Time to sputum culture conversion and its associated factors among multidrug-resistant tuberculosis patients in Eastern Africa: A systematic review and meta-analysis

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A B S T R A C T

Objective: This study aimed to consider the estimated time to multi-resistant tuberculosis culture conversion, and associated factors, in order to enhance evidence utilization in eastern Africa.
Methods: We systematically identified available articles on multidrug-resistant tuberculosis culture conversion using PubMed, Scopus, Cochrane Library, Web of Science core collection, and Science Direct databases. A random-effects model was employed using the R 3.6.1 version and Stata/se 14 software.
Results: Nine articles with a sample size of 2458 multidrug-resistant tuberculosis patients were included. The two-month culture conversion rate was 75.4%, with a median time of 61.2 days (interquartile range: 48.6-73.8). In the included studies, favorable treatment outcomes of MDR-TB patients were seen in 75% of the cases, while unfavorable treatment outcomes were seen in 18% (10% deaths, 7% defaulted, and 1% treatment failure) of the cases. The independent factor for delayed sputum culture conversion was body mass index below 18.5 kg/m^2 (HR = 3.1, 95% CI: 2.0, 6.7).
Conclusion: The median time to sputum culture conversion was 61.2 days, which is a reasonably short time. Body mass index was the identified associated factor leading to delayed culture conversion. Therefore, there is a need for awareness of how to improve the nutritional status of multidrug-resistant tuberculosis patients through appropriate nutritional supports.
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1. Background

Globally, tuberculosis (TB) was responsible for morbidities in 10 million cases and 1.5 million deaths in 2018 (WHO, 2018, 2019a). Also, public health and health security threats continued to grow due to the emergence of multidrug-resistant TB (MDR-TB); it remains an impediment to eliminating TB, with 44% of patients not successfully treated among compressed treatment recipients (WHO, 2019a). Therefore, monitoring treatment responses is essential to control MDR-TB and prevent the emergence of extensively drug-resistant (XDR-TB) strains that arise from the mismanagement of MDR-TB individuals (WHO, 2019a,b).

Multidrug-resistant tuberculosis involves long term treatment, expensive and toxic regimens, and significant risks for drug-resistant infections (Chan et al., 2004). Shifting from the intensive phase (usually two months) to the continuation phase (usually four to seven months) in the treatment regime is based on the microbiological status of patients' sputum culture. Thus, close monitoring is essential during treatment to assess responses by doing cultures monthly until conversion (World Health Organization, 2010). The status of early culture conversion has been widely used as an indicator of favorable treatment outcome and a cardinal index in monitoring treatment response (Kurbatova et al., 2012; Holtz et al., 2006). Culture conversion is reflected in two consecutive negative sputum cultures taken at least 30 days apart following an initial positive culture (WHO, 2017).

In general, culture conversion is used by clinicians in the management of patients with TB and MDR-TB therapeutically treated in any setting and is considered as the most essential interim efficacy indicator of treatment (Organization, 2000; Laserson et al., 2005). Therefore, predicting the initial time to culture conversion plays a vital role in planning and implementing respiratory isolation (Brown et al., 2016) to determine the duration of injectable agents and to ascertain the overall length of MDR-TB treatment (Taylor et al., 2005).

The known risk factors influencing delayed culture conversion are cavitary TB (Akalu et al., 2018; Bastard et al., 2019), smoking (Velayutham et al., 2016), body mass index (BMI) (Kurbatova et al., 2012; Velayutham et al., 2016; Magee et al., 2014), sputum smear grade (Akalu et al., 2018), age (Holtz et al., 2006), residence (Megerso, 2019), alcohol use (Akalu et al., 2018), type of resistance (Akalu et al., 2018), HIV status (Bastard et al., 2019; Shibabaw et al., 2018), and co-morbidities other than HIV (Shibabaw et al., 2018).

Culture conversion has not only been well investigated but also has been replete with inconsistent reported findings. Hence, we were motivated to conduct this systematic review and meta-analysis to improve MDR-TB treatment outcomes. Therefore, the aim of this study is to consider the evidence to estimate the pooled time to culture conversion and its associated factors, to enhance the utility of evidence in informing practice and policies for eastern Africa.

2. Methods

2.1. Source of information

Systematic review and meta-analysis from databases and the grey literature

2.2. Study settings

Eastern Africa is the part of sub-Saharan Africa including Eastern and Horn-of-Africa nations. The Eastern Africa region hosts seven of the world's top 30 tuberculosis burdened countries (Ethiopia, Kenya, Mozambique, Tanzania, Zambia, Zimbabwe, and Somalia) (WHO, 2015).

2.3. Searching strategies

Preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines were used to prepare and present this systematic review and meta-analysis (Liberati et al., 2009). To identify relevant articles, a comprehensive search was conducted from November 5 to December 27, 2019, in Cochrane Library, Web of Science (core collection), Scopus, PubMed, and Science Direct. Published and grey literature were searched using reference lists, conference presentations, and hand searches. Studies identified by our search strategy were retrieved and managed using Endnote X7 (Thomson Reuters, Philadelphia, PA, USA) software. During the search process, the authors used the following keywords and MeSH terms: sputum culture conversion AND multidrug-resistant pulmonary tuberculosis AND associated factors AND the 20 eastern African region countries, one by one.

2.4. Eligibility

All English language published and unpublished cohort study design studies reporting median time to culture conversion among adult (>18 years) MDR-TB patients in the Eastern Africa region.

Exclusion criteria: Case reports, national reports, clinical studies, reviews, and inaccessible articles leading to an inability to assess quality.

2.5. Outcomes and definitions

Time to sputum culture conversion was the time to achieve two consecutive negative sputum cultures taken 30 days apart after the initial positive culture. Mono-resistant TB is resistant to one first-line anti-TB drug only, whereas multi-resistant TB is resistant to at least both isoniazid and rifampicin; poly-resistant TB is resistant to more than one first-line anti-TB drug, other than both isoniazid and rifampicin. Favorable treatment outcomes include cure and treatment completion, while unfavorable treatment outcome includes treatment failure, death, and/or default.

2.6. Selection of studies and data management

References were stored and managed using Endnote X7. Two independent authors (DBK and MA) screened titles and abstracts of a random sample of 665 eligible studies generated by our search. Agreement on inclusion for a full-text screening of >80% between the two independent authors was considered as good (Feldmann et al., 2019), and the remaining references were divided among the authors for further screening and discussion with a third author (MAA) to find consensus as required.

2.7. Data extraction

Data extraction using a standardized Microsoft™ Excel data extraction tool was carried out by two independent authors (DBK and MA) for each study, and inconsistencies were resolved by consultation with a third author (MAA). In instances of duplicate/multiple reports of the same research and/or reporting the same follow-up time, we retained the article with the largest sample size for extraction. Treatment success (cure and treatment completion), death, lost to follow up (LTFU), failure (default), primary authors, publication year, study country, study design, mean age, sample size, median conversion time, and two-month culture conversion status were extracted.

2.8. Quality assessment

The quality of the included studies was assessed using a modified version of the Newcastle-Ottawa Scale (NOS) for cohort studies, which has three main sections with eight criteria (Wells, 2001). The first section scored, based on one to four stars, focuses on the selection. The second section of the tool considers the comparability of the study based on design, with a possibility of one star to be gained. The third and last section is concerned with outcomes with the possibility of three stars. Also, a quality appraisal of included studies was evaluated independently by two authors (CTL and DBK); any discrepancies were resolved by a third author (MAA). The studies that reached at least five stars on NOS criteria were considered high-quality studies and were included in this review.

2.9. Data processing and analysis

A Microsoft™ Excel spreadsheet form was used to present the extracted data from the primary studies, and further analysis was done by R Version 3.6.1 and Stata/se 14. Heterogeneity was assessed by computing p-values of Higgins's I^2 test statistics and Q-statistics among reported median time of culture conversion. The Higgins's I^2 statistic measures the difference between sample quartile estimation, which is due to heterogeneity due to random error rather than to sampling error. In this case, the pooled effect was estimated with a random-effects meta-analysis model. Subgroup analysis was computed to identify the possible sources of heterogeneity by considering sample size, country, and publication year. Median time was presented in quartile estimation, and the associated factors of

sputum culture conversion were determined by a log hazard ratio at a 95% level of significance.

3. Results

A total of 665 sputum culture conversion studies were extracted from the web-based databases. We excluded 466 articles due to duplication, and the remaining 199 studies were assessed for eligibility. In the next phase, 163 articles were removed after reading the title and abstract. Finally, nine of 36 articles were found eligible, accessible, and were included in the final analysis after reading the full text (Fig. 1).

3.1. Description of included studies

As described in Table 1, nine acceptable quality observational cohort articles with a total sample size of 2458 from five countries were included. The smallest sample size was 25 in Tanzania (Ndusilo et al., 2015), while the largest sample size was 634 in Mozambique (multicenter) (Bastard et al., 2019). Regarding the time to sputum culture conversion, the shortest was 34 days in Ethiopia (Megerso, 2019), while the longest was 90 days in Rwanda (Muvunyi et al., 2019).

3.2. Type of resistance and treatment outcomes

This meta-analysis found 45.6% mono resistant and 54.4% poly/multi-resistant TB cases (Figs. 2 and 3). As we have found from primary study reports, only baseline sputum smear grades before treatment were included. The status of sputum smear grade was 37% grade 1^+, 42.1% grade 2^+ and 21.9% grade 3^+. Favorable treatment outcomes of MDR-TB patients in the included studies were seen in 75% (95 CI: 61, 81) of cases, while 18% had unfavorable treatment outcomes (10% died, 7% defaulted and 1% treatment failure) (Fig. 4). Three quarters (75.4%) of the MDR-TB patients had culture conversion in the second month (Fig. 5).

3.3. Time to sputum culture conversion among MDR-TB patients in eastern Africa

The median time to sputum culture conversion was 61.2 days (IQR: 48.6–73.8) ($I^2 = 99.2\%$, p-value <0.001). The pooled median time of culture conversion in this meta-analysis showed high heterogeneity, according to the Higgins I^2 test ($I^2 = 99.2$, $p < 0.001$). Thus, we carried out a subgroup analysis to identify the sources of heterogeneity (Table 2).
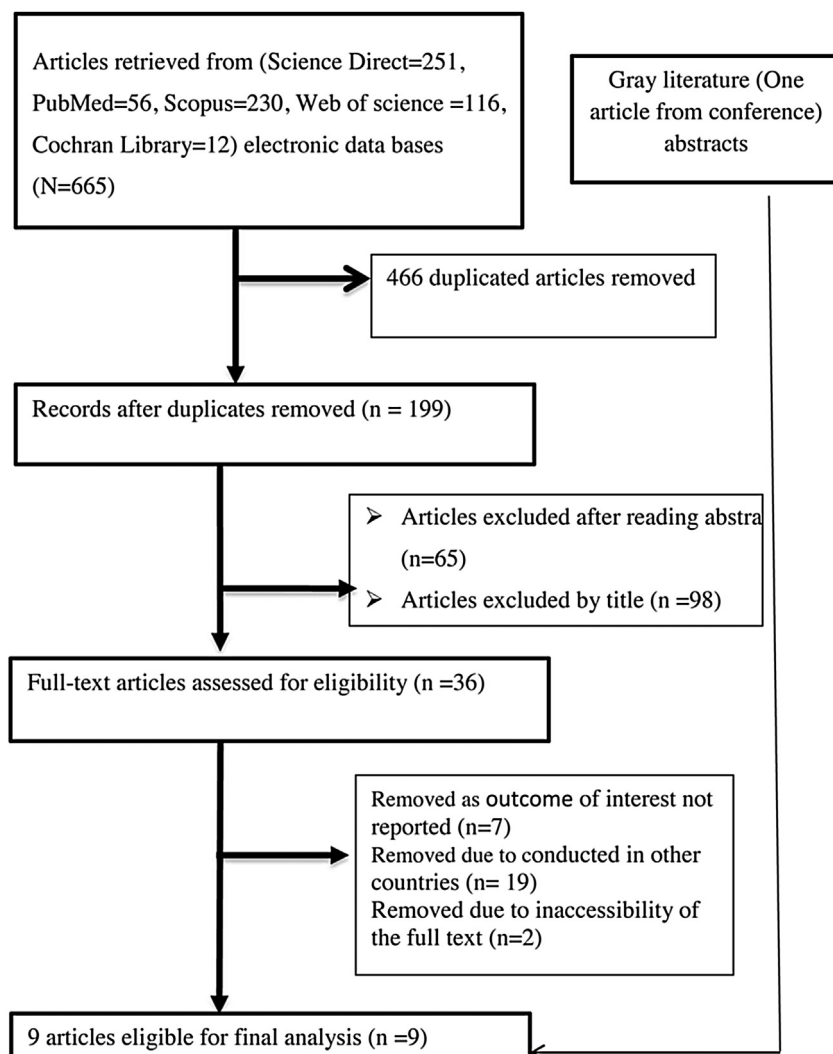

Fig. 1. Flow chart of selecting articles for systematic review and meta-analysis in eastern Africa.

Table 1
Descriptive summary of sputum culture conversion among MDR-TB patients in eastern Africa.

Authors	Publication (yr)	Country	Design	Mean age (yrs)	Sample	Median time (IQR)	2nd-month conversion (%)	Treatment outcomes		Resistant	
								Favorable	Unfavorable	Mono	Multi
Mpagama et al. (2013)	2013	Tanzania	Retrospective	NA	70	60 (30,90)	85	77	16	46	54
Ndusilo et al. (2015)	2015	Tanzania	Retrospective	37	25	45 (45,90)	84	72	28	84	16
Huerga et al. (2017)	2016	Kenya	Retrospective	29	125	60 (60,90)	74	66	20	NA	NA
Akalu et al. (2018)	2018	Ethiopia	Retrospective	29.5	392	65 (60,700)	56	58	19	51	49
Shibabaw et al. (2018)	2018	Ethiopia	Retrospective	30	235	72 (44,123)	NA	62	24	10	60
Megerso (2019)	2019	Ethiopia	Retrospective	28.5	513	34 (19,40)	84	NA	NA	NA	NA
Seung et al. (2019)	2019	Kenya & Ethiopia	Prospective	NA	325	42 (28,68)	NA	NA	4	28	72
Bastard et al. (2019)	2019	Mozanbique	Retrospective	35	634	88 (57,138)	76.8	73	28	59	41
Muvunyi et al. (2019)	2019	Rwanda	Retrospective	40	173	90 (30,210)	NA	87	12	19	81
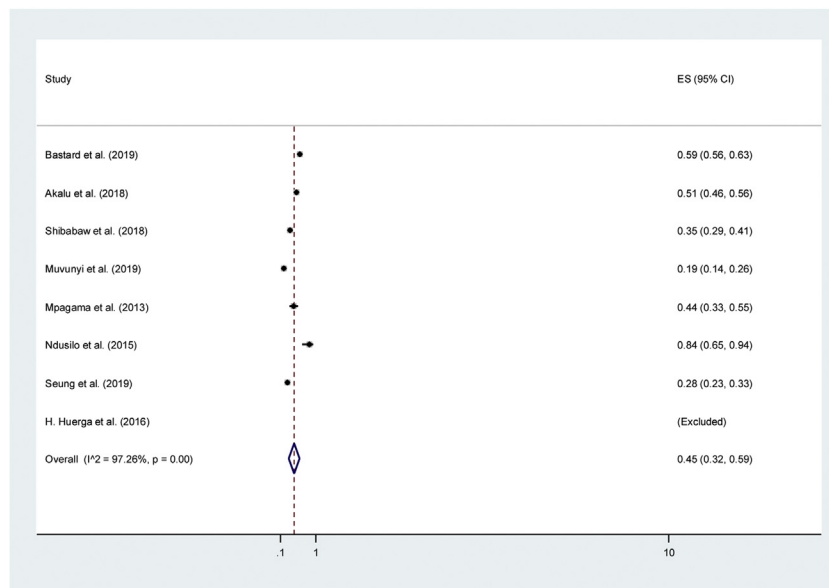
Fig. 2. Mono drug-resistant patients from systematic review and meta-analysis in eastern Africa.

3.4. Associated factors of MDR-TB culture conversion

In this study, the associated factors identified were cavitation, residence, cigarette smoking, alcohol use, body mass index (BMI), sputum smear grading, and type of resistance, HIV status, and co-morbidities other than HIV. However, only BMI was reported across three of the included studies and found to be statistically significant.

Mono-resistant TB with an odds ratio of 0.73 (95% CI: 0.42, 1.28), cigarette smoking with an odds ratio of 1.08 (95% CI: 0.61, 1.90), negative HIV status 0.63 (95% CI: 0.45, 0.86), co-morbidities other than HIV were reported in single studies, so we were not able to pool to generate the effect size of the factors on culture conversion.

The associations between cavitation, alcohol use, and urban residence with time to culture conversion were calculated from two studies. Thus, none of the three factors were found significantly associated with the time to culture conversion with a pooled ratio of 2.32 (95% CI: 0.96, 3.63), 1.11 (95% CI: 0.72, 1.51), and 1.15 (95% CI: 0.91, 1.41) respectively.

The association between BMI and time to culture conversion was calculated from three studies. The median time to culture conversion was three times more likely to be delayed among patients whose BMI was below 18.5 kg/m^2 compared to patients whose BMI was above 18.5 kg/m^2 (HR = 0.32, 95% CI: 0.15, 0.5) at a given follow-up time.

4. Discussion

In the Eastern African setting, there is a high burden of drug-resistant tuberculosis. This review aimed to further legitimize time to sputum culture conversion as a useful interim efficacy index and prognostic tool for monitoring treatment response and predicting treatment success in TB patients. Three-quarters of MDR-TB patients on treatment achieved favorable treatment outcomes (cure and treatment completed). In contrast, the proportion of unfavorable treatment outcome in this study was 18% which is consistent with the studies conducted in Nigeria (15%) (Oladimeji et al., 2014) and Botswana 17% (Hafkin et al., 2013) but lower than studies reported in South Africa (31.6%) (Seung et al., 2009) and

Fig. 3. Poly/multidrug-resistant patients from systematic review and meta-analysis in eastern Africa.
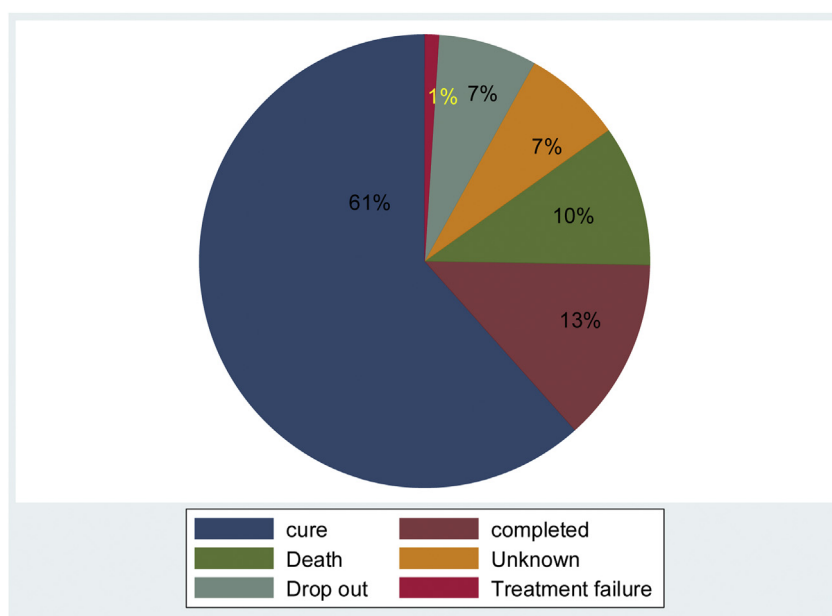

Fig. 4. Treatment outcomes of MDR-TB patients from systematic review and meta-analysis in eastern Africa.

India (38%) (Isaakidis et al., 2011). The observed differences might be due to sample size, study design, study period, or study setting – we used the pooled effect of five countries with different settings; also, other studies did consider unknown treatment outcomes.

The rate of culture conversion in the second month was 76%, and the median time was 61.2 days. The median time to sputum culture conversion is consistent with studies in Peru, 59 days (Tierney et al., 2014), South Korea, 56 days (Kim et al., 2016), Indonesia, 60 days (Putri et al., 2014), the Dominican Republic, 60 days (Rodriguez et al., 2013), Latvia, 60 days (Holtz et al., 2006) and Georgia, 68 days (Magee et al., 2014). Our finding showed a shorter duration than the studies conducted in Delhi, 91.3 days (Velayutham et al., 2016), and London, 91 days (Rieu et al., 2015). This variation could be explained by the sample size, study settings, methodology, and the time when they are conducted.

We have found low BMI as a significant factor for delayed sputum culture conversion. In our study, the likelihood of time to sputum culture conversion is prolonged in those with low BMI (i.e.,
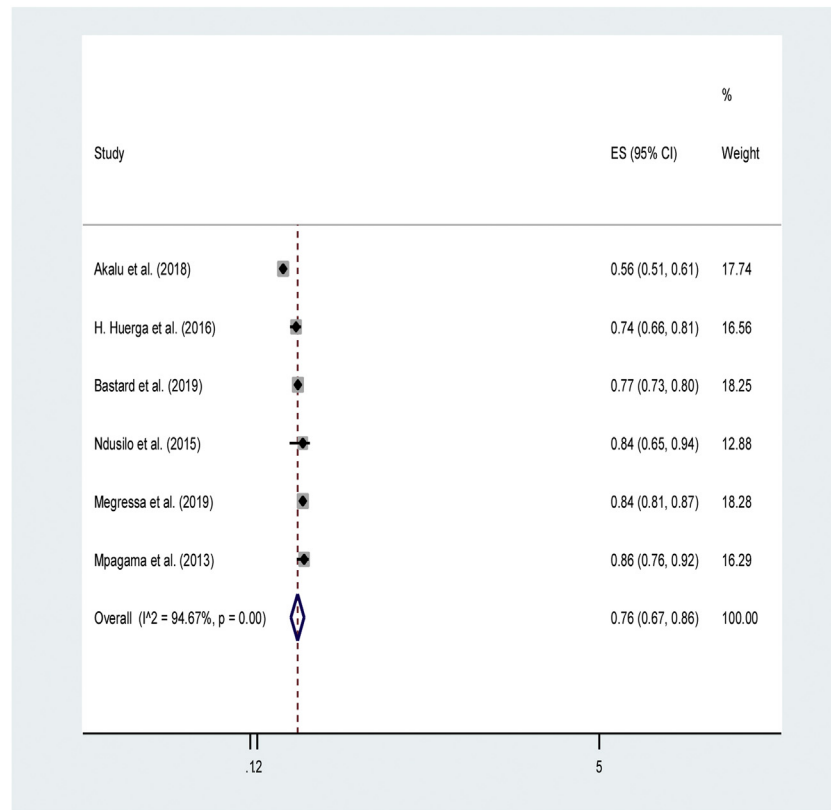
Fig. 5. Rate of second-month culture conversion among MDR-TB patients from systematic review and meta-analysis in eastern Africa.

Table 2
Subgroup analysis of sputum culture conversion among MDR-TB patients.

Variables	Characteristics	No articles included	Sample size	Median time (IQR)	p-value
Country of eastern Africa	Ethiopia	4	1491	52.9 (35.3, 70.6)	<0.001
	Tanzania	2	95	53.7 (39.2,68.22)	<0.001
	Kenya	2	450	50.9 (33.3,68.6)	<0.001
Sample size	Below median (263)	5	1864	(52.5,76.5)	<0.001
	Above median (263)	4	594	57.2 (33.4,81)	<0.001
Publication	Prior 2017	3	220	59 (54.3,63.6)	<0.001
	Post 2017	6	2238	64.3 (45.8,82.7)	<0.001

below 18.5 kg/m^2), a finding congruent with studies in Georgia (Magee et al., 2014), Delhi (Velayutham et al., 2016), Indonesia (Rodriguez et al., 2013), South Korea (Park et al., 2016), and five other low-income countries (Kurbatova et al., 2012). This variation could be due to BMI being a measure of the level of malnutrition. In patients with tuberculosis, malnutrition leads to a reduction in appetite, nutrient and micronutrient mal-absorption, and altered metabolism leading to wasting. Thus, malnourished tuberculosis patients have delayed recovery and higher mortality rates than well-nourished patients (Gupta et al., 2009) due to the suppression of immunity, leading to increased susceptibility to infectious and non-infectious diseases.

In general, early sputum culture conversion is an important index in monitoring treatment outcomes by increasing patients' comfort by shortening the intensive phase duration of injectable drugs and decreasing transmission of the disease when precautions are not adequate. Moreover, improved nutritional status and supplementation of patients will represent a novel approach for the rapid recovery of MDR-TB patients.

4.1. Limitation of the study

Only English language reports were considered in this study, which may have restricted the inclusion of some relevant eastern African studies. Some of the studies included in this review had a relatively small sample size, which may reduce generalizability. This meta-analysis represented only studies reported from five of 22 countries due to the unavailability of other studies.

5. Conclusion

The median time to sputum culture conversion was 61.2 days, which is a reasonably short time. Low BMI was the identified associated factor leading to delayed culture conversion. Therefore, there is a need for awareness on how to improve the nutritional status of multidrug-resistant tuberculosis patients through appropriate dietary supports.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

All available data are within the paper.

Competing interests

The authors declare that they have no competing interests.

Author contributions

MAA: conception of the research protocol, study design, literature review, data extraction, data analysis, interpretation, and drafting of the manuscript.

MA: study design, literature review, data extraction, data analysis, interpretation, and manuscript review.

CTL: data extraction, data analysis, quality assessment, interpretation, and manuscript review.

PMP: quality assessment and critically reviewed and validated the manuscript.

DBK: study design and contribute to data extraction, quality assessment, data analysis, and manuscript review. All authors have read and approved the manuscript.

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