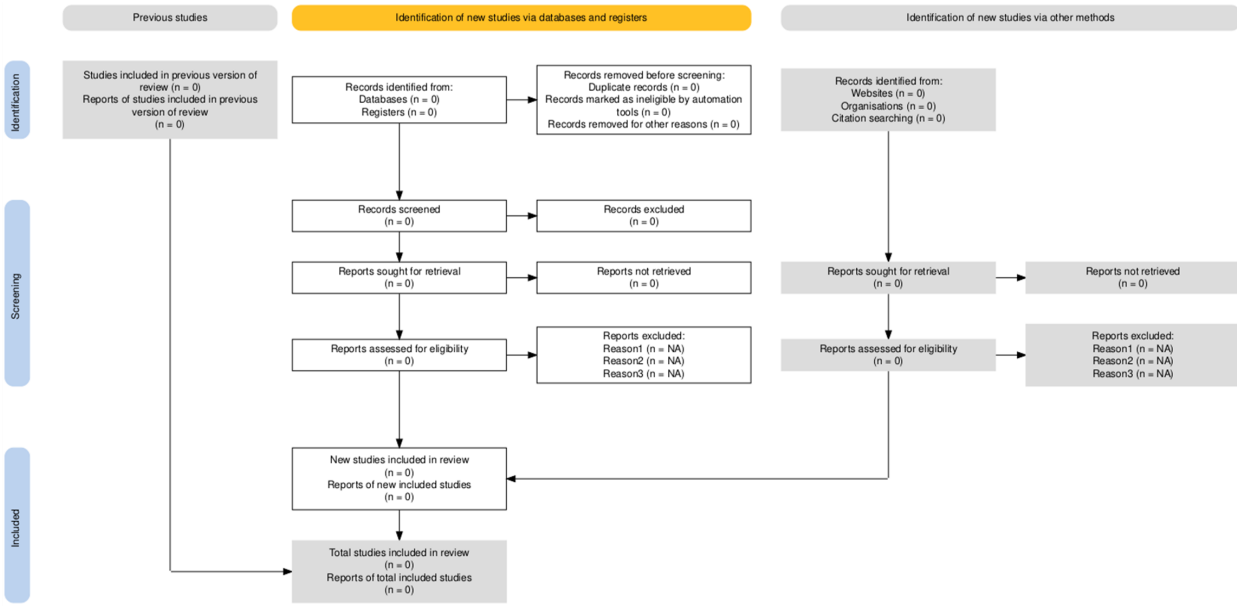
This systematic review and meta-analysis protocol is part of the study entitled "Effect of Body Mass Index on Mortality in Adult Patients with Tuberculosis and HIV Co-infection in Asia and Africa." This study aims to analyze the effect of body mass index on mortality in patients living with TB and HIV co-infection in Asia and Africa by presenting more comprehensive facts based on primary research results.

Data Sources and Search Strategy

A systematic review and meta-analysis will be conducted by systematically searching three databases: Medline/PubMed, Scopus, and ProQuest. All search keywords (terms) used are listed in Table 1. The PRISMA flow diagram is a standardized tool used to transparently present the process of study selection in systematic reviews. It will be used in this study to illustrate the identification, screening, eligibility assessment, and inclusion of studies throughout the review process (Figure 1).

The search strategy was carried out by combining these keywords using Boolean operators. Thus, the search strategy used was ("Coinfection"[Mesh] OR "Co-infection" OR "Multiple infections") AND ("Tuberculosis"[Mesh] OR "TB" OR "Tuberculosis") AND ("HIV Infections"[Mesh] OR "HIV" OR "Human Immunodeficiency Virus" OR "TB?HIV") AND ("Adult"[Mesh] OR "Mature" OR "Person over 18") AND ("Body Mass Index"[Mesh] OR "BMI") AND ("Mortality"[Mesh] OR "Fatal*" OR "Death" OR "Case fatality rate" OR "Mortality rate") AND ("Cohort Studies"[Mesh] OR "Cohort

Figure 1
PRISMA Flow Diagram Tool



study" OR "Cohort"). The search strategy was considered adequate to reduce the risk of selection and detection bias. The search results will be exported in RIS format.

Inclusion and Exclusion Criteria

Eligible studies must report their findings on the relationship between body mass index and mortality in patients living with TB and HIV co-infection. Included studies were cohort studies (prospective or retrospective), the sample was adults (>18 years), conducted in countries in Asia or Africa, written in English, and published in the period January 2000 – June 2024.

To be able to conduct a meta-analysis, included studies must report quantitative data including the total sample; the number of patients who died in the low BMI group (<18.5) and the normal/high BMI group (≥18.5); the number of patients who survived in both groups; the total sample in both groups; adjusted relative risk (aRR), adjusted hazard ratio (aHR), confidence interval, and p-value. These data can help to calculate the association (effect size) between BMI and mortality.

Children and patients with multidrug-resistant (MDR) TB will be excluded. In addition, studies that did not report the number of deaths, prevalence, and incidence, as well as literature review studies, case reports, conference abstracts, and qualitative studies were also excluded. This aims to minimize bias and avoid double data calculation.

The duplication detection and screening process is carried out using the Rayyan application (https://new.rayyan.ai/). Screening is carried out in two stages. The first stage is screening the title and abstract. The second stage is full-text screening. This stage aims to find studies that are relevant to the research. Screening is carried out by three reviewers in a blinded manner so that the included journals are obtained independently. If there are differences of opinion, they will be resolved by consensus. Furthermore, three reviewers jointly carry out data extraction.

Assessment of Methodological Quality

Quality assessment is crucial in systematic reviews to ensure the validity and reliability of the findings. It is conducted using the Hoy Risk of Bias instrument. This instrument was chosen because it is appropriate for observation-

Table 2
HOY Risk of Bias

No.	Risk of Bias Item	Criteria for Answers
1	Was the study's target population a close representation of the national population in relation to relevant variables, e.g. age, sex, occupation?	Yes (LOW RISK): The study's target population was a close representation of the national population. No (HIGH RISK): The study's target population was clearly NOT representative of the national population.
2	Was the sampling frame a true or close representation of the target population?	Yes (LOW RISK): The sampling frame was a true or close representation of the target population. No (HIGH RISK): The sampling frame was NOT a true or close representation of the target population.
3	Was some form of random selection used to select the sample, OR, was a census undertaken?	Yes (LOW RISK): A census was undertaken, OR, some form of random selection was used to select the sample (e.g. simple random sampling, stratified random sampling, cluster sampling, systematic sampling). No (HIGH RISK): A census was NOT undertaken, AND some form of random selection was NOT used to select the sample.
4	Was the likelihood of non-response bias minimal?	Yes (LOW RISK): The response rate for the study was >/=75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders No (HIGH RISK): The response rate was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders.
5	Were data collected directly from the subjects (as opposed to a proxy)?	Yes (LOW RISK): All data were collected directly from the subjects. No (HIGH RISK): In some instances, data was collected from a proxy.
6	Was an acceptable case definition used in the study?	Yes (LOW RISK): An acceptable case definition was used. No (HIGH RISK): An acceptable case definition was NOT used.
7	Was the study instrument that measured the parameter of interest (e.g. prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes (LOW RISK): The study instrument had been shown to have reliability and validity (if this was necessary), e.g. test-re- test, piloting, validation in a previous study, etc. No (HIGH RISK): The study instrument had NOT been shown to have reliability or validity (if this was necessary).
8	Was the same mode of data collection used for all subjects?	Yes (LOW RISK): The same mode of data collection was used for all subjects. No (HIGH RISK): The same mode of data collection was NOT used for all subjects.
9	Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes (LOW RISK): The shortest prevalence period for the parameter of interest was appropriate (e.g.point prevalence, one-week prevalence, one-year prevalence). No (HIGH RISK): The shortest prevalence period for the parameter of interest was not appropriate (e.g. lifetime prevalence).
10	Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes (LOW RISK): The paper presented appropriate numerator(s) AND denominator(s) for the parameter of interest (e.g. the prevalence of low back pain). No (HIGH RISK): The paper did present numerator(s) AND denominator(s) for the parameter of interest but one or more of these were inappropriate.

Sources: Hoy et al. (2012)

al studies and has been reviewed by the three reviewers. The Hoy Risk of Bias consists of 10 questions that address four domains of bias plus a summary risk of bias assessment. Hoy et al. found the tool easy to use, and there was high inter-rater agreement: overall agreement was 91% and Kappa statistic was 0.82 (95% CI: 0.76–0.86). This instrument assesses study quality at three levels: high risk (score <6), moderate risk (score 7–8), and low risk (score 9 –10). Studies that fall into the high-risk level will be excluded (Hoy et al., 2012). The instrument can be seen in Table 2.

Ethical Considerations

Although this study did not involve primary data collection, ethical considerations were addressed through strict adherence to the PRISMA 2020 reporting guidelines. These guidelines promote transparency, reproducibility, and accountability in the systematic review process. All included studies were previously published, peer-reviewed research, and this review respects their original ethical approvals.

RESULTS

Participants

The population in this study was adults in various countries who were diagnosed with TB and HIV co-infection in Asia and Africa. There were no restrictions on respondent characteristics such as gender, ethnicity, or other demographics. Because this study aims to determine the relationship between body mass index (BMI) and mortality, this indicator is used as a correlate and/or moderator in the meta-analysis. A minimum of two studies is sufficient to conduct a meta-analysis (Valentine et al., 2010).

Meta-Analytic Approach

The meta-analytic approach in this study is designed to combine data from various existing studies using pooled effect sizes based on a random effects model. This model was chosen because it accounts for variability between studies, allowing the analysis results to better reflect the diversity of the study population (Borenstein et al., 2009). The calculations in this analysis were performed using the DerSimonian-Laird (DL) method, which is a standard approach for estimating between-study variance in the random effects model (DerSimonian & Laird, 1986). The analysis process was performed using SPSS version 29, which provides systematic and accurate meta-analytic features.

The primary statistical method used is the Mantel-Haenszel method, which enables the pooling of risk ratios (RRs) while considering the weight of each study (Mantel & Haenszel, 1959). RR serves as the primary effect measure in this meta-analysis, and the interpretation of results is based on a 95% confidence interval (CI). This approach aims to provide a reliable estimate of the relationship between the studied variables while accounting for inter-study variations.

Homogeneity and heterogeneity analyses are conducted to evaluate the consistency of results across studies. Homogeneity is assessed using Cochran's Q test, which examines whether the variation in results among studies is purely due to random factors (Cochran, 1954). The null hypothesis of this test states that all studies have homogeneous results. If the test result shows $p < 0.05$, the null hypothesis is rejected, indicating significant variation that cannot be explained solely by random factors. On the other hand, heterogeneity is analyzed using the I^2 statistic and tau-squared (τ^2), where I^2 indicates the proportion of total variance caused by true heterogeneity, while τ^2 measures the absolute variance between studies (Higgins, 2003).

Additionally, a funnel plot is used to visually detect potential publication bias, and Egger's test is applied to statistically identify such bias (Egger et al., 1997). This approach ensures that the interpretation of meta-analysis results is based on comprehensive and reliable statistical assessments.

DISCUSSION

This study conducted a systematic review and meta-analysis to explore the relationship between Body Mass Index (BMI) and mortality among patients living with TB and HIV co-infection in Asia and Africa. Given the high burden of TB/HIV co-infection in these regions, this study aimed to provide deeper insights into how nutritional status (measured through BMI) influences mortality risk. The meta-analysis integrated findings from various studies to deliver more reliable pooled estimates and identify factors that may moderate or mediate the relationship between BMI and mortality.

It is well-established that malnutrition significantly compromises immune function, particularly cellular immunity, thereby increasing susceptibility to infections such as TB and accelerating disease progression in HIV patients (Boadu et al., 2024; Fan et al., 2022; Fâcă et al., 2025). A low BMI (<18.5) has been consistently associated with higher mortality among co-infected individuals due to its strong link to immune suppression and treatment complications (Alebel et al., 2023; Gatechompol, et al., 2022). Conversely, patients with a BMI in the overweight or mildly obese range have shown lower mortality risks, possibly due to better nutritional reserves and metabolic stability (Gavriilidou et al., 2024; Zhang et al., 2025).

Additionally, this research seeks to uncover when and how BMI contributes to increased TB and HIV severity among patients. These findings can help to design nutrition-based interventions to reduce mortality risk in vulnerable populations. Studies show that underweight patients are more likely to present late-stage HIV and develop extrapulmonary TB, which are both independent predictors of mortality (Cho et al., 2022; Dlatu et al., 2025; Min et al., 2023). Nutritional deterioration during the initial phase of ART is also a significant prognostic marker, and early nutritional interventions have been linked to improved treatment response and immune recovery (Geng et al., 2021; Fuseini et al., 2021).

Furthermore, evidence indicates that BMI monitoring over time is a cost-effective and practical prognostic tool in low-resource settings. Rapid declines in BMI may serve as early warning signs for clinical deterioration, while sustained undernutrition during TB treatment is linked to higher relapse and lower cure rates (Baluku et al., 2021; Sinha et al., 2023; Wagnew et al., 2024).

By establishing BMI as a more frequently monitored prognostic indicator, this study could support adjustments to TB and HIV co-infection treatment protocols that better align with patient needs in these regions. There is growing consensus that integrating routine nutritional screening and supplementation into TB/HIV programs can significantly reduce mortality and improve overall treatment outcomes (Lin et al., 2021; Sossen et al., 2025). The World Health Organization now recommends nutritional assessment and support as part of standard care for TB and HIV patients, especially in high-burden countries in Asia and Africa (World Health Organization, 2021).

Ultimately, this study underscores the importance of adopting a holistic treatment approach that not only addresses infection control and pharmacological management, but also actively incorporates nutritional interventions tailored to BMI profiles. This approach holds promise in enhancing survival rates and reducing health disparities in TB-HIV co-infected populations across Asia and Africa.

Several limitations must be considered. First, publication bias may occur as this review includes only peer-reviewed published articles, which may favor studies with statistically significant results. Funnel plot analysis and Egger's test will be employed to assess potential bias. Second, the geographic and demographic scope is focused only on Asia and Africa, which may limit the generalizability of the findings but remains appropriate given the high burden of TB/HIV and undernutrition in these regions (World Health Organization, 2021).

Third, measurement limitations exist due

to BMI variability across studies. BMI cut-off thresholds for undernutrition may differ between countries, and BMI does not differentiate between muscle mass and fat, potentially affecting its validity as a nutritional indicator (Ayenew et al., 2024). Fourth, the design limitations of observational studies, despite being valuable for risk estimation, include susceptibility to residual confounding and inability to establish causality. Finally, differences in data quality and adjustment for confounders across studies (e.g., age, ART adherence, immunological status) may influence pooled estimates and will be addressed through subgroup analysis and sensitivity testing where possible. Despite these limitations, the rigorous application of PRISMA 2020 guidelines and quality assessment tools enhances the credibility and transparency of this review.

This review has some inherent limitations related to the scope of included populations and the nutritional indicators used. Specifically, it did not include vulnerable groups such as children, prisoners, and patients with multidrug-resistant tuberculosis (MDR-TB), which limits the applicability of the findings to these important subpopulations. Moreover, the exclusive focus on Body Mass Index as a nutritional measure does not capture the complexity of body composition and nutritional status, potentially oversimplifying the relationship between nutrition and mortality in co-infected individuals.

To build on these findings, future research should incorporate these underrepresented populations to provide a more comprehensive understanding of nutritional influences across diverse patient groups. Additionally, exploring more detailed and precise nutritional markers such as muscle mass assessments, fat distribution, or biochemical nutritional indicators could improve risk stratification and intervention targeting. Expanding study designs and including data from different geographical regions beyond Asia and Africa would also enhance the generalizability and depth of evidence on the role of nutrition in TB and HIV outcomes.

CONCLUSIONS

This protocol outlines a structured and transparent plan for conducting a systematic review and meta-analysis to investigate the relationship between Body Mass Index (BMI) and mortality among patients living with TB and HIV co-infection in Asia and Africa. By adhering to PRISMA-P guidelines, this preparatory document ensures methodological rigor in identifying, selecting, and analyzing relevant studies, thereby laying a strong foundation for generating high-quality evidence.

The anticipated findings from the upcoming review aim to inform clinical practice and public health policy by clarifying the prognostic value of BMI in TB-HIV care. This evidence could support the development of clinical guidelines that integrate nutritional assessment into routine care, strengthen nutrition support programs for high-risk populations, and guide more effective resource allocation in TB-HIV management, especially in resource-limited settings. Ultimately, the protocol is designed to facilitate evidence-based strategies that improve survival and health outcomes among co-infected patients.

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AUTHORS' CONTRIBUTIONS
Mufti A. M. Irzal and Yunis M. Wahyono was the project's initiator and has been responsible for writing the protocol. Mufti A. M. Irzal is the guarantor of the review. Putri N. C. Insani, Welstin W. Loa, and Leopardo A. Ngetwa contributed to the development of the project and idea development. All authors have read and approved the protocol.

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COMPETING INTERESTS

The authors confirm that all of the text, figures, and tables in the submitted manuscript work are original work created by the authors and that there are no competing professional, financial, or personal interests from other parties.

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