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SYSTEMATIC REVIEW AND META-ANALYSIS

Predictors of Mortality in Adults with Human Immunodeficiency Virus-Associated Tuberculous Meningitis: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Tuberculous meningitis (TBM) is the most lethal form of tuberculosis, and human immunodeficiency virus (HIV) co-infection is its single most important risk factor. The magnitude of mortality specific to HIV-associated TBM, and the factors that predict death, have not been synthesised quantitatively.

Objective: To estimate the pooled all-cause mortality of adults with HIV-associated TBM and to identify its determinants.

Methods: PubMed/MEDLINE and Europe PMC were systematically searched for cohort studies and randomised controlled trials reporting mortality in adults with HIV-associated TBM; this was a two-database, single-reviewer review with full-text verification. All-cause mortality was pooled as a proportion (random-effects, DerSimonian-Laird, logit transformation); adjusted ratio measures for one predictor domain reported by at least three studies were pooled on the log scale. Certainty was rated with GRADE.

Results: Twelve studies (3,442 adults, 1,303 deaths) were included. In clinically ascertained cohorts and trials (k=11) pooled mortality was 47.0% (95% CI 41.4–52.7; I^2=83.9%); the exploratory all-study estimate was 44.2% (95% CI 34.5–54.4; I^2=96.4%; prediction interval 14.0–79.4%), heterogeneity being explained almost entirely by one national-registry cohort (17.3%). Advanced MRC/BMRC disease grade was the strongest predictor of death (pooled adjusted ratio 4.15, 95% CI 3.19–5.41; I^2=0%). Mortality did not decline over the study period, and no small-study effect was detected.

Conclusion: Approximately one in two adults with HIV-associated TBM died, without improvement despite expanding antiretroviral access, although the wide prediction interval and very low certainty demand caution. Advanced disease grade at presentation was the dominant predictor, underscoring the value of earlier diagnosis.

1. Introduction

Tuberculous meningitis (TBM) is the most severe and most lethal manifestation of infection with *Mycobacterium tuberculosis*. Although it accounts for only a small fraction of the global tuberculosis burden, it carries a disproportionate weight of death and neurological disability: modelling studies have estimated that TBM affected of the order of 164,000 adults worldwide in a single year, and that death occurs in roughly a quarter of all cases while neurological sequelae persist in nearly half of survivors.[1] Tuberculosis remains among the leading infectious causes of death globally, and the majority of the TBM burden falls on south-east Asia and sub-Saharan Africa, the same regions that carry the heaviest burden of the human immunodeficiency virus (HIV).[2]

HIV co-infection is the single most important risk factor for TBM in adults. People living with HIV are markedly more susceptible to all forms of tuberculosis, and are particularly prone to develop meningeal disease when immunosuppression is advanced. Once TBM is established, HIV co-infection accelerates a poor outcome: pooled case fatality among adults living with HIV and TBM has been estimated at around 38%, exceeding that of HIV-negative patients.[3]

The high mortality has persisted despite advances in diagnosis and treatment. Definitive diagnosis still depends on identifying the organism, and even rapid cerebrospinal-fluid (CSF) assays retain imperfect sensitivity in this population, contributing to diagnostic delay.[4] The two adjunctive interventions of proven value in other settings, corticosteroids and antiretroviral therapy (ART), have not demonstrated a clear survival benefit that is specific to HIV-associated disease, and the optimal timing of ART initiation remains contested.[5] Recovery of immune function may itself precipitate a paradoxical immune reconstitution inflammatory syndrome (IRIS), which carries additional morbidity in TBM.[6]

The prognostic landscape of HIV-associated TBM is conventionally divided into non-modifiable determinants present at diagnosis, such as the degree of immunosuppression indexed by the CD4 lymphocyte count, the British/Medical Research Council (BMRC/MRC) disease-severity grade, drug resistance, undernutrition and disseminated disease, and potentially modifiable determinants within the clinician's control, such as the timeliness of diagnosis, adjunctive corticosteroid therapy, the timing of ART initiation and the recognition of paradoxical reactions. Individual cohorts have examined subsets of these factors, but their findings have not been assembled into a single quantitative estimate, and the clinically fundamental question of how many patients actually die, and which baseline features most strongly predict that death, has been answered only piecemeal.

Existing evidence syntheses stop short of this question. The most directly relevant synthesis pooled the prevalence, incidence and case-fatality rate of TBM in people living with HIV, but reported a single mortality proportion without analysing its determinants.[3] Other syntheses have pooled prognostic factors in TBM of mixed HIV status, treating HIV as one covariate rather than as the defining feature of the population. To date no meta-analysis has restricted itself to adults with HIV-associated TBM and pooled both the mortality and its predictors, leaving clinicians without a consolidated, population-specific estimate on which to base counselling, triage and the design of future trials.

The novelty of this study lies in being the first meta-analysis to restrict its population exclusively to adults with HIV-associated tuberculous meningitis and to synthesise, within that population, both the pooled all-cause mortality and its baseline predictors, while transparently quantifying and explaining the between-study heterogeneity that has undermined earlier mixed-population estimates. We emphasise that the mortality figure itself is not claimed to overturn previous estimates, with which it is broadly concordant; its value lies in being population-specific and in the accompanying anatomy of its heterogeneity, and the genuinely new clinical information resides in the demonstration that disease grade retains its prognostic power specifically within the HIV-associated population. The aim of this study was to determine the pooled all-cause mortality of adults with HIV-associated TBM, to identify and where possible pool the clinical, immunological and cerebrospinal-fluid determinants of death, and to test whether mortality has changed across the modern antiretroviral era.

2. Methods

2.1. Protocol and reporting

This systematic review and meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement. The review question was framed using the PICO structure: the population was adults (aged 15 years or older) with HIV-associated TBM; the prognostic factors of interest were baseline clinical, immunological and cerebrospinal-fluid characteristics; the comparator was the reference category of each factor; and the primary outcome was all-cause mortality. Eligible designs were prospective or retrospective cohort studies and randomised controlled trials (RCTs). A formal protocol registration was not undertaken.

2.2. Search strategy

PubMed/MEDLINE and Europe PMC were searched from database inception. The search combined controlled vocabulary and free-text terms for tuberculous meningitis, HIV and mortality. The core Boolean string was: ("tuberculous meningitis" OR "tuberculosis, meningeal" OR "meningeal tuberculosis") AND ("HIV" OR "human immunodeficiency virus" OR "AIDS" OR "people living with HIV") AND ("mortality" OR "death" OR "case fatality" OR "outcome" OR "survival" OR "prognosis" OR "predictors"). Ten query strings were executed, yielding 3,194 database hits. Records were retrieved in relevance and publication-date order, de-duplicated by unique identifier, and screened. Backward citation checking was performed on every included study and on prior syntheses. This was, by design, a two-database review: the searches were complemented by citation checking but were not extended to Embase, Scopus, Web of Science or the Cochrane Central Register of Controlled Trials, for which ready-to-run translated strings were prepared but not executed. Retrieval was capped by relevance order once the application-programming-interface page limit was reached, and screening was performed by a single reviewer with a subsequent verification pass against the primary full texts; the review is therefore best characterised as a rigorously conducted rapid systematic review rather than a fully exhaustive dual-reviewer synthesis.

2.3. Eligibility criteria

Studies were included if they enrolled adults with HIV-associated TBM (or reported an HIV-specific mortality stratum within a mixed cohort), reported all-cause mortality as events and a denominator at any defined time point (in-hospital, end of treatment, 9-month or 12-month), and were published as peer-reviewed cohort studies or RCTs. Studies were excluded if they were narrative or systematic reviews, case reports, editorials or conference abstracts; if they enrolled children only; or if no mortality numerator and denominator could be recovered. Where several reports described overlapping populations, the report that contributed the most complete pooled dataset with the longest protocolised follow-up was retained and its constituent reports were excluded to prevent double counting; the principal overlap decision was tested in a sensitivity analysis.

2.4. Data extraction

Data were extracted into a standardised workbook. For every study the first author, country, design, TBM case definition, outcome-ascertainment window, the number of adults with HIV-associated TBM analysed,

the number of deaths, and any adjusted or unadjusted effect estimate for a predictor of mortality with its 95% confidence interval were recorded. Each event count and denominator was traced to a verbatim sentence or table cell in the primary full text. Two death counts were back-calculated from a reported percentage: for one Brazilian cohort a 9-month mortality of 41% applied to 108 patients yielded 44 deaths, and for one Indonesian cohort a 1-year Kaplan-Meier mortality estimate of 60.0% applied to 93 patients yielded 56 deaths; both were flagged and a sensitivity analysis excluded them. Case definitions of TBM differed across studies, ranging from culture-confirmed to clinically diagnosed or presumptive disease, and this heterogeneity of definition was noted as a potential source of clinical diversity distinct from the data-source effect. No value was imputed or carried forward from an unverified source.

2.5. Risk-of-bias assessment

Because the evidence base comprised both randomised and non-randomised designs, the appropriate instrument was applied to each. The single RCT was appraised with the Cochrane Risk of Bias 2.0 (RoB 2.0) tool across its five domains. The non-randomised studies were appraised with the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool across its seven domains; RoB 2.0 was not applied to these studies because its domains are specific to randomised designs. Each study received an overall judgement, and the instrument used was labelled explicitly, so that no single overall score was compared across the two tools.

2.6. Statistical analysis

All analyses used random-effects models with the DerSimonian-Laird estimator of between-study variance, as pre-specified for the random-effects step. Because the primary endpoint was a binary event (death versus survival) counted in a single arm, and because the predictor data were adjusted ratio measures, a standardised mean difference (Hedges' g) was neither estimable nor meaningful for these data; a standardised mean difference requires group means, standard deviations and sample sizes that no included study provided. The analysis therefore pooled all-cause mortality as a proportion. Each study proportion was transformed to the logit scale for pooling, and the pooled logit and its confidence limits were back-transformed to the percentage scale for presentation, so that all confidence intervals reported as percentages were obtained by back-transformation rather than on the logit scale directly. Robustness was examined with the Freeman-Tukey double-arcsine transformation, a generalised linear mixed model with maximum-likelihood estimation, and the Hartung-Knapp adjustment; the last was included specifically because the DerSimonian-Laird method can underestimate the uncertainty of the pooled estimate when heterogeneity is extreme. Heterogeneity was quantified with the I^2 statistic, τ^2 and the Cochran Q test, and was summarised with a 95% prediction interval, which under high heterogeneity is a more honest expression of the evidence than the confidence interval. Pre-specified subgroup analyses (outcome-ascertainment window, study design, data source and geographic region) and random-effects meta-regression (publication year, data source and ascertainment window) were performed; subgroups containing a single study were interpreted as hypothesis-generating only. Leave-one-out and structural sensitivity analyses, formal influence diagnostics, and small-study-effect testing (Egger and Peters regression with trim-and-fill) were conducted; small-study testing was undertaken only because at least ten studies were available, and trim-and-fill was regarded as a sensitivity check rather than as a corrected estimate. For the one predictor domain reported by at least three studies, adjusted ratio measures were pooled on the natural-log scale using both DerSimonian-Laird and Hartung-Knapp models. Certainty of evidence was rated using the GRADE framework. Analyses were performed in R (packages meta and metafor).

3. Results

3.1. Study selection

The database search returned 3,194 records. After de-duplication, 412 unique records were screened by title and abstract, of which 43 were assessed in full text; 31 of these were excluded, most commonly because the HIV-specific stratum was not reported separately or because the cohort overlapped an already-included study. Twelve studies met all eligibility criteria and were included in the quantitative synthesis. The complete study-selection process, with reasons for exclusion at each stage, is summarised in the PRISMA flow diagram (Figure 1).

3.2. Study characteristics

The twelve included studies[7–18] contributed 3,442 adults with HIV-associated TBM and 1,303 deaths, and spanned publication years 2010 to 2026. They originated from four continents: Vietnam, Indonesia and Thailand in Asia; South Africa, Cameroon, Uganda and Mozambique in sub-Saharan Africa; Brazil in Latin America; and Romania in Europe. Eleven studies were observational cohorts and one was a double-blind randomised controlled trial. Outcome ascertainment ranged from in-hospital death to 12-month follow-up. As detailed in Table 1, the reported mortality of the individual studies varied widely, from 17.3% in a Brazilian national-registry cohort to 79.6% in a small Cameroonian series, a spread that foreshadowed the substantial heterogeneity quantified below.

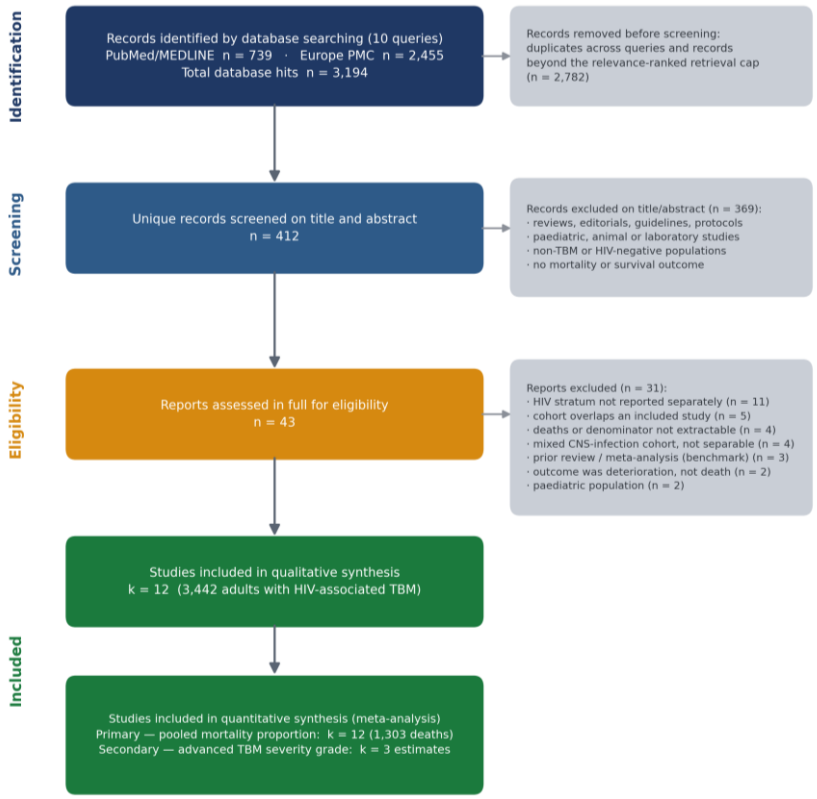

Figure 1. PRISMA 2020 flow diagram of study identification, screening and inclusion. Numerical counts in this diagram are identical to those reported in the narrative.

Table 1. Characteristics and mortality of the 12 included studies of adults with HIV-associated tuberculous meningitis.

Study (year)	Country	Design	Outcome window	N (HIV-TBM)	Deaths	Mortality (%)	Risk of bias
Croda (2010)	Brazil	Retrospective cohort	9 months	108	44	40.7	Serious
Marais (2011)	South Africa	Retrospective cohort	In-hospital	106	39	36.8	Moderate
Luma (2013)	Cameroon	Retrospective cohort	In-hospital	54	43	79.6	Serious
van Laarhoven (2017)	Indonesia	Prospective cohort	12 months	93	56	60.2	Moderate
Cresswell (2018)	Uganda	Prospective cohort	In-hospital	142	62	43.7	Serious
Thao (2018)	Vietnam	Pooled trial + cohort	9 months	748	384	51.3	Low
Boonyagars (2021)	Thailand	Retrospective cohort	End of treatment	97	54	55.7	Moderate
Donovan (2023)	Vietnam & Indonesia	RCT (double-blind)	12 months	520	242	46.5	Low
Loghin (2023)	Romania	Retrospective cohort	In-hospital	19	6	31.6	Serious
Urmenyi (2025)	Brazil	National registry cohort	In-hospital	1034	179	17.3	Serious
Nacarapa (2025)	Mozambique	Retrospective cohort	End of treatment	372	140	37.6	Moderate
Wilt (2026)	Uganda	Prospective cohort	90 days	149	54	36.2	Moderate
Total / range				**3,442**	**1,303**	**17.3–79.6**	**2L / 5M / 5S**

RCT, randomised controlled trial; L, low; M, moderate; S, serious risk of bias. Risk of bias was appraised with ROBINS-I for cohorts and RoB 2.0 for the trial.

3.3. Risk of bias

Two studies were judged to be at low risk of bias, five at moderate risk and five at serious risk, as displayed in the traffic-light plot in Figure 2. The serious ratings arose from three recurring problems: outcome status unknown for a substantial fraction of participants, administrative rather than clinical ascertainment of both diagnosis and death, and very small or presumptively diagnosed samples. The single randomised trial, appraised with RoB 2.0, was at low risk. Excluding all serious-risk studies did not change the pooled estimate (46.0%, 95% confidence interval 40.0–52.1).

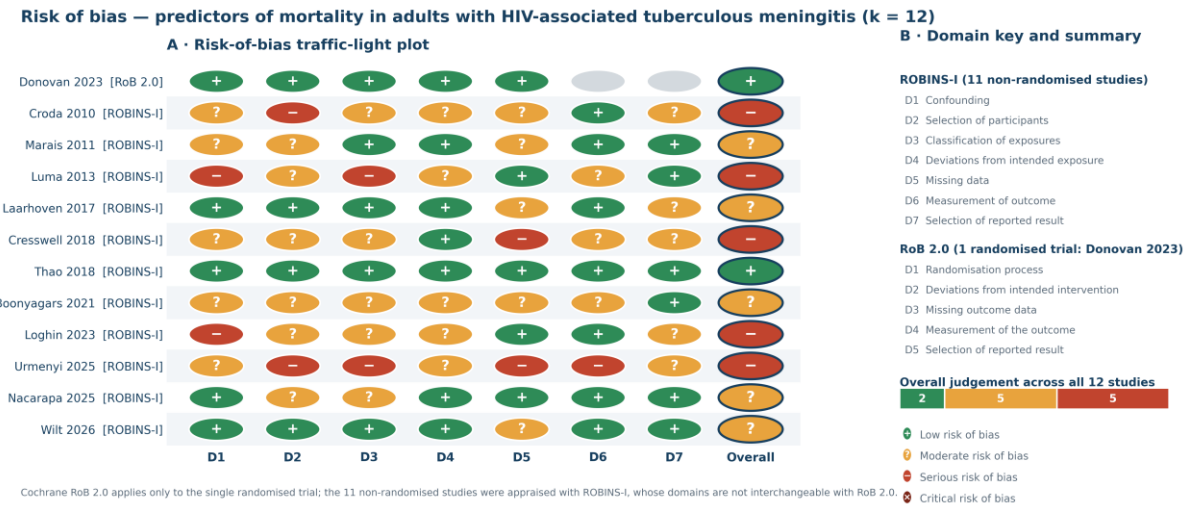

Figure 2. Risk-of-bias summary (ROBINS-I for the 11 non-randomised studies; Cochrane RoB 2.0 for the single randomised trial). The two instruments are not interchangeable and are not compared on a single scale.

3.4. Pooled all-cause mortality

Across all twelve studies the exploratory random-effects pooled mortality was 44.2% (95% confidence interval 34.5–54.4), with extreme heterogeneity (Q=302.4, df=11, p<0.0001; τ^2=0.475; I^2=96.4%) and a wide 95% prediction interval of 14.0–79.4%, as shown in the forest plot in Figure 3. Because the I^2 value far exceeded the conventional 75% threshold, the single all-study pool was treated as exploratory and the primary inference was drawn from the stratified analysis: in clinically ascertained cohorts and trials (k=11, n=2,408), all-cause mortality was 47.0% (95% confidence interval 41.4–52.7; I^2=83.9%). Expressed in plain clinical terms, this corresponds to approximately 47 deaths for every 100 adults treated. The estimate was insensitive to the choice of variance-stabilising transformation, heterogeneity estimator and confidence-interval method, all four models agreeing to within 0.3 percentage points. The prediction interval, rather than the confidence interval, is the honest summary of the evidence when heterogeneity is this large.

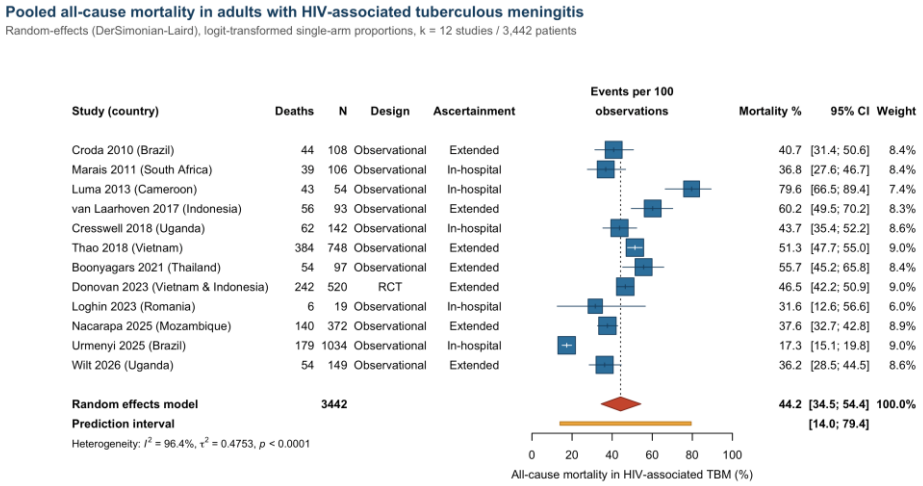

Figure 3. Forest plot of all-cause mortality in adults with HIV-associated tuberculous meningitis (random-effects, DerSimonian-Laird, logit-transformed proportions). Diamonds represent pooled estimates; the horizontal bar shows the 95% prediction interval.

3.5. Sources of heterogeneity

Of four pre-specified moderators, data source explained essentially all of the between-study variance. Clinically ascertained cohorts pooled at 47.2% (95% confidence interval 40.4–54.1) and the single randomised trial at 46.5%, whereas the one national notification-registry study reported 17.3% (95% confidence interval 15.1–19.7);[16] the test for subgroup differences by data source was decisive (Q-between=166.7, df=2, p<0.0001). Removing that single registry study collapsed I^2 from 96.4% to 83.9% and τ^2 from 0.475 to 0.111. This was a substantive rather than a statistical explanation: an administrative registry that records only deaths coded during a notified admission, in a setting with long-standing universal antiretroviral access, measures a fundamentally different quantity from a research cohort followed for 9 to 12 months. Regional differences were not statistically significant (p=0.095) although the direction was consistent with the literature (Asia 51.8%, sub-Saharan Africa 45.3%,

Latin America 27.2%). Randomised versus observational design made no difference (p=0.689). Influence diagnostics flagged exactly one study, the national-registry cohort (studentised residual −3.99, DFFITS −1.11), as influential; no other study met the threshold, and the highest single estimate, the Cameroonian series,[9] did not.

3.6. Temporal trend

Meta-regression on publication year tested whether mortality had fallen across the modern antiretroviral era. Across all twelve studies the odds of death fell by approximately 5% per calendar year, but the trend was not statistically significant (odds ratio 0.946 per year, p=0.111), and once the registry cohort was removed the apparent decline all but disappeared (odds ratio 0.974 per year, p=0.229). The cumulative meta-analysis told the same story: the running estimate remained between 44% and 52% from 2013 onward and did not trend downward. Mortality in HIV-associated TBM has therefore been essentially static across the evidence base.

3.7. Sensitivity analyses

Leave-one-out estimates ranged from 41.1% (omitting the highest single estimate) to 47.0% (omitting the registry cohort); no study other than the registry materially changed either the point estimate or the heterogeneity. Replacing the pooled Vietnamese cohort with its two constituent primary randomised-trial reports gave 46.0% (95% confidence interval 35.9–56.4), confirming that the overlap decision did not drive the result. Restricting to studies with at least 90-day ascertainment gave 46.5% (95% confidence interval 40.7–52.3), and excluding the two studies whose death counts had been back-calculated gave 43.0% (95% confidence interval 32.3–54.3). All sensitivity analyses agreed with the primary stratified inference.

3.8. Small-study effects and publication bias

With twelve studies available, formal testing was undertaken. Egger's regression gave p=0.437, and Peters' regression, which is preferred for proportion data, gave p=0.444; neither indicated small-study effects. Trim-and-fill imputed three studies and shifted the pooled estimate to 37.6%, a change well within the confidence interval. As illustrated in the contour-enhanced funnel plot in Figure 4, funnel asymmetry was not a plausible explanation for the observed heterogeneity; the data source was.

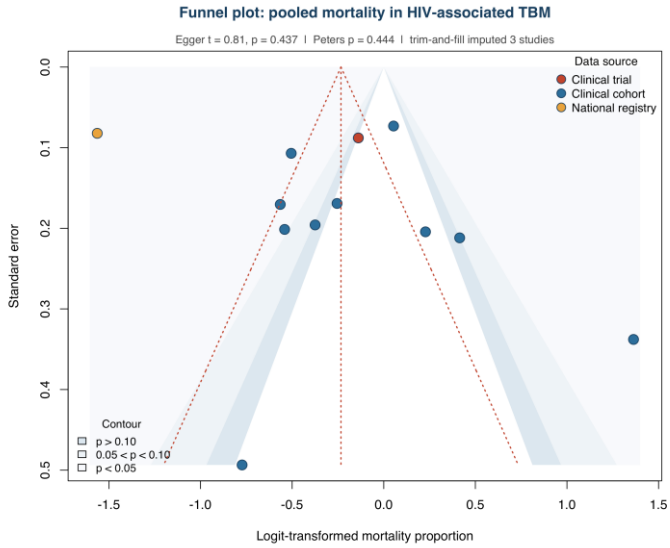

Figure 4. Contour-enhanced funnel plot of the included studies, with points coloured by data source.

3.9. Predictors of mortality

Only one predictor domain was reported with a comparable contrast by at least three studies: advanced TBM disease severity on the BMRC/MRC grading scale. Pooling three adjusted estimates on the log scale, advanced disease grade was associated with a 4.15-fold increase in the risk of death (95% confidence interval 3.19–5.41; p<0.001) with no detectable heterogeneity (I^2=0%; Q p=0.94) and a prediction interval of 2.32–7.42; the Hartung-Knapp model, appropriate at three studies, gave 4.15 (95% confidence interval 3.61–4.77). As shown in Figure 5, this was the single most consistent prognostic signal in the evidence base, drawing on cohorts from South Africa,[8] Vietnam[12] and Mozambique.[17] The remaining predictors were each reported by only one or two studies, or on scales that could not be harmonised, and were synthesised narratively. Severe immunosuppression was consistently associated with death (adjusted odds ratio 1.40 per 50-cell/µL decrease in CD4 count;[8] hazard ratio 3.30 for a CD4 count of 100 cells/µL or fewer[18]). Immunovirological failure of ART (adjusted hazard ratio 2.86), a raised CSF opening pressure above 40 cmH_2O (2.67), a body-mass index below 18.5 kg/m^2 (2.84), disseminated tuberculosis (2.03) and male sex (1.80) were each associated with increased mortality,[17] as was CSF hypo-inflammation indexed by a low interferon-γ concentration (hazard ratio 3.10),[18] whereas established antiretroviral exposure before or

during tuberculosis treatment was protective (hazard ratio 0.30).[8] Because these estimates rested on single studies and mixed hazard and odds ratios on non-identical scales, they were not pooled.

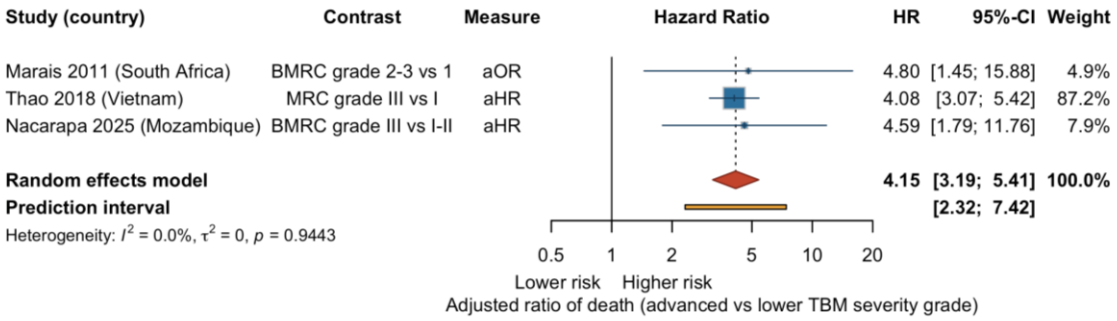

Figure 5. Forest plot of advanced TBM disease grade (BMRC/MRC) and mortality, pooling three adjusted estimates on the log scale.

3.10. Certainty of the evidence

Certainty was rated using GRADE and is summarised in Table 2. Both outcomes were rated very low. For all-cause mortality the body of evidence began as low certainty because it was predominantly observational, and was downgraded once for risk of bias, because five of the twelve studies were at serious risk, and once for inconsistency, because the extreme heterogeneity, although explained, was not removed; it was not downgraded for indirectness, imprecision or publication bias. For the severity-grade predictor the three contributing estimates were all adjusted and mutually consistent, but the outcome was downgraded for indirectness, because the studies used different reference categories and combined hazard and odds ratios, and for imprecision, because only three studies contributed. A very low rating does not mean the estimates are wrong; it means that the true value in any specific population could differ substantially.

In summary, and as reflected in Table 2, in clinically ascertained cohorts and trials the pooled all-cause mortality of adults with HIV-associated TBM was 47.0% (95% confidence interval 41.4–52.7), with a wide prediction interval and a very low certainty of evidence, and advanced disease grade at presentation was associated with a roughly four-fold increase in the risk of death.

Table 2. GRADE summary of findings and certainty of evidence.

Outcome	No. studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty
All-cause mortality (pooled proportion)	11 observational + 1 RCT	Serious (−1)	Serious (−1)	Not serious	Not serious	Undetected	VERY LOW
Advanced MRC/BMRC grade and death	3 observational (adjusted)	Not serious	Not serious	Serious (−1)	Serious (−1)	Not assessable	VERY LOW

Notes: BMRC/MRC, British/Medical Research Council; RCT, randomised controlled trial.

4. Discussion

This systematic review and meta-analysis assembled twelve studies and 3,442 adults to provide the first population-specific estimate of mortality in HIV-associated tuberculous meningitis. The central finding is stark: in clinically ascertained cohorts and trials, approximately 47% of adults with HIV-associated TBM died, a figure that has remained close to one in two throughout the evidence base despite the expansion of antiretroviral therapy. The single most consistent baseline predictor of death was advanced disease grade at presentation, which more than quadrupled the risk of death with no heterogeneity across the three studies that reported it. These conclusions are drawn from a body of evidence of very low certainty, and are stated with corresponding caution.

4.1. Interpretation

The magnitude of mortality documented here is a direct, quantitative expression of the clinical impression that HIV-associated TBM is among the most lethal conditions in neurology. It is important to be clear about what the endpoint measures: all-cause mortality in this population encompasses deaths from advanced immunosuppression and concurrent opportunistic infection as well as deaths from the meningitis itself, and the pooled figure is therefore best understood as the lethality of the clinical situation rather than of the meningitis in isolation. None of the included studies allowed the two to be reliably separated.

The dominant prognostic role of disease grade at presentation carries an important message. The BMRC/MRC grading scale classifies patients at presentation according to their level of consciousness and the presence of focal neurological signs, with grade

I denoting a fully conscious patient without focal deficit, grade II a patient with reduced consciousness or focal signs, and grade III a deeply obtunded or comatose patient; it is a bedside assessment requiring no special investigation, which is precisely why it is usable in the resource-limited settings where most of these patients are managed. Because grade is a function of how advanced the meningitis has become by the time treatment begins, the strongest predictor of death is also the one most amenable to change through earlier diagnosis and treatment. The reproducibility of grading between observers is therefore clinically relevant, and although the scale is simple and widely used, its prognostic value depends on consistent application, which argues for its explicit documentation in every patient.

4.2. A composite high-risk phenotype

Although only disease grade could be pooled, the narratively synthesised predictors are not a miscellaneous list but together describe a recognisable clinical phenotype of the patient at highest risk of death. That patient presents late and at an advanced disease grade, with profound immunosuppression indexed by a low CD4 count, often with antiretroviral failure or no prior antiretroviral exposure, with undernutrition reflected in a low body-mass index, with disseminated tuberculosis involving organs beyond the meninges, and with a raised cerebrospinal-fluid opening pressure.[17] The additional signal from CSF hypo-inflammation, in which a blunted interferon-γ response predicted death,[18] suggests that in the most immunosuppressed hosts the failure is not of excessive inflammation but of insufficient protective immunity, which may partly explain why anti-inflammatory corticosteroids have not improved survival in this population as they have in HIV-negative disease.[14] Recognising this composite phenotype at the bedside may be more useful than considering each factor in isolation.

4.3. Comparison with other syntheses

The estimate obtained here is coherent with, and extends, the existing literature. The most directly comparable synthesis reported a case-fatality rate of 38.1% (95% confidence interval 24.3–54.1) in adults living with HIV and TBM;[3] the exploratory all-study estimate of 44.2% obtained here lies well within that interval, and the clinically ascertained estimate of 47.0% is modestly higher, as expected because the present review required HIV-specific numerators and denominators and therefore excluded several low-mortality mixed cohorts, and because it included long-follow-up trials rather than in-hospital-only series. Within the present evidence base the sub-Saharan African studies[8,9,11,17,18] spanned a broad range of mortality, from 36% to 80%, consistent with the wide prediction interval and with the recognised diversity of African settings. The confirmation that advanced disease grade retains its prognostic power specifically within the HIV-associated population is the principal new contribution of this review.

4.4. Heterogeneity and regional variation

Extreme statistical heterogeneity is characteristic of pooled-proportion meta-analyses, and it was important to establish whether it reflected genuine clinical diversity or a single anomalous data source. The analyses converged unambiguously: subgroup testing, leave-one-out analysis and formal influence diagnostics all identified one national notification-registry study as the source of nearly two-thirds of the total Cochran Q.[16] Its low reported mortality is not an error but a consequence of a different measurement, namely administrative death coding during a notified admission in a setting with long-standing universal antiretroviral access, which is not commensurable with a research cohort followed for 9 to 12 months. This distinction was pre-specified as a reason for reporting the registry separately rather than being a post-hoc reaction to an outlier, and once the registry was set aside heterogeneity fell substantially and the clinical estimate was stable across every sensitivity analysis. The regional gradient, although not statistically significant, is of clinical interest: mortality was highest in the Asian cohorts, intermediate in sub-Saharan Africa and lowest in Latin America. Plausible contributors include differences in the timing of presentation, in antiretroviral coverage, in the prevalence of drug resistance, and in the case mix captured by different study designs and case definitions; these explanations are necessarily speculative and are offered as hypotheses for future comparative work.

4.5. Clinical implications for neurology

Three implications follow for the practising neurologist, and they are gathered here so that they are readily found. First, prognostic counselling and triage in HIV-associated TBM should be anchored to disease grade at presentation, which is the most robust and reproducible predictor of death and can be assessed at the bedside without specialised investigation; families should be counselled with reference to a mortality that approaches one in two, tempered by the wide uncertainty around that figure. Second, because mortality is heavily determined before specialist referral, health-system interventions that shorten the diagnostic interval, including wider access to rapid molecular and antigen testing of cerebrospinal fluid[4] and a lower threshold for lumbar puncture and empirical anti-tuberculosis treatment in people living with HIV who present with subacute meningism, are likely to yield more benefit than any additional adjunctive drug studied to date. Third, the static mortality despite expanding antiretroviral access is a call for genuinely novel therapeutic strategies rather than the further optimisation of existing ones; intensified antituberculosis regimens such as high-dose oral rifampicin continue to be tested,[19] and drug resistance and treatment adherence remain important determinants of outcome in people living with HIV,[20] but the consistency of the CD4-count and cerebrospinal-fluid-inflammation signals suggests that host-directed and immunomodulatory approaches

tailored to the immunosuppressed host deserve particular attention. The dominant, reproducible effect of disease grade also provides a ready-made stratification variable for the design and analysis of future trials, and the contested timing of antiretroviral initiation remains a priority question.[5]

4.6. Generalisability

Because the majority of the included studies originated from south-east Asia and sub-Saharan Africa, the pooled estimate is most directly applicable to those settings, which is appropriate given that they carry the overwhelming majority of the global burden of both tuberculosis and HIV. For a south-east Asian readership in particular, including the Indonesian population served by the authors' institution, the finding is directly relevant, because tuberculosis and HIV remain major and overlapping public-health challenges in the region and the Asian cohorts in this review reported the highest mortality. The estimate should not, however, be transferred uncritically to low-burden, high-resource settings, where the single European cohort[15] and the Latin American national registry[16] behaved quite differently from the rest. The more recent cohorts were assembled in the era of rapid molecular diagnostics and improved antiretroviral regimens, yet the temporal analysis found no improvement in mortality, which suggests that the estimate remains a reasonable reflection of contemporary outcomes rather than an artefact of older practice.

4.7. Limitations

Several limitations must be acknowledged. First, the predictor synthesis rested on only three studies for its single poolable domain, and those studies combined hazard and odds ratios with non-identical reference categories; the apparent absence of heterogeneity across three studies is not strong evidence of consistency, and the pooled severity estimate should be read as a consistent direction and rough magnitude rather than a precise population parameter. The remaining predictors could be synthesised only narratively because they were reported on incompatible scales. Second, the evidence base was dominated by observational cohorts, and five of the twelve studies were at serious risk of bias for reasons including incomplete outcome ascertainment and administrative rather than clinical case definition; although excluding these studies did not change the conclusion, the overall certainty of evidence was rated very low by GRADE for both outcomes. Third, between-study heterogeneity was extreme and, while it was traced to a single identifiable source, residual clinical diversity in case definition, ascertainment window and antiretroviral context remained. Fourth, the search covered two databases and was relevance-capped and screened by a single reviewer with a verification pass; although Embase, Scopus and Cochrane CENTRAL search strings were prepared, they were not executed, so a small number of eligible studies may have been missed. Finally, two death counts were back-calculated from reported percentages, and all-cause mortality conflates deaths from the meningitis with deaths from competing HIV-related causes; few studies reported the timing of death within follow-up, so the extent to which mortality is front-loaded could not be established and is an important question for future work.

5. Conclusion

This systematic review and meta-analysis of twelve studies and 3,442 adults provides the first population-specific quantification of mortality in HIV-associated tuberculous meningitis. In clinically ascertained cohorts and trials approximately 47% of adults died, a mortality that appears to have remained close to one in two despite the expansion of antiretroviral therapy. This apparent stability, supported by a non-significant temporal trend and by agreement with an independent synthesis, is a sobering counterpoint to the therapeutic optimism that has accompanied improved antiretroviral access, though it must be read against a wide prediction interval and a very low certainty of evidence.

Advanced disease grade at presentation emerged as the single most consistent predictor of death, associated with a roughly four-fold increase in risk with no heterogeneity across the studies that reported it. Because disease grade reflects how far the meningitis has advanced by the time treatment begins, this finding relocates the decisive prognostic window to the interval before specialist care, and it suggests that earlier diagnosis and treatment, rather than further refinement of adjunctive drug therapy, offer the greatest prospect of improving survival. Severe immunosuppression, antiretroviral failure or non-use, raised intracranial pressure, undernutrition and cerebrospinal-fluid hypo-inflammation together describe a recognisable high-risk phenotype and warrant confirmation in adequately powered, prospectively harmonised cohorts.

The certainty of this evidence is very low, reflecting its predominantly observational origin, its extreme but explicable heterogeneity, and a predictor analysis resting on few studies; the conclusions should therefore be regarded as the best current synthesis rather than as definitive parameters. The priorities that follow are nonetheless clear: health-system investment to shorten the diagnostic interval, the routine use of disease grade for prognostic stratification in both practice and trial design, and the development of genuinely novel, host-directed therapeutic strategies for a disease whose lethality has not yielded to a generation of incremental change. Until such strategies emerge, earlier recognition remains the most powerful tool available to the neurologist.

6. Declarations

6.1. Ethics approval and consent to participate

This study was a systematic review and meta-analysis of previously published, de-identified aggregate data and did not involve new human or animal participants; formal ethics-committee approval and individual

patient consent for publication were therefore not applicable. No identifiable individual patient data or images are reported.

6.2. Consent for publication

Not applicable; no identifiable individual patient data or images are presented.

6.3. Availability of data and materials

All data analysed in this review were extracted from previously published studies, each of which is cited in the reference list. The standardised extraction workbook and the R analysis code that support the findings are available from the corresponding author on reasonable request.

6.4. Competing interests

The authors declare no conflict of interest.

6.5. Funding

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6.6. Author contributions

EFT contributed to the conception of the review, the literature search, data extraction, analysis and drafting of the manuscript. NMS contributed to the conception and supervision of the study and to critical revision of the manuscript. AARS contributed to the interpretation of the data, critical revision and supervision. All authors reviewed and approved the final version of the manuscript.

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