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Prevalence of long-term physical sequelae among patients treated with multi-drug and extensively drug-resistant tuberculosis: a systematic review and meta-analysis

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Summary

Background Physical sequelae related to multi-drug resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are emerging and under-recognised global challenges. This systematic review and meta-analysis aimed to quantify the prevalence and the types of long-term physical sequelae associated with patients treated for MDR- and XDR-TB.

Methods We systematically searched CINAHL (EBSCO), MEDLINE (via Ovid), Embase, Scopus, and Web of Science from inception through to July 1, 2022, and the last search was updated to January 23, 2023. We included studies reporting physical sequelae associated with all forms of drug-resistant TB, including rifampicin-resistant TB (RR-TB), MDR-TB, Pre-XDR-TB, and XDR-TB. The primary outcome of interest was long-term physical sequelae. Meta-analysis was conducted using a random-effect model to estimate the pooled proportion of physical sequelae. The sources of heterogeneity were explored through meta-regression using study characteristics as covariates. The research protocol was registered in PROSPERO (CRD42021250909).

Findings From 3047 unique publications identified, 66 studies consisting of 37,380 patients conducted in 30 different countries were included in the meta-analysis. The overall pooled estimate was 44.4% (95% Confidence Interval (CI): 36.7–52.1) for respiratory sequelae, 26.7% (95% CI: 23.85–29.7) for hearing sequelae, 10.1% (95% CI: 7.0–13.2) for musculoskeletal sequelae, 8.4% (95% CI: 6.5–10.3) for neurological sequelae, 8.1% (95% CI: 6.3–10.0) for renal sequelae, 7.3% (95% CI: 5.1–9.4) for hepatic sequelae, and 4.5% (95% CI: 2.7–6.3) for visual sequelae. There was substantial heterogeneity in the estimates. The stratified analysis showed that the pooled prevalence of hearing sequelae was 26.6% (95% CI: 12.3–40.9), neurological sequelae was 31.5% (95% CI: 5.5–57.5), and musculoskeletal sequelae were 21.5% (95% CI: 9.9–33.1) for patients with XDR-TB, which were higher than the pooled prevalence of sequelae among patients with MDR-TB. Respiratory sequelae were the highest in low-income countries (59.3%) and after completion of MDR-TB treatment (57.7%).

Interpretation This systematic review found that long-term physical sequelae such as respiratory, hearing, musculoskeletal, neurological, renal, hepatic, and visual sequelae were common among survivors of MDR- and XDR-TB. There was a significant difference in the prevalence of sequelae between patients with MDR- and XDR-TB. Post-MDR- and XDR-TB treatment surveillance for adverse outcomes needs to be incorporated into the current programmatic management of MDR-TB to enable early detection and prevention of post-treatment sequelae.

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Keywords: Multidrug-resistant tuberculosis; Extensively drug-resistant tuberculosis; Physical sequelae; Systematic review; Meta-analysis

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Research in context

Evidence before this study

The burden of physical sequelae among Multidrug-Resistant Tuberculosis (MDR-TB) and Extensively Drug-Resistant Tuberculosis (XDR-TB) is expected to be higher than the burden from drug-susceptible tuberculosis (DS-TB) due to the high toxicity and longer duration of MDR- and XDR-TB treatment. We performed systematic searches in CINHAL (EBSCO), MEDLINE (via OVID), Embase, Scopus, and Web of Science databases from inception until July 01, 2022, without language restrictions using keywords related to "MDR-TB", "XDR-TB" and "sequelae". One meta-analysis combined with 131 studies showed that the global pooled prevalence of long-term disabilities among patients with DS-TB was 15–60%. Another meta-analysis reported the prevalence of mental health disorders, social stressors, and health-related quality of life in patients with MDR-TB. However, we did not identify any systematic review and meta-analysis that quantified the burden of long-term physical sequelae among patients with MDR-TB and XDR-TB only.

Added value of this study

The findings of our study showed that long-term physical sequelae (i.e., respiratory, hearing, musculoskeletal, neurological, renal, hepatic, and visual sequelae) were frequent among survivors of MDR- and XDR-TB. We found that the risk of developing physical sequelae was much higher among patients with XDR-TB than among patients with MDR-TB.

Implications of all the available evidence

Our study findings highlight the prevalence of physical sequelae among survivors of MDR- and XDR-TB. The strong relationship between the burden of long-term physical sequelae and the timing after completion of treatment indicates the need for incorporating post-MDR- and XDR-TB treatment surveillance into the current programmatic management of MDR-TB.

Introduction

Globally, Multidrug-resistant tuberculosis (MDR-TB) and Extensively Drug-Resistant Tuberculosis (XDR-TB) pose a major threat to human health. Patients treated with MDR/XDR-TB are at higher risk of long-term sequelae, which arise because of the disease process or side effects related to the use of second-line drugs.[1] For instance, respiratory sequelae are mainly caused by the progression of the disease process.[2,3] On the other hand, hearing sequelae is mainly drug-related sequelae, particularly to aminoglycoside agents such as Kanamycin, Amikacin, and Capreomycin.[4] One challenge to tackling MDR/XDR-TB sequelae is a lack of understanding of the burden of the problem, as there is no routine post-treatment follow-up done as part of the surveillance system, and data are sparse.[5] The current World Health Organization (WHO) guidelines for MDR-TB management define 'treatment success' using microbiological outcomes and survival only. Moreover, MDR/XDR-TB-associated morbidity remains solely focused on the period before and during treatment. The global End-TB strategies neglect post-treatment care and a lack of follow-up to TB or MDR-TB survivors after treatment completion.

The treatment of MDR/XDR-TB requires the use of second-line TB medicines, which provided for longer than drug-susceptible (DS)-TB (nine months to two years for MDR-TB, compared to six to nine months) and include medicines that cause serious adverse events. Therefore, the burden of physical sequelae is thought to be higher in patients with MDR- and XDR-TB than in patients with DS-TB,[6] although this has not been empirically quantified. Physical sequelae related to MDR/XDR-TB also vary according to the affected body site. For example, people with a history of pulmonary MDR-TB would suffer from a range of long-lasting respiratory sequelae: Chronic Obstructive Pulmonary Disease (COPD), bronchiectasis, chronic pulmonary aspergillosis, pulmonary hypertension, and pulmonary fibrosis.[7–11] Spinal MDR-TB can result in paraparesis and quadriparesis that occurs due to spinal deformity and damage to the neural structures, resulting in permanent physical sequelae.[12,13]

Long-term sequelae increase the risk of permanent disability, premature mortality, ongoing stigma, and poor quality of life.[14] Previous studies demonstrated that the prevalence of long-term physical sequelae: respiratory, visual, neurological, and hearing sequelae, and mental health disorders were frequently reported among patients with DS-TB.[15,16] Studies have also estimated end-of-treatment outcomes for MDR/XDR-TB in specific locations.[17–19] There are also systematic reviews and modeling studies investigating the burden of long-term sequelae among DS-TB. A recently published report by Alene et al. on the global burden of TB-related disability showed that the prevalence of respiratory function sequelae among survivors of TB ranged from 15 to 60%.[20] However, previous studies were mainly focused on DS-TB and presented single estimates only for MDR-TB, without stratified the analysis by study level characteristics. Moreover, the previous systematic review by Alene et al. did not cover physical sequelae among patients with XDR-TB, and included studies only published in English and reported data from 2000 to 2019. To our knowledge, there has not been a comprehensive study estimating the global prevalence and identifying the common types of physical sequelae following MDR- and XDR-TB treatment.

Quantifying the burden and identifying the type of sequelae arising as a result of MDR/XDR-TB or their medications are essential to inform service providers and policymakers, particularly in countries where MDR- and XDR-TB are common, in the design of effective preventive strategies.[21] Therefore, we conducted this systematic review and meta-analysis to estimate the pooled proportion of long-term sequelae and identify the most common types of sequelae among patients with MDR- and XDR-TB.

Methods

Search strategy and selection criteria

We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[22] The research protocol was registered in PROSPERO (CRD42021250909). We searched CINAHL(EBSCO), MEDLINE (via Ovid), PsycINFO, Embase, and Web of science for articles without restrictions on language, geography, or year of publication from the inception of each database to 01 July 2022. The last search was updated to 23 January 2023 to identify studies published since our initial search. We used relevant Medical Subject Heading (MeSH) headings and keywords for DR-TB and sequelae. Reference lists of included studies were checked for additional studies. Additionally, we searched the grey literature using the Google search engine. Corresponding authors were contacted by email when additional information was required. Our search strategy was developed by consulting a medical librarian. A detailed summary of all search terms can be found in Supplementary Information (Supplementary file: Table S1).

Study selection and eligibility criteria

Studies were eligible for inclusion if they reported any types of physical sequelae among patients with MDR- or XDR-TB. Studies that reported at least one of the primary outcomes (i.e., physical sequelae with a permanent residual effect, which could include respiratory sequelae, radiological abnormalities, hearing sequelae, renal sequelae, hepatic sequelae, blindness, neurological or other abnormalities). Mental health sequelae were not included as they were outside the scope of this study and will be considered in further research. All relevant studies reporting permanent or long-term physical sequelae were included in the study. Studies reporting temporary side effects of medications only were excluded. We also excluded case reports, case series, correspondence, reviews, abstracts, and animal studies. Studies conducted only on drug-susceptible TB or latent TB were also excluded. We used Google Translate for non-English language articles.

Outcomes of the study

The primary outcome of interest was the prevalence of any form of physical sequelae that occurred due to MDR/XDR-TB or its medication, which included but was not limited to hearing sequelae, respiratory sequelae, renal sequelae, neurological sequelae, visual sequelae, hepatic sequelae, and musculoskeletal sequelae. The primary outcome was measured as the proportion of patients with MDR and/or XDR-TB who developed any form of physical sequelae. The definition of each physical sequelae is summarised in the supplementary document (Supplementary file: Table S2).

Data extraction

All articles identified through our search strategies were imported into an EndNote Library (Thomson Reuters, London) and all duplicates were removed. The articles were then exported to Rayyan software for screening. Two reviewers (TYA and HFW) independently screened the titles, abstracts, and full texts to identify eligible studies. Differences were resolved by discussion with a third reviewer (KAA). Data from the included studies were independently extracted by the same two investigators, and information was collected in a Microsoft Excel (version 2014) spreadsheet. We collected information about the characteristics of the studies (the name of the first author, year of publication, country of the study, study setting, and study design), characteristics of the participants (study population such as MDR-TB, XDR-TB, or both, mean or median age, the proportion of participants who were male, sample size, type of MDR/XDR-TB medications, duration of treatments, and comorbidities, including HIV and diabetes mellitus (DM)), and outcomes of interest (type of physical sequelae, and the proportion of people with the sequela).

Quality assessment

The quality of the included studies was assessed by the same two researchers (TYA and HFW). The Newcastle–Ottawa Scale (NOS) was used to assess the methodological quality and risk of bias for cohort and case–control studies and a modified version was used for cross-sectional studies.[23] The tools contained criteria for the selection of study groups (4 points), comparability of groups (2 points), and ascertainment of the outcome of interest (3 points). The tools allocated scores ranging from zero to nine, with low (1–4), medium (5–7), and high (8–9) quality groupings.

Data synthesis

Owing to the heterogeneity between studies, meta-analysis was performed using random-effects models for each of the long-term sequelae when two or more studies were available for the outcome of interest. The pooled prevalence and 95% confidence intervals (CI) were presented as summary effect estimates for each type of sequelae. The sources of heterogeneity were explored through meta-regression using study characteristics as covariates. An adjusted odds ratio with a 95% CI was used to interpret the findings. Sub-group analysis was conducted by drug-resistant type, region, the timing of sequelae, study design, countries' income level, and HIV prevalence. We assessed publication bias by visual inspection of funnel plots and Egger's regression test. The analyses were performed by STATA version 17 software. Finally, sensitivity analysis was performed by trimming low-quality studies.

Ethics
Ethical review was not applicable since it was a systematic review and meta-analysis of the data from published literature.

Role of the funding source
The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Search results
A total of 5498 records were identified from the database searches. After removing duplicates, 3047 unique publications were screened by title and abstract and 247 publications were eligible for full-text review. After a full-text review, 66 publications (comprising 184 datasets)[3,7,11,24–86] including data on 37,380 patients were included (Fig. 1).

Characteristics of included studies
The characteristics of the included studies are summarised in Table 1. The studies were conducted in 30 different countries and the data were collected from 1995 to 2022. Among the included studies, 30 (16.3%) studies were from India, 29 (15.8%) were from South Africa, and 15 (8.2%) were from China. The mean/median age of study participants was 35.66 years, with a standard deviation of 9.8 years. Nearly two-thirds (63.3%) of cases were males. Nearly two-thirds (64.1%, n = 118) of studies included MDR-TB only, 14.7% (n = 27) of studies included both MDR- and XDR-TB, 11.4% (n = 21) of studies were unclassified, and 9.8% (n = 18) of studies included XDR-TB only.

Approximately half of the studies (46.7%, n = 86) included patients with pulmonary MDR/XDR-TB only (25.0%, n = 46) studies included both pulmonary and extrapulmonary, and 3 (1.6%) studies included extrapulmonary MDR/XDR-TB only. However, 49 (26.6%) studies did not mention the affected body sites. The HIV status of study participants was reported in 72.3% (n = 133) of studies, and the prevalence of HIV infection in these studies varied from 0% to 100%. The review showed that 9.8% (n = 18) of studies were reported from Low-Income Countries (LICs). The majority, 44.0% (n = 81) and 37.0% (n = 68) studies were reported from lower-middle-income countries (LMICs) and upper-middle-income countries (UMICs), respectively. All the studies reported the timing of sequelae, and most studies (92.4%, n = 170) reported that sequelae occurred during treatment. Only 58 (31.5%) of included articles had data on the duration of treatment (Table 1).

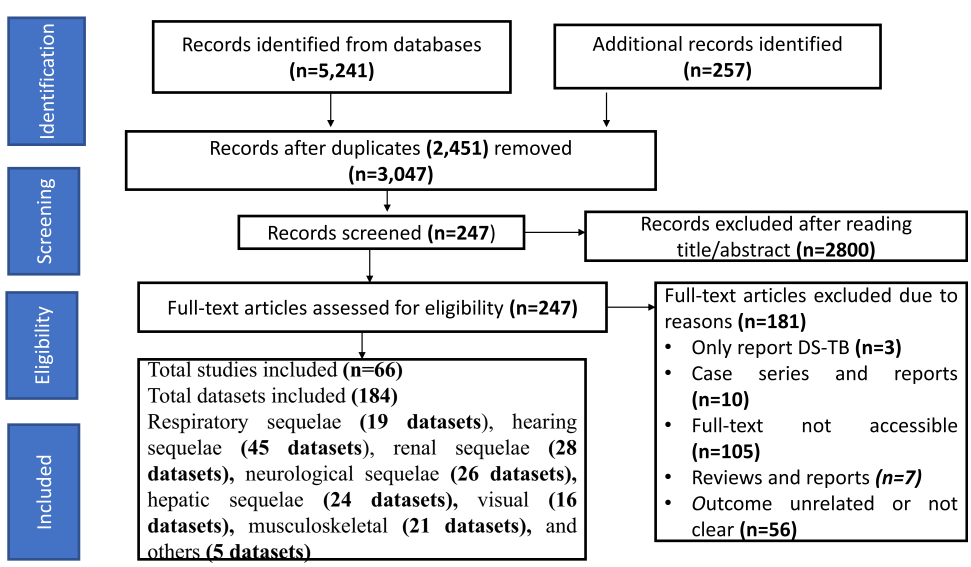

Fig. 1: **Study profile**. DS-TB = drug susceptible tuberculosis.

First Author	Publication year	Country	Country income	Type of DR-TB	Year of data collection	Study design	Male proportion (%)	Mean age (years)	Sample size (n)
Respiratory sequelae									
Anthony et al.	2017	Peru	UMICs	MDR-TB	2014	Prospective cohort	57.6	29	33
Godoy et al.	2012	Brazil	UMICs	MDR-TB	2008–2012	Cross-sectional	67	43.7	18
Muñoz et al.	2020	Multicounty	UMICs	MDR- & XDR-TB	2014–2019	Cross-sectional	59.3	43.7	27
Murniati et al.	2020	Indonesia	LMICs	MDR- & XDR-TB	2017	Cross-sectional	51.7	42.3	60
Edwin et al.	2020	Uganda	LICs	MDR-TB	2018	Cross-sectional	60	39	95
Sana et al.	2017	Pakistan	LMICs	MDR-TB	2014–2015	Cohort	78.5	45.5	100
Neeta et al.	2009	India	LMICs	MDR-TB	2009	Cross-sectional	55.6	33.5	51
Rupak et al.	2018	India	LMICs	MDR-TB		Cross-sectional	54.3	27.6	46
Syed et al.	2021	Pakistan	LMICs	MDR- & XDR-TB	2014–2017	Retrospective cohort	NA	NA	19
Sergo et al.	2019	Georgia	UMICs	MDR- & XDR-TB		Cross-sectional	57	31	58
Geerligs et al.	2000	Netherlands	HICs	MDR-TB	1985–1999	Retrospective cohort	70.5	33	44
Piubella et al.	2014	Niger	LICs	MDR-TB	2008–2010	Prospective cohort	81.5	31	65
Nianlan et al.	2022	China	UMICs	Unclassified	2008–2017	Retrospective cohort	61.2	45.8	516
Farouq et al.	2021	Nigeria	LMICs	Unclassified	2018–2020	Prospective cohort	87.2	32	39
Atif et al.	2017	India	LMICs	MDR-TB	2010–2014	Retrospective cohort	71.2	35.7	147
Gina et al.	2019	Italy	HICs	MDR- & XDR	2008–2016	Retrospective cohort	58.1	32	74
Aziz et al.	2018	Indonesia	LMICs	MDR-TB	2013–2015	Cross-sectional	52	39.9	183
Duo et al.	2017	China	UMICs	MDR-TB	2012–2016	Retrospective cohort	65.2	39	89
Oladimeji et al.	2022	Nigeria	LMICs	MDR- & XDR	2010–2016	Retrospective cohort	66.93	NA	2555
Hearing impairment									
Sana et al.	2017	Pakistan	LMICs	MDR-TB	2014–2015	Cohort	78.5	45.5	100
Sagwa et al.	2016	Nambia	UMICs	MDR-TB	2015	Cross-sectional	56	45.5	36
Delicia et al.	2016	South Africa	UMICs	MDR-TB	NA	Cohort	52	34	52
Jager et al.	2001	Netherlands	HICs	MDR-TB	1995–2000	Retrospective cohort	73.6	35.7	110
Geerligs et al.	2000	Netherlands	HICs	MDR-TB	1985–1998	Retrospective cohort	70.5	33	44
Chawangwa et al.	2014	Botswana	UMICs	MDR-TB	2006–2012	Retrospective cohort	55	38	437
Kiran et al.	2018	India	LMICs	MDR-TB	2014–2015	Retrospective cohort	66.7	32	108
Piubella et al.	2014	Niger	LICs	MDR-TB	2008–2010	Prospective cohort	81.5	31	65
Rajendra et al.	2015	India	LMICs	MDR-TB	2009–2010	Prospective cohort	69.4	29.3	98
Lebogang et al.	2012	South Africa	UMICs	MDR & XDR	Not reported	Cross-sectional	49.1	33	53
Sagwa et al.	2015	Namibia	UMICs	MDR-TB	2004–2014	Retrospective cohort	56.1	36.5	353
Hind et al.	2012	Lesotho	LMICs	MDR-TB	2007–2011	Retrospective cohort	53	8	19
Kathryn et al.	2016	South Africa	UMICs	MDR-TB	2012–2014	Retrospective cohort	49	35	94
Usha et al.	2020	India	LMICs	MDR-TB	2017–2018	Retrospective cohort	73.6	44.97	110
Karen et al.	2013	South Africa	UMICs	XDR-TB	2014–2015	Retrospective cohort	NA	NA	115
Yang et al.	2017	China	UMICs	MDR-TB	2009–2016	Retrospective cohort	73.2	44	751
Sen et al.	2020	China	UMICs	MDR-TB	1999–2015	Retrospective cohort	68.6	31.2	272
Pelden et al.	2021	Bhutan	LMICs	MDR-TB	2018–2019	Prospective cohort	47.6	28.3	42
Alexander et al.	2021	Uzbekistan	LMICs	MDR-TB	2018–2020	Retrospective cohort	70.5	45.6	45
Olusola et al.	2017	Nigeria	LMICs	Unclassified	2014–2015	Prospective cohort	65.9	34.5	132
Olusola et al.	2017	Nigeria	LMICs	Unclassified	2014–2015	Prospective cohort	62.9	34.6	70
Jonathan et al.	2020	South Africa	UMICs	MDR-TB	2011–2015	Prospective cohort	36	33	174
Amber et al.	2017	UK	HICs	MDR & XDR-TB		Retrospective cohort	68	28	93
Muhammad et al.	2017	Pakistan	LMICs	MDR- & XDR-TB	2014–2015	Retrospective cohort	53.8	37.2	80
Parvaneh et al.	2011	Iran	LMICs	MDR-TB	2006–2009	Retrospective cohort	55	40.6	80
Buziashvili et al.	2019	Georgia	UMICs	MDR- & XDR-TB	2010–2012	Retrospective cohort	65	35.3	147
Atif et al.	2017	India	LMICs	MDR-TB	2010–2015	Retrospective cohort	71.2	35.7	147
Safurah et al.	2021	India	LMICs	MDR-TB	2015–2018	Prospective cohort	76	40.3	400
Jing et al.	2021	China	UMICs	MDR- & XDR-TB	2018–2020	Prospective cohort	70	36	1162
Gina et al.	2019	Italy	HICs	MDR- & XDR-TB	2008–2016	Retrospective cohort	58.1	32	74
Harouna et al.	2019	Niger	LICs	MDR-TB	2008–2013	Retrospective cohort	82.5	31	120
Hong et al.	2020	South Africa	UMICs	MDR-TB	2014–2017	Prospective cohort	54	35	1315
Huerga et al.	2017	Kenya	LMICs	MDR-TB	2006–2012	Retrospective cohort	55	29	169

(Table 1 continues on next page)

First Author	Publication year	Country	Country income	Type of DR-TB	Year of data collection	Study design	Male proportion (%)	Mean age (years)	Sample size (n)
(Continued from previous page)									
Petros et al.	2011	India	LMICs	MDR-TB	2007–2011	Prospective cohort	56	35	71
Kalpesh et al.	2013	India	LMICs	MDR-TB	2009–2011	Prospective cohort	62	31.4	130
Innocent et al.	2020	DR. Congo	LICs	XDR-TB	2015–2017	Retrospective cohort	56.3	32.4	32
Kuban et al.	2015	Cameroon	LMICs	MDR-TB	2008–2012	Prospective cohort	51.3	33.7	106
Ronnie et al.	2020	Zimbabwe	LMICs	MDR-TB	2010–2015	Retrospective cohort	48.6	34	473
Nair et al.	2017	India	LMICs	MDR-TB	2009–2011	Retrospective cohort	68	NA	788
Seda et al.	2021	Turkey	UMICs	MDR-TB	2011–2018	Retrospective cohort	73.2	75.9	13
Nesri et al.	2020	South Africa	UMICs	XDR-TB	2014–2015	Prospective cohort	47.7	33	151
Natasha et al.	2021	Canada	HICs	MDR- & XDR-TB	2010–2016	Retrospective cohort	55	31	49
Sagwa et al.	2012	Namibia	UMICs	XDR-TB	2008–2010	Cross-sectional	64	34.7	59
Koirala et al.	2021	Nepal	LMICs	MDR-TB	2018–2020	Prospective cohort	71.8	34	301
Vishal et al.	2016	India	LMICs	MDR-TB	2012–2014	Prospective cohort	66.7	37.5	100
Renal impairment									
Sana et al.	2017	Pakistan	LMICs	MDR-TB	2014–2015	Cohort	78.5	45.5	100
Jager et al.	2001	Netherlands	HICs	MDR-TB	1995–2001	retrospective cohort	73.6	37.7	110
Geerligs et al.	2000	Netherlands	HICs	MDR-TB	1985–1998	retrospective cohort	70.5	33	44
Rajendra et al.	2016	India	LMICs	MDR-TB	2009–2010	Prospective cohort	69.4	29.3	98
Hind et al.	2012	Lesotho	LMICs	MDR-TB	2007–2011	retrospective cohort	53	8	19
Karen et al.	2013	South Africa	UMICs	XDR-TB	2002–2008	retrospective cohort	NA	NA	115
Yang et al.	2017	China	UMICs	MDR-TB	2009–2016	Retrospective cohort	73.2	44	751
Aleksande et al.	2021	Uzbekistan	LMICs	MDR-TB	2018–2020	Retrospective cohort	70.5	45.6	45
Ilse et al.	2020	South Africa	UMICs	MDR-TB	2018–2019	Retrospective cohort	59.8	35	62
Jonathan et al.	2021	South Africa	UMICs	MDR-TB	2011–2016	Prospective cohort	36	33	206
Muhammad et al.	2017	Pakistan	LMICs	MDR- & XDR-TB	2014–2015	Retrospective cohort	53.8	37.2	80
Mehari et al.	2019	Ethiopia	LICs	MDR- & XDR-TB	2010–2017	Retrospective cohort	56.8	28	570
Parvaneh et al.	2011	Iran	LMICs	MDR-TB	2006–2009	Retrospective cohort	55	40.6	80
Mariana et al.	2021	Georgia	UMICs	MDR-& XDR-TB	2016–2018	Retrospective cohort	78.3	39.6	73
Buziashvili et al.	2019	Georgia	UMICs	MDR- & XDR-TB	2010–2012	Retrospective cohort	65	35.3	147
Safurah et al.	2021	India	LMICs	MDR-TB	2015–2020	Prospective cohort	76	40.3	400
Jing et al.	2021	China	UMICs	MDR- & XDR-TB	2018–2020	Prospective cohort	70	36	1162
Gina et al.	2019	Italy	HICs	MDR- & XDR-TB	2008–2016	Retrospective cohort	58.1	32	74
Harouna et al.	2019	Niger	LICs	MDR-TB	2008–2013	Retrospective cohort	82.5	31	120
Hong et al.	2020	South Africa	UMICs	MDR-TB	2014–2017	Prospective cohort	54	35	1313
Huerga et al.	2017	Kenya	LMICs	MDR-TB	2006–2012	Retrospective cohort	55	29	169
Petros et al.	2011	India	LMICs	MDR-TB	2007–2011	Prospective cohort	56	35	71
Jackie et al.	2019	South Africa	UMICs	Unclassified	2015–2016	Retrospective cohort	38	30	32
Nair et al.	2017	India	LMICs	MDR-TB	2009–2011	Retrospective cohort	68	NA	788
Seda et al.	2021	Turkey	UMICs	MDR-TB	2011–2018	Retrospective cohort	73.2	75.9	13
Nesri et al.	2020	South Africa	UMICs	XDR-TB	2014–2015	Prospective cohort	47.7	33	151
Natasha et al.	2021	Canada	HICs	MDR-& XDR-TB	2010–2016	Retrospective cohort	55	31	49
Yimer et al.	2019	Ethiopia	LICs	MDR-TB	2012–2014	Cross-sectional	53.6	32.7	250
Neurological impairment									
Geerligs et al.	2000	Netherlands	HICs	MDR-TB	1985–1998	retrospective cohort	70.5	33	44
Rajendra et al.	2016	India	LMICs	MDR-TB	2009–2010	Prospective cohort	69.4	29.3	98
Hind et al.	2012	Lesotho	LMICs	MDR-TB	2007–2011	retrospective cohort	53	8	19
Karen et al.	2013	South Africa	UMICs	XDR-TB	2002–2008	retrospective cohort	NA	NA	115
Yang et al.	2017	China	UMICs	MDR-TB	2009–2016	Retrospective cohort	73.2	44	751
Sen et al.	2019	China	UMICs	MDR-TB	199–2015	retrospective cohort	68.6	31.2	272
Ilse et al.	2020	South Africa	UMICs	MDR-TB	2018–2019	retrospective cohort	59.8	35	62
Muhammad et al.	2017	Pakistan	LMICs	MDR- & XDR-TB	2014–2015	retrospective cohort	53.8	37.2	80
Mehari et al.	2019	Ethiopia	LICs	MDR- XDR-TB	2010–2017	retrospective cohort	56.8	28	570
Parvaneh et al.	2011	Iran	LMICs	MDR-TB	2006–2009	retrospective cohort	55	40.6	80
Mariana et al.	2021	Georgia	UMICs	MDR- & XDR-TB	2016–2020	retrospective cohort	78.3	39.6	73

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First Author	Publication year	Country	Country income	Type of DR-TB	Year of data collection	Study design	Male proportion (%)	Mean age (years)	Sample size (n)
(Continued from previous page)									
Farouq et al.	2021	Nigeria	LMICs	Unclassified	2018–2020	Prospective cohort	87.2	32	39
Safurah et al.	2021	India	LMICs	MDR-TB	2015–2019	Prospective cohort	76	40.3	400
Jing et al.	2021	China	UMICs	MDR- & XDR-TB	2018–2020	Prospective cohort	70	36	1162
Gina et al.	2019	Italy	HICs	MDR- & XDR-TB		retrospective cohort	58.1	32	74
Harouna et al.	2019	Niger	LICs	MDR-TB	2008–2013	retrospective cohort	82.5	31	120
Huerga et al.	2017	Kenya	LMICs	MDR-TB	2006–2012	retrospective cohort	55	29	169
Petros et al.	2011	India	LMICs	MDR-TB	2007–2011	Prospective cohort	56	35	71
Kalpesh et al.	2013	India	LMICs	MDR-TB	2009–2011	Prospective cohort	62	31.4	130
Innocent et al.	2020	DR. Congo	LICs	XDR-TB	2015–2017	retrospective cohort	56.3	32.4	32
Ronnie et al.	2020	Zimbabwe	LMICs	MDR-TB	2010–2015	retrospective cohort	48.6	34	473
Olatunde et al.	2019	South Africa	UMICs	XDR-TB	2014–2018	Prospective cohort	61.9	37	63
Seda et al.	2021	Turkey	UMICs	MDR-TB	2011–2018	retrospective cohort	73.2	75.9	13
Nesri et al.	2020	South Africa	UMICs	XDR-TB	2014–2015	Prospective cohort	47.7	33	151
Sagwa et al.	2012	Namibia	UMICs	MDR- & XDR-TB	2008–2010	Cross-sectional	64	34.7	59
Yimer et al.	2019	Ethiopia	LICs	MDR-TB	2012–2014	Cross-sectional	53.6	32.7	250
Hepatic impairment									
Sana et al.	2017	Pakistan	LMICs	MDR-TB	2014–2015	Cohort	78.5	45.5	100
Geerligs et al.	2000	Netherlands	HICs	MDR-TB	1985–1998	Retrospective cohort	70.5	33	44
Kiran et al.	2018	India	LMICs	MDR-TB	2014–2015	Retrospective cohort	66.7	32	108
Hind et al.	2012	Lesotho	LMICs	MDR-TB	2007–2011	Retrospective cohort	53	8	19
Yang et al.	2017	China	UMICs	MDR-TB	2009–2016	Retrospective cohort	73.2	44	751
Sen et al.	2019	China	UMICs	MDR-TB	1999–2015	Retrospective cohort	68.6	31.2	272
Aleksandr et al.	2021	Uzbekistan	LMICs	MDR-TB	2018–2020	Retrospective cohort	70.5	45.6	45
Ilse et al.	2020	South Africa	UMICs	MDR-TB	2018–2019	Retrospective cohort	59.8	35	62
Muhammad et al.	2017	Pakistan	LMICs	MDR- & XDR-TB	2014–2015	Retrospective cohort	53.8	37.2	80
Parvaneh et al.	2011	Iran	LMICs	MDR-TB	2006–2009	Retrospective cohort	55	40.6	80
Mariana et al.	2021	Georgia	UMICs	MDR- & XDR-TB	2016–2018	Retrospective cohort	78.3	39.6	73
Atif et al.	2017	India	LMICs	MDR-TB	2010–2016	Retrospective cohort	71.2	35.7	147
Jing et al.	2021	China	UMICs	MDR- & XDR-TB	2018–2020	Prospective cohort	70	36	1162
Gina et al.	2019	Italy	HICs	MDR- & XDR-TB	2008–2016	Retrospective cohort	58.1	32	74
Kalpesh et al.	2013	India	LMICs	MDR-TB	2009–2011	Prospective cohort	62	31.4	130
Innocent et al.	2020	DR. Congo	LICs	XDR-TB	2015–2017	Retrospective cohort	56.3	32.4	32
Keshavjee et al.	2013	India	LMICs	MDR-TB	2000–2004	Retrospective cohort	82	34	568
Ronnie et al.	2020	Zimbabwe	LMICs	MDR-TB	2010–2015	Retrospective cohort	48.6	34	473
Nair et al.	2017	India	LMICs	MDR-TB	2009–2011	Retrospective cohort	68	NA	788
Seda et al.	2021	Turkey	UMICs	MDR-TB	2011–2018	Retrospective cohort	73.2	75.9	13
Nesri et al.	2021	South Africa	UMICs	XDR-TB	2014–2015	Prospective cohort	47.7	33	151
Sagwa et al.	2012	Namibia	UMICs	MDR- & XDR	2008–2010	Cross-sectional	64	34.7	59
Yimer et al.	2019	Ethiopia	LICs	MDR-TB	2012–2014	Cross-sectional	53.6	32.7	250
Koirala et al.	2021	Nepal	LMICs	MDR-TB	2018–2019	Prospective cohort	71.8	34	301
Visual impairment									
Sana et al.	2017	Pakistan	LMICs	MDR-TB	2014–2015	Cohort	78.5	45.5	100
Geerligs et al.	2000	Netherlands	HICs	MDR-TB	1985–1998	Retrospective cohort	70.5	33	44
Hind et al.	2012	Lesotho	LMICs	MDR-TB	2007–2011	Retrospective cohort	53	8	19
Karen et al.	2013	South Africa	UMICs	Unclassified	2002–2008	Retrospective cohort	NA	NA	115
Yang et al.	2017	China	UMICs	MDR-TB	2009–2016	Retrospective cohort	73.2	44	751
Aleksandr et al.	2021	Uzbekistan	LMICs	MDR-TB	2018–2020	Retrospective cohort	70.5	45.6	45
Ilse et al.	2020	South Africa	UMICs	MDR-TB	2018–2019	Retrospective cohort	59.8	35	62
Jonathan et al.	2021	South Africa	UMICs	MDR-TB	2011–2018	Prospective cohort	36	33	187
Farouq et al.	2021	Nigeria	LMICs	Unclassified	2018–2020	Prospective cohort	87.2	32	39
Atif et al.	2017	India	LMICs	Unclassified	2010–2013	Retrospective cohort	71.2	35.7	147
Harouna et al.	2019	Niger	LICs	MDR-TB	2008–2013	Retrospective cohort	82.5	31	120
Innocent et al.	2020	DR. Congo	LICs	XDR-TB	2015–2017	Retrospective cohort	56.3	32.4	32

(Table 1 continues on next page)

First Author	Publication year	Country	Country income	Type of DR-TB	Year of data collection	Study design	Male proportion (%)	Mean age (years)	Sample size (n)
(Continued from previous page)									
Ronnie et al.	2020	Zimbabwe	LMICs	MDR-TB	2010–2015	Retrospective cohort	48.6	34	473
Seda et al.	2021	Turkey	UMICs	MDR-TB	2011–2018	Retrospective cohort	73.2	75.9	13
Nesri et al.	2020	South Africa	UMICs	XDR-TB	2014–2015	Prospective cohort	47.7	33	151
Sagwa et al.	2012	Namibia	UMICs	MDR- & XDR-TB	2008–2010	Cross-sectional	64	34.7	59
Musculoskeletal impairment									
Safurah et al.	2021	India	LMICs	MDR-TB	2015–2021	Prospective cohort	76	40.3	400
Gina et al.	2019	Italy	HICs	MDR- & XDR-TB	2008–2016	Retrospective cohort	58.1	32	74
Kalpesh et al.	2013	India	LMICs	MDR-TB	2009–2011	Prospective cohort	62	31.4	130
Jackie et al.	2019	South Africa	UMICs	Unclassified	2015–2016	Prospective cohort	38	30	32
Innocent et al.	2020	DR. Congo	LICs	XDR-TB	2015–2017	Retrospective cohort	56.3	32.4	32
Olatunde et al.	2019	South Africa	UMICs	XDR-TB	2014–2018	Prospective cohort	61.9	37	63
Nesri et al.	2020	South Africa	UMICs	XDR-TB	2014–2015	Prospective cohort	47.7	33	151
Sagwa et al.	2012	Namibia	UMICs	MDR- & XDR-TB	2008–2010	Cross-sectional	64	34.7	59
Rajendra et al.	2016	India	LMICs	MDR-TB	2009–2010	Prospective cohort	69.4	29.3	98
Piubella et al.	2014	Niger	LICs	MDR-TB	2008–2010	Prospective cohort	81.5	31	65
Hind et al.	2012	Lesotho	LMICs	MDR-TB	2007–2011	Retrospective cohort	53	8	19
Karen et al.	2013	South Africa	UMICs	XDR-TB	2002–2008	Retrospective cohort	NA	NA	115
Ilse et al.	2020	South Africa	UMICs	MDR-TB	2018–2019	Retrospective cohort	59.8	35	62
Aleksandr et al.	2021	Uzbekistan	LMICs	MDR-TB	2018–2020	Retrospective cohort	70.5	45.6	45
Yang et al.	2017	China	UMICs	MDR-TB	2009–2016	Retrospective cohort	73.2	44	751
Muhammad et al.	2017	Pakistan	LMICs	MDR- & XDR-TB	2014–2015	Retrospective cohort	NA	NA	80
Parvaneh et al.	2011	Iran	LMICs	MDR-TB	2006–2009	Retrospective cohort	55	40.6	80
Farouq et al.	2021	Nigeria	LMICs	Unclassified	2018–2020	Prospective cohort	87.2	32	39
Atif et al.	2017	India	LMICs	MDR-TB	2010–2013	Retrospective cohort	71.2	35.7	147
Huerga et al.	2017	Kenya	LMICs	MDR-TB	2006–2012	Retrospective cohort	55	29	169
Petros et al.	2011	India	LMICs	MDR-TB	2007–2011	Prospective cohort	56	35	71

DR.Congo: Democratic Republic of Congo, **DR-TB**: Drug Resistant Tuberculosis, **HICs**: High-Income Countries, **LICs**: Low-Income Countries, **LMICs**: Lower-Middle-Income Countries, **MDR-TB**: Multidrug Resistant Tuberculosis, **UK**: United Kingdom, **UMICs**: Upper-Middle-Income Countries, and **XDR-TB**: Extensively Drug-Resistant Tuberculosis.

Table 1: **Characteristics of included studies.**

The global prevalence of sequelae and source of heterogeneity

The most common type of sequelae was respiratory sequelae (44.40%, 95% CI: 36.70–52.10), followed by hearing sequelae (26.7%, 95% CI: 23.9–29.7), renal sequelae (8.1%, 95% CI: 6.3–10.0), neurological sequelae (8.4%, 95% CI: 6.5–10.3), visual sequelae (4.5%, 95% CI: 2.7–6.3), hepatic sequelae (7.3% with a 95% CI: 5.1–9.4), and musculoskeletal sequelae (10.1% 7.0–13.2) (Supplementary file: Figs. S2, S4–S9). Other physical sequelae reported in a few studies were cardiac failure and multiple organ failure (Table 2).

Large heterogeneity in the prevalence of sequelae was identified in the included studies. Nine variables namely: the type of MDR-TB, the country's income status, HIV prevalence, the timing of sequelae, WHO region, study design, median age, Diabetes Mellitus (DM) status, and site of MDR-TB, were identified as sources of heterogeneity and used as a primary stratification. The pooled prevalence of sequelae did not differ significantly by any of the following study characteristics: median/mean age of study participants, study design, Human Immune Deficiency Virus (HIV) status, and DM status. The results of each physical sequelae were summarised in Tables 3 and 4.

Respiratory sequelae

A total of 18 papers reported respiratory sequelae, and the pooled prevalence was 44.40% (95% CI: 36.70–52.10) Table 2 and Supplementary file, Fig. S2. The prevalence of respiratory sequelae was 52.3% (95% CI: 40.0, 64.6) (I^2 = 100%, p = 0.000) for patients with MDR-TB, and there was no report among patients with XDR-TB only. The sub-group analysis finding showed that the highest prevalence of respiratory sequelae 57.7% (95% CI: 47.3, 68.2) (overall, DL I^2 = 100%, p = 0.000) was reported after completion of DR-TB treatment compared to sequelae during treatment 29.8% (95% CI: 18.7, 41.0) (Overall, DL I^2 = 100%, p = 0.000) (Table 3). The meta-regression analysis showed that the prevalence of respiratory sequelae after DR-TB treatment completion was nearly five times higher than during treatment (AOR = 5.42, 95% CI: 1.38–21.28 (Table 4).

Categories	Respiratory impairment		Hearing impairment		Renal impairment		Neurologic impairment		Visual impairment		Hepatic impairment		Musculoskeletal impairment	
	Number of studies	Prevalence of sequelae	Number of studies	Prevalence of sequelae	Number of studies	Prevalence of sequelae	Number of studies	Prevalence of sequelae	Number of studies	Prevalence of sequelae	Number of studies	Prevalence of sequelae	Number of studies	Prevalence of sequelae
Overall	19	44.4	45	26.8	28	8.1	26	8.4	16	4.5	24	7.3	21	10.1
Countries income														
HICs	2	10.2	5	23.6	4	13.6	2	14.6	1	2.3	2	22.9	1	37.8
UMICs	6	45.8	16	35.2	11	15.9	10	9.9	7	6.6	9	11.1	7	12.8
LMICs	9	48.1	21	22.4	10	1.3	10	8.4	6	3.5	11	2.9	11	5.3
LICs	2	59.3	3	17.7	3	5.2	4	7.1	2	3.7	2	1.9	2	24.1
Type of TB														
MDR-TB	11	52.3	31	25.0	19	4.9	17	5.6	10	3.7	16	6.1	11	7.3
XDR-TB	NA	NA	4	26.6	2	17.6	3	31.5	3	11.3	3	3.1	2	21.5
MDR &XDR	5	45.1	6	32.6	4	24.2	3	10.0	NA	NA	4	16.7	4	20.4
Unclassified	3	15.1	4	31.6	3	7.8	3	12.1	3	2.1	1	2.0	4	5.6
Timing of sequelae														
During treatment	9	29.8	43	27.0	27	8.4	26	8.4	15	4.2	23	7.2	21	10.1
After treatment	10	57.7	2	22.0	1	2.0	NA	NA	1	10.0	1	10.0	NA	-NA
Region														
Southeast Asia	6	62.8	13	18.1	6	0.68	5	6.4	2	6.5	7	2.6	7	2.8
Sub-Saharan	4	43.0	20	36.2	11	10.2	13	13.6	10	5.2	7	3	7	13.1
European& CA	4	28.3	7	29.9	7	23.0	4	12.7	3	3.0	6	19.7	6	26.6
East Asia & Pacific	3	29.9	3	4.7	2	3.2	3	2.5	2.5	3	3	10.0	2.6	17.4
MENA	NA	NA	1	10.0	1	3.8	1	8.8	NA	NA	1	5.0	1	7.5
Region of America	2	48.1	1	12.2	1	10.2	NA	NA	NA	NA	NA	NA	NA	NA
Study design														
Prospective cohort	3	46.7	16	31.0	7	10.1	8	16.2	3	11.1	4	7.2	9	7.2
Retrospective cohort	8	35.5	26	22.6	20	7.9	16	6.0	12	2.7	18	8.1	11	12.9
Cross-sectional	8	52.3	3	37.5	1	4.8	2	3.7	1	4.5	2	0.9	1	11.9
HIV status														
<1%	5	62.8	2	27.3	1	1.0	1	21.4	NA	NA	1	16.0	1	2.0
1–50%	5	33.0	19	29.2	13	10.0	10	11.2	5	3.4	10	4.9	10	12.8
51–100%	2	18.4	10	31.4	7	14.1	8	14.2	7	6.9	6	4.9	6	11.1
Not recorded	7	45.6	14	13.1	7	3	7	3.0	4	3.4	7	8.2	4	7.8
Median age														
Not reported	2	64.1	2	6.5	2	3.3	1	11.3	1	0.9	1	0.8	1	2.6
< median age	8	49.3	28	29.4	21	7.5	17	10.2	10	5.8	14	5.8	13	10.9
Median age & above	9	35.3	15	24.6	5	3.5	8	6.5	5	4.2	9	10.8	6	11.7
Site of DR-TB														
Not reported	1	8.8	17	36.6	8	8.6	5	3.2	5	2.6	6	8.1	4	12.3
Pulmonary	17	48.8	17	21.4	11	9.9	12	18.2	8	7.3	10	5.3	10	7.7
Extrapulmonary	NA	NA	1	0.4	NA	NA	1	2.2	NA	NA	1	2.2	NA	NA
Both	1	6.8	10	24.7	9	6.8	8	5.5	3	3.7	7	10.8	6	17.0

(Table 2 continues on next page)

Categories	Respiratory impairment		Hearing impairment		Renal impairment		Neurologic impairment		Visual impairment		Hepatic impairment		Musculoskeletal impairment	
	Number of studies	Prevalence of sequelae	Number of studies	Prevalence of sequelae	Number of studies	Prevalence of sequelae	Number of studies	Prevalence of sequelae	Number of studies	Prevalence of sequelae	Number of studies	Prevalence of sequelae	Number of studies	Prevalence of sequelae
(Continued from previous page)														
DM status														
Not reported	10	46.9	26	29.9	18	7.5	19	8.1	10	5.3	10	6.7	11	8.4
<1%	2	84.1	1	20.0	NA	NA	NA	NA	NA	NA	NA	NA	1	3.1
1–50%	6	26.3	18	22.6	10	11.0	7	18.3	6	3.5	14	8.7	8	10.5
≥50%	1	51.9	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

CA: Central Asia, DM: Diabetes Mellitus, DR-TB: Drug-Resistant Tuberculosis, HICs: High-Income Countries, HIV: Human Immune Deficiency Virus, LICs: Low-Income Countries, LMICs: Lower-Middle-Income Countries, MENA: Middle East and North Africa, MDR-TB: Multi-drug Resistant Tuberculosis, NA: No data reported, TB: Tuberculosis, UMICs: Upper-Middle-Income Countries, and XDR-TB: Extensively Drug-Resistant Tuberculosis.

Table 2: **Pooled prevalence of respiratory impairment, hearing impairment, renal impairment, neurological impairment, visual impairment, hepatic Impairment, and musculoskeletal impairment, stratified by study characteristics.**

Types of respiratory sequelae

Cavitations, bronchiectasis, fibrosis, atelectasis, and destroyed lung disease were the commonest types of respiratory sequelae reported among patients with MDR- and XDR-TB (Fig. 2).

Hearing sequelae

A total of 45 papers reported hearing sequelae, and the pooled prevalence was 26.65% (95% CI: 20.81–32.50) (Table 2 and Supplementary file: Fig. S4). The pooled prevalence of hearing sequelae was 25.0% (95% CI: 21.6, 28.4) (overall, DL $I^2 = 99.3\%$, $p = 0.000$) for patients with MDR-TB and 26.6% (95% CI: 12.3, 40.9) (overall, DL $I^2 = 99.3\%$, $p = 0.000$) for patients with XDR-TB (Table 3). The meta-regression analysis showed that patients with XDR-TB had a 70% higher risk of developing hearing sequelae than patients with MDR-TB (AOR = 1.70, 95% CI: 1.1–2.7). The prevalence of developing hearing sequelae after completion of DR-TB treatment was nearly two times compared with during DR-TB treatment (AOR = 2.1, 95% CI: 1.3–3.3) (Table 4).

Renal sequelae

A total of 28 papers reported renal sequelae, and the pooled prevalence was 8.13% (95% CI: 6.25–10.00) (Table 2 and Supplementary file: Fig. S5). The highest prevalence of renal sequelae reported in UMICs was 15.9% (95% CI: 11.2, 20.5) (overall, DL $I^2 = 95.1\%$, $p = 0.000$) and High-Income Countries (HICs) 13.6% (95% CI: 3.5, 23.6) (overall, DL $I^2 = 95.1\%$, $p = 0.000$) countries. The lowest prevalence of renal sequelae reported in LMICs was 1.3% (95% CI: 0.5, 2.0) (Overall, DL $I^2 = 95.1\%$, $p = 0.000$) and Low-Income Countries (LICs) (5.2%) countries (Overall, DL $I^2 = 95.1\%$, $p = 0.000$) (Table 3). The prevalence of renal sequelae among LICs was nearly 90% lower than HICs (AOR = 0.07, 95% CI (0.1, 0.5)) (Table 4).

Neurological sequelae

A total of 26 papers reported neurological sequelae, and the pooled prevalence was 8.41% (95% CI: 6.52–10.29) (Table 2 and Supplementary file: Fig. S6). The highest prevalence of neurological sequelae was reported in patients with XDR-TB; 31.5% (95% CI: 5.5, 57.5) (overall, DL $I^2 = 92.1\%$, $p = 0.000$) and was nearly seven times higher than in patients with MDR-TB 5.6% (95% CI: 3.8, 7.5) (overall, DL $I^2 = 92.1\%$, $p = 0.000$). The highest prevalence of neurological sequelae was reported among patients with pulmonary DR-TB; 18.2% (95% CI: 11.4, 25.0) (Overall, DL $I^2 = 92.1\%$, $p = 0.000$) (Table 3). The prevalence of neurological sequelae among patients with XDR-TB was nearly eight times higher risk than patients with MDR-TB (AOR = 7.8, 95% CI: 1.4–42.7). Similarly, the prevalence of neurological sequelae among patients with DM was nearly 14 times

Stratification variable	Respiratory sequelae	Hearing sequelae	Renal sequelae	Neurologic sequelae	Hepatic sequelae	Visual sequelae	Musculoskeletal sequelae
Type of TB							
MDR-TB	52.3 (40.0, 64.6)	25.0 (21.6, 28.4)	4.9 (3.2, 6.7)	5.6 (3.8, 7.5)	6.1 (4.0, 8.3)	3.7 (1.7.5.8)	7.3 (3.3, 11.2)
XDR-TB	–	26.6 (12.3, 40.9)	17.6 (3.6, 31.6)	31.5 (5.5, 57.5)	3.1 (0.9, 5.3)	11.3 (−0.1, 22.8)	21.5 (9.9, 33.1)
MDR &XDR	45.1 (28.3, 61.9)	32.6 (14.9, 50.3)	24.2 (3.8, 44.6)	10.0 (1.7, 18.3)	16.7 (6.6, 26.9)	–	20.4 (13.0, 53.8)
Unclassified	15.1 (9.4, 20.7)	31.6 (11.3, 52.0)	7.8 (5.81, 9.7)	12.12 (3.0, 21.3)	2.0 (0.2, 4.3)	2.1 (−0.1, 4.2)	5.6 (0.3, 10.9)
Overall, DL	I^2 = 100%, P = 0.000	I^2 = 99.3%, p = 0.000	I^2 = 95.1%, p = 0.000	I^2 = 92.1%, p = 0.000	I^2 = 94.7%, p = 0.000	I^2 = 85.1%, p = 0.000	I^2 = 94.7%, p = 0.000
By country income							
HI	10.2 (3.5, 16.9)	13.6 (3.5, 23.6)	13.6 (3.5, 23.6)	14.6 (1.2, 30.4)	22.9 (9.4, 36.4)	2.3 (−2.1, 6.7)	37.8 (28.8, 48.9)
UMI	45.8 (26.5, 65.1)	15.9 (11.2, 20.5)	15.9 (11.2, 20.5)	9.9 (6.4, 13.4)	11.1 (6.1, 16.1)	6.6 (3.0, 10.2)	12.8 (5.9, 19.7)
LMI	48.1 (35.0, 61.2)	1.3 (0.5, 2.0)	1.3 (0.5, 2.0)	8.4 (4.7, 12.0)	2.9 (1.5, 4.3)	3.5 (0.5, 6.5)	5.3 (2.7, 7.8)
LI	59.3 (11.5, 130)	5.2 (2.0, 8.5)	5.2 (2.0, 8.5)	7.1 (2.1, 12.1)	1.9 (0.2.4, 6.1)	3.7 (0.7, 6.7)	24.1 (18.7, 67.0)
Overall, DL	I^2 = 100%, P = 0.000	I^2 = 99.3%, p = 0.000	I^2 = 95.1%, p = 0.000	I^2 = 92.1%, p = 0.000	I^2 = 94.7%, p = 0.000	I^2 = 85.1%, p = 0.000	I^2 = 94.7%, p = 0.000
Timing of sequelae							
During treatment	29.8 (18.7, 41.0)	27.0 (24.0–30.0)	8.44 (6.5, 10.4)	8.4 (6.5, 10.3)	7.2 (5.0, 9.4)	4.2 (2.4, 6.0)	10.1 (7.0, 13.2)
After treatment	57.7 (47.3, 68.2)	22.0 (16.1–27.8)	2.00 (−0.7, 4.7)	–	10.0 (4.1, 15.9)	10.0 (4.1, 15.9)	–
Overall, DL	I^2 = 100%, P = 0.000	I^2 = 99.3%, p = 0.000	I^2 = 95.1%, p = 0.000	I^2 = 92.1%, p = 0.000	I^2 = 94.7%, p = 0.000	I^2 = 85.1%, p = 0.000	I^2 = 94.7%, p = 0.000
By study design							
Prospective cohort	46.7 (15.5, 77.8)	3.01 (17.6.44.5)	10.1 (6.0, 14.2)	16.2 (10.3, 22.0)	7.2 (0.1, 14.4)	11.1 (1.2, 21.0)	10.9 (6.8, 15.0)
Retrospective cohort	35.5 (25.6, 45.3)	22.7 (16.7, 28.6)	7.9 (5.5, 10.4)	6.0 (4.0, 7.9)	8.1 (5.6, 10.6)	2.7 (1.2, 4.2)	11.7 (4.3, 19.1)
Cross-sectional	52.3 (39.0, 65.6)	37.5 (12.3, 62.7)	4.8 (2.2, 7.5)	3.7 (1.3, 6.0)	0.9 (0.2, 1.9)	5.1 (0.5, 10.7)	2.6 (−0.3, 5.5)
Overall, DL	I^2 = 100%, P = 0.000	I^2 = 99.3%, p = 0.000	I^2 = 95.1%, p = 0.000	I^2 = 92.1%, p = 0.000	I^2 = 94.7%, p = 0.000	I^2 = 85.1%, p = 0.000	I^2 = 94.7%, p = 0.000
By HIV status							
Not recorded	45.6 (39.1, 52.2)	16.3 (13.3.19.2)	3.0 (1.2, 4.8)	3.5 (1.7, 5.3)	8.2 (2.7, 13.6)	3.4 (0.5, 6.3)	7.8 (0.4, 15.2)
<1%	62.8 (44.1, 81.4)	26.6 (22.6.30.5)	1.0 (0.9, 3.0)	21.4 (13.3, 29.6)	16.0 (13.0, 19.0)	–	2.0 (0.8, 4.8)
1%–50%	33.0 (17.2, 48.8)	32.3 (25.9.38.8)	10.0 (6.1, 13.9)	11.2 (7.2, 15.2)	4.85 (2.64, 7.07)	3.4 (1.6, 5.2)	12.8 (7.5, 18.0)
51%–100%	18.4 (9.1, 27.7)	30.9 (20.7.41.1)	14.1 (4.8, 23.4)	14.2 (6.6, 21.7)	4.9 (1.7, 8.1)	6.88 (1.9, 11.9)	11.1 (4.5, 17.7)
Overall, DL	I^2 = 100%, P = 0.000	I^2 = 99.3%, p = 0.000	I^2 = 95.1%, p = 0.000	I^2 = 92.1%, p = 0.000	I^2 = 94.7%, p = 0.000	I^2 = 85.1%, p = 0.000	I^2 = 94.7%, p = 0.000
By region							
South Asia	62.8 (40.5, 85.0)	18.1 (14.6, 21.6)	0.7 (0.3, 1.1)	6.4 (2.6, 10.2)	2.6 (1.0, 4.3)	6.5 (0.8, 12.2)	2.8 (0.6, 5.0)
SSA	43.0 (33.0, 53.0)	36.2 (28.4, 44.0)	10.19 (6.1, 14.3)	13.6 (9.4, 17.8)	2.6 (0.9, 4.4)	5.2 (2.4, 7.9)	13.1 (8.0, 18.2)
ECA	28.3 (16.6, 39.9)	29.9 (14.2, 45.6)	21.99 (8.0, 36.0)	12.7 (4.2, 21.2)	19.7 (14.9, 24.5)	3.0 (1.4, 7.3)	26.7 (4.8, 48.5)
EAP	29.9 (20.3, 39.4)	4.7 (0.4, 9.7)	3.19 (0.6, 5.8)	2.45 (0.4, 4.5)	10.0 (1.3, 18.66)	2.5 (1.4, 3.7)	17.4 (14.3, 20.2)
MENA	–	10.0 (9.3, 10.7)	3.8 (0.4, 7.9)	8.75 (2.6, 14.9)	5.00 (0.2, 10.0)	–	7.5 (1.7, 13.3)
North America	48.1 (1.1, 95.1)	12.2 (11.3, 13.2)	10.2 (1.7, 18.7)	–	–	–	–
Overall, DL	I^2 = 100%, P = 0.000	I^2 = 99.3%, p = 0.000	I^2 = 95.1%, p = 0.000	I^2 = 92.1%, p = 0.000	I^2 = 94.7%, p = 0.000	I^2 = 85.1%, p = 0.00	I^2 = 94.7%, p = 0.000
By DM status							
Not reported	46.9 (36.0, 57.7)	29.8 (21.5, 38.1)	7.3 (5.1, 9.5)	8.1 (5.7, 10.5)	6.7 (3.0, 10.4)	5.3 (2.5, 8.2)	8.4 (4.9, 11.9)
<1%	84.1 (61.4, 106.8)	20.0 (10.3, 29.7)	–	–	–	–	3.1 (1.1, 7.3)
1%–50%	26.3 (20.0, 32.6)	22.4 (14.8, 30.1)	11.0 (6.3, 15.8)	18.3 (9.6, 27.0)	8.7 (5.3, 12.1)	3.5 (1.8, 5.3)	10.5 (4.3, 16.7)
51%–100%	–	–	–	–	–	–	–
Overall, DL	I^2 = 100%, P = 0.000	I^2 = 99.3%, p = 0.000	I^2 = 95.1%, p = 0.000	I^2 = 92.1%, p = 0.000	I^2 = 94.7%, p = 0.000	I^2 = 85.1%, p = 0.000	I^2 = 94.7%, p = 0.000
Mean/median age							
< median age	49.3 (36.7, 61.9)	29.4 (19.9, 38.9)	9.8 (6.7, 12.8)	10.2 (7.2, 13.1)	5.8 (3.5, 8.2)	5.8 (2.3, 9.2)	10.9 (6.8, 15.0)
≥median age	35.3 (30.1, 40.5)	24.5 (15.3, 33.8)	3.6 (1.2, 6.0)	6.5 (3.4, 9.5)	10.8 (5.8, 15.7)	4.2 (1.5, 6.9)	11.7 (4.3, 19.1)
Not reported	64.1 (4.4, 123.8)	5.8 (1.7, 9.8)	3.3 (0.3, 9.9.6)	11.3 (5.5, 17.1)	0.8 (3.5, 8.2)	0.9 (0.2, 2.6)	2.6 (0.3, 5.5)
Overall, DL	I^2 = 100%, P = 0.000	I^2 = 99.3%, p = 0.000	I^2 = 95.1%, p = 0.000	I^2 = 92.1%, p = 0.000	I^2 = 94.7%, p = 0.000	I^2 = 85.1%, p = 0.000	I^2 = 94.7%, p = 0.000

(Table 3 continues on next page)

Stratification variable	Respiratory sequelae	Hearing sequelae	Renal sequelae	Neurologic sequelae	Hepatic sequelae	Visual sequelae	Musculoskeletal sequelae
(Continued from previous page)							
Site of DR-TB							
Pulmonary	48.8 (40.5, 57.1)	21.2 (13.0, 29.4)	9.9 (5.7, 14.0)	18.2 (11.4, 25.0)	5.3 (2.7, 7.9)	7.3 (2.8, 11.8)	7.7 (4.0, 11.3)
Extra pulmonary	-	0.6 (0.2, 1.1)	-	2.2 (0.5, 4.0)	2.2 (0.5, 4.0)	-	-
Both	6.8 (6.6, 6.9)	23.7 (14.7, 32.8)	6.8 (4.2, 9.5)	5.5 (3.4, 7.7)	10.8 (3.5, 18.1)	3.7 (0.4, 7.0)	17.0 (6.7, 27.3)
Not reported	8.8 (8.7, 9.0)	35.0 (21.1, 48.9)	8.6 (5.0, 12.2)	3.2 (1.3, 5.2)	8.1 (3.2, 13.0)	2.6 (0.7, 4.5)	12.3 (2.8, 21.9)
Overall, DL	I^2 = 100%, P = 0.000	I^2 = 99.6%, P = 0.000	I^2 = 95.1%, p = 0.000	I^2 = 92.1%, p = 0.000	I^2 = 94.7%, p = 0.000	I^2 = 85.1%, p = 0.000	I^2 = 94.7%, p = 0.000

EAP: East Asia and Pacific, **ECA**: European and Central Asia, **DM**: Diabetes Mellitus, **DR-TB**: Drug-Resistant Tuberculosis, **HI**: High Income, **HIV**: Human Immune Deficiency Virus, **LMI**: Lower Middle Income, **LI**: Low Income, **MDR-TB**: Multidrug-resistant Tuberculosis, **MENA**: Middle East and North Africa, **UMI**: Upper Middle Income, **SSA**: Sub-Saharan Africa, **XDR-TB**: Extensively Drug-Resistant Tuberculosis. –Indicates no study reported in that specific category.

Table 3: **Sub-group analysis on the pooled prevalence of physical sequelae.**

higher than among patients without DM (AOR = 13.8, 95% CI: 3.12, 60.7) (Table 4).

Visual sequelae

A total of 16 studies reported visual sequelae, and the pooled prevalence was 4.51% (95% CI: 2.71–6.30) (Table 2 and Supplementary file: Fig. S7). Patients with XDR-TB were at nearly six times higher risk than patients with MDR-TB (AOR = 6.4, 95% CI: 1.3, 31.8) (Table 4).

Hepatic sequelae

A total of 24 papers reported hepatic sequelae, and the pooled prevalence was 7.27% (95% CI: 5.11–9.43) (Table 2 and Supplementary file: Fig. S8). HICs had the highest prevalence of hepatic sequelae at 22.9% (95% CI: 9.4, 36.4) (Overall, DL I^2 = 94.7%, p = 0.000), followed by UMICs countries at 11.1% (95% CI: 6.1, 16.1) (Overall, DL I^2 = 94.7%, p = 0.000). The prevalence of hepatic sequelae was 10.0% (95% CI: 4.1, 15.9) (Overall, DL I^2 = 94.7%, p = 0.000) two years after completion of MDR-TB treatment. The prevalence of hepatic sequelae was 6.1% (95% CI: 4.0, 8.3) for MDR-TB (Overall, Dl I^2 = 94.7%, p = 0.000) (Table 3). The prevalence of hepatic sequelae among LMICs (AOR = 0.2, 95% CI (0.008, 0.34)) and LICs (AOR = 0.02, 95% CI: 0.004, 0.86) was lower than HICs (Table 4).

Musculoskeletal sequelae

A total of 21 articles reported musculoskeletal sequelae, and the pooled prevalence was 10.1% (95% CI: 6.97–13.7) (Table 2 and Supplementary file: Fig. S9). The prevalence of musculoskeletal sequelae among patients with MDR-TB was 7.3% (95% CI: 3.3, 11.2) (overall, DL I^2 = 94.7%, p = 0.000), for patients with XDR-TB; 21.5% (95% CI: 9.9, 33.1) (overall, DL I^2 = 94.7%, p = 0.000). The highest prevalence of musculoskeletal sequelae was reported among people from communities or studies with HIV prevalence of 1–50%; 12.8% (95% CI: 7.5, 18.0) (Overall, DL I^2 = 94.7%, p = 0.000) and HIV prevalence >50%; 11.1% (95% CI: 4.5, 17.7) (Overall, DL I^2 = 94.7%, p = 0.000) compared with studies with HIV prevalence of <1% (Overall, DL I^2 = 94.7%, p = 0.000) (Table 3). Meta-regression output showed that the prevalence of musculoskeletal sequelae among patients with XDR-TB was nearly eight times higher than among patients with MDR-TB (AOR = 7.7, 95% CI: 1.1, 51.9) (Table 4).

Publication bias

The asymmetrical funnel plots and Egger's test indicate potential publication bias among the included studies for almost all types of physical sequelae. However, the Egger test showed no evidence of

Variable	Respiratory sequelae		Hearing sequelae		Renal sequelae		Neurological sequelae	
	AOR with 95% CI	P-value	AOR with 95% CI	P-value	AOR with 95% CI	P-value	AOR with 95% CI	P-value
Type of TB								
MDR	1		1		1		1	
XDR-TB	NA	NA	1.7 (1.1, 2.7)		1.6 (0.2, 13.8)	0.638	7.8 (1.4, 42.7)	0.021
MDR- & XDR-TB	3.30 (0.36, 30.07)	0.069	1.5 (0.8, 3.0)		1.0 (0.1, 22.5)	0.996	1.3 (0.2, 8.4)	0.761
Unclassified	2.79 (0.45, 17.18)	0.018	1.1 (0.6, 2.0)		1.2 (0.1, 12.8)	0.875	2.5 (0.3, 19.1)	0.347
DM Status								
<1%	1						1	
1–50%	0.05 (0.01, 0.21)	0.015	NA	NA	NA	NA	13.8 (3.12, 60.7)	0.002
51–100%	0.06 (0.002, 0.40)	0.001					–	–
Not reported	0.14 (0.05, 0.41)	0.011					2.5 (0.99, 6.2)	0.052
Timing of sequelae								
During treatment	1		1		1			
After treatment	5.42 (1.38, 21.28)	0.004	2.1 (1.3, 3.3)		0.6 (0.2, 1.9)	0.335	NA	NA
Site of DR-TB								
Pulmonary			1				1	
Extrapulmonary	NA	NA	0.4 (0.2, 0.6)		NA	NA	0.14 (0.05, 0.4)	0.001
Both			1.1 (0.6, 2.1)				0.2 (0.1, 0.8)	0.031
Not reported			1.2 (0.7, 1.9)				0.2 (0.1, 0.5)	0.003
Country Income								
HI			1		1			
UMI	NA	NA	0.6 (0.3, 0.9)		0.39 (0.35, 4.5)	0.437	NA	NA
LMI			0.7 (0.5, 1.2)		0.2 (0.01, 1.6)	0.109		
LI			1.2 (0.6, 2.2)		0.07 (0.1, 0.5)	0.007		
Median age								
<Median	NA	NA	NA	NA	NA	NA	NA	
Median & above								
Unclassified								
Study design								
Prospective cohort	NA	NA	NA	NA	NA	NA	NA	
Retrospective cohort								
Cross-sectional								
HIV status								
0–50%	NA	NA	NA	NA	NA	NA	NA	
51–100%								
Unclassified								

Meta-regression output continued

Variable	Hepatic sequelae		Visual sequelae		Musculoskeletal sequelae	
	AOR with 95% CI	P-value	AOR with 95% CI	P-value	AOR with 95% CI	P-value
Type of TB						
MDR	1		1		1	
XDR-TB	1.02 (0.3, 31.2)	0.993	6.4 (1.3, 31.8)	0.028	7.7 (1.1, 51.9)	0.038
MDR- & XDR-TB	0.4 (0.2, 9.0)	0.525	1.1 (0.3, 4.7)	0.868	0.8 (0.04, 17.9)	0.884
Unclassified	0.4 (0.2, 6.3)	0.451	–	–	–	–
DM Status						
<1%						
1–50%	NA	NA	NA	NA	NA	NA
51–100%						
Not reported						
Timing of sequelae						
During treatment	NA	NA	NA	NA	NA	NA
After treatment						
Site of DR-TB						
Pulmonary	1					
Extrapulmonary	0.2 (0.01, 5.3)	0.309	NA	NA	NA	NA

(Table 4 continues on next page)

Meta-regression output continued						
Variable	Hepatic sequelae		Visual sequelae		Musculoskeletal sequelae	
	AOR with 95% CI	P-value	AOR with 95% CI	P-value	AOR with 95% CI	P-value
(Continued from previous page)						
Both	0.7 (0.5, 8.3)	0.718				
Not reported	0.3 (0.27, 4.0)	0.352				
Country Income						
HICs	1					
UMICs	0.03 (0.008, 0.79)	0.038	NA	NA	NA	NA
LMICs	0.2 (0.008, 0.34)	0.012				
LICs	0.02 (0.004, 0.86	0.043				
Median age						
<Median	1		1			
Median & above	3.58 (0.24.53.01)	0.323	1.1 (0.9, 11.9)	0.957	NA	NA
Unclassified	0.18 (0.03, 1.23)	0.075	0.4 (0.1, 3.0)	0.320		
Study design						
Prospective cohort			1		NA	NA
Retrospective cohort	NA	NA	0.7 (0.2, 3.4)	0.623		
Cross-sectional			0.3 (0.1, 1.4)	0.124		
HIV status						
0–50%					1	
51–100%	NA	NA	NA	NA	0.5 (0.1, 4.7)	0.485
Unclassified					0.1 (0.03, 0.6)	0.009

NA: Not significant in the bivariable analysis at a p-value of <0.2. **MDR-TB**: **DM**: Diabetes Mellitus, **HICs**: **XDR-TB**: Extensively Drug-Resistant Tuberculosis, High-Income Countries, **HIV**: Human Immune Deficiency Virus, **LICs**: Low-Income Countries, **LMI**: Lower Middle-Income Countries, Multidrug-Resistant Tuberculosis, **UMICs**: Upper Middle-Income Countries.

Table 4: **Meta-regression output for respiratory sequelae, hearing sequelae, renal sequelae, neurological sequelae, visual sequelae, hepatic sequelae, and musculoskeletal sequelae.**

substantial publication bias for respiratory sequelae ($p = 0.544$) according to our significance level (Supplementary file: Figs. S10–16). We have applied trim and fill methods to adjust for the publication bias in the analysis. As a result, the pooled prevalence after adjusting the publication bias was reduced significantly for each physical sequelae. However, the funnel plot asymmetry was corrected after adjusting the therorethical missing studies by the trim and fill methods. The finding is summarized in the Supplementary file: Figs. S17–22.

Quality assessment

The overall quality assessment for the included studies was low to high, with a median score of 6 points and an Inter Quartile Range (IQR) of 3 points. Of 66 included studies, seven had eight or nine points, regarded as high-quality studies. The majority, 42 (63.63%), studies had 5 to 7 points, classified as medium-quality studies. The other studies having a score of 4 points or lower were low-quality studies.

Sensitivity analysis

Sensitivity analysis was conducted by removing low-quality studies (Supplementary file: Figs. S23–29). The pooled prevalence of respiratory sequelae after removing low-quality studies was 45.13% (95% CI: 39.97–50.29) (Overall, DL ($I^2 = 100\%$, $p = 0.000$)) (Fig. S23). The finding after adjustment was the same as before adjustment (43.77% (95% CI: 40.09–47.48)). The prevalence of hearing sequelae after trimming poor-quality studies was 23.32% (95% CI: 18.49–28.15) (overall, DL ($I^2 = 98.7\%$, $p = 0.000$)) (Fig. S24). However, there was no significant difference in estimates between the original (26.65% (95% CI: 20.81–32.50)) and trimmed prevalence.

The prevalence of renal sequelae after adjustment of low-quality studies was 8.63% (95% CI: 5.81–10.93) (overall, DL ($I^2 = 95.7\%$, $p = 0.000$)) (Fig. S25). However, the finding showed that there was no difference between the original (8.13% (95% CI: 6.25–10.00)) and trimmed prevalence (9.37% (95% CI: 7.03–11.7)). The prevalence of neurological sequelae after trimming of low-quality studies was 9.37% (95% CI: 7.03–11.7) (overall, DL ($I^2 = 92.3\%$, $p = 0.000$)) (Fig. S26). However, there was no difference between the prevalence of neurological sequelae between the original (8.41% (95% CI: 6.52–10.29)) and after trimming of low-quality studies. Moreover, the prevalence of hepatic sequelae after trimming of low-quality studies was 8.37% (95% CI: 5.81–10.93) (overall, DL ($I^2 = 95.7\%$, $p = 0.000$)) (Fig. S27). However, there was no difference in the prevalence of hepatic sequelae between the original (7.27% (95% CI: 5.11–9.43)) and the trimmed prevalence.

The prevalence of visual sequelae after trimming of low-quality studies was 4.47 (95% CI: 2.40–6.53)

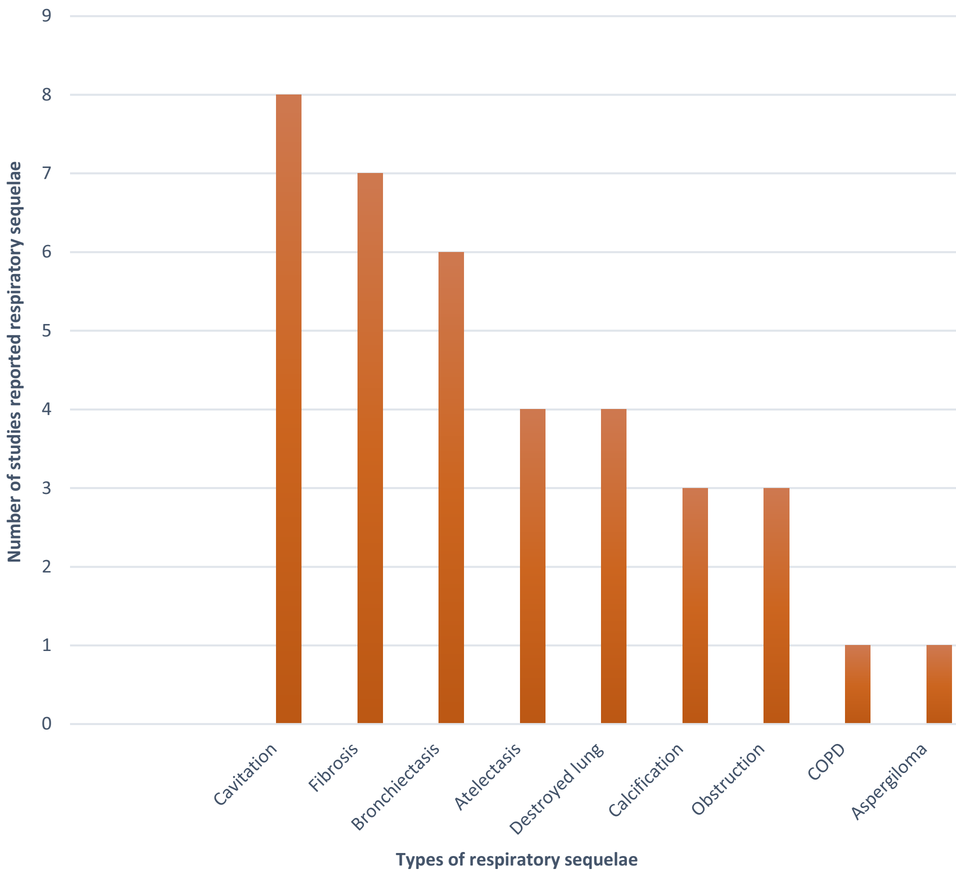

Fig. 2: **Respiratory sequelae reported among patients with MDR-TB and XDR-TB**. MDR-TB = multi-drug resistant tuberculosis. XDR-TB = extensively drug-resistant tuberculosis.

(overall, DL (I^2 = 92.3%, p = 0.000)) (Fig. S28). However, there was no difference in the prevalence of visual sequelae between the original (4.51% (95% CI: 2.71–6.30)) and after trimming of low-quality studies. The overall prevalence of musculoskeletal sequelae after removing low-quality studies was 9.33 (95% CI (5.58–13.09) (overall, DL (I^2 = 92.3%, p = 0.000))) (Fig. S29). However, there was no difference between the original (10.1% (95% CI: 6.97–13.7)) and trimmed prevalence.

Discussion

To the best of our knowledge, this is the first reported comprehensive systematic review and meta-analysis to quantify the prevalence of physical sequelae among patients with MDR/XDR-TB and to identify the most common types of sequelae. The prevalence of long-term physical sequelae was high among patients with MDR/XDR-TB. The most common types of sequelae that have been reported in the existing literature were respiratory, hearing, renal, neurological, hepatic, visual, and musculoskeletal sequelae.

We found that respiratory and hearing sequelae were the most common type of long-term sequelae among patients with MDR/XDR-TB, with an overall pooled prevalence of 43.8% and nearly 30%, respectively. Our finding is significantly higher than a systematic review conducted among patients with DS-TB amongst whom the pooled prevalence of respiratory sequelae was 33.1%[87] and 14.5% of patients developed hearing sequelae.[87] The higher hearing sequelae could be due to the inclusion of aminoglycoside agents in MDR-TB treatment regimens, which are the major cause of ototoxicity.[88]

Previously the WHO used to recommend the treatment of MDR-TB with an intensive phase of injectable aminoglycosides (amikacin, kanamycin, and capreomycin), which can lead to hearing sequelae.[89] However, the WHO currently recommends MDR-TB treatment without aminoglycosides[90] to minimise drug-related hearing sequelae. Therefore, the high prevalence of hearing sequelae in the current study could be due to the inclusion of aminoglycosides in the past treatment regimens of MDR- and XDR-TB.

In our review, nearly one in twenty patients with MDR-TB developed visual sequelae. The finding was lower than for a systematic review conducted among patients with DS-TB (11.9%). A possible reason could be due to the prolonged use of the drug ethambutol in patients with DS-TB,[91] which is not used in patients with MDR-TB. Ethambutol is a potent anti-TB drug that commonly affects the optic nerve and can cause irreversible visual sequelae.[92]

The prevalence of physical sequelae was heterogeneous when stratified by type of TB, the timing of treatment, country income, and DM status. For instance: respiratory sequelae were more prevalent among patients with MDR-TB after completing their treatment compared with patients with MDR-TB during treatment. This could be explained by the endobronchial involvement that causes extended parenchymal destruction[11] further resulting in poor compliance, bronchiectasis, aspergilloma, and other parenchymal airway diseases.[93] It is also expected that chemotherapy-cured patients with MDR-TB, who usually end-up with significant lung destruction and chronic complications like fibrosis, bronchiectasis, and cavitations.[94] Although patients become negative bacteriologically, a significant number of patients with MDR-TB are left with persistent symptoms and lung function sequelae.[95] A likely explanation is the occurrence of common residual conditions like fibrosis, scarring, cavitation, and distortion of lung architecture that led to volume loss and bronchiectasis.[95] Pulmonary TB also involves airways and results in hyperplasia and hypertrophy of mucous glands, thus affecting the functioning of airways, and causing a reduction of total lung capacity. Hence, there will be a significant increase in functional limitations among patients with MDR-TB.[96]

The highest prevalence of respiratory sequela was reported among studies conducted in LICs countries (59.3%). The possible reason could be due to weak healthcare systems, inadequate financing, poverty, and poor access (in terms of quality, geographic access, financial access, and acceptability of services) in LICs and LMICs countries as compared with HICs and UMICs countries.[97,98] The other possible reason could be due to the presence of possible diagnosis delay, treatment delay, and the long and less effective medication regimens of patients with MDR-TB in LICs and LMICs countries.[95] Moreover, low-income countries have poor access to education and poor health insurance,[99] which improves the patient's health outcome.[100] Non-invasive respiratory support and adjunct surgical resection, which is less affordable in LICs and LMICs countries, were associated with an increase in maintaining a residual capacity to prevent lung complications[101] and improved symptoms of respiratory sequelae by enhancing pulmonary function and elastic recoil.[81] The high burden of respiratory sequelae may also relate to the high burden of TB in LICs and LMIC countries. Moreover, patients with MDR-TB might be exposed to multiple exposures like smoking, occupational exposures, and indoor biomass fuels that could further result in respiratory failure.[102]

On the other hand, we found that the prevalence of hearing, renal, and hepatic sequelae was higher in UMICs and HICs countries than in LMICs and LICs countries. The lower prevalence of hearing sequelae in LICs and LMICs could be due to a lack of audiometric tools to measure hearing sequelae in LICs and LMICs countries.[103] The lower prevalence of renal and hepatic sequelae in LICs and LMICs countries could be due to the high burden of DM[104] and hypertension[105] in HICs and UMICs countries. DM and hypertension commonly increase the risk of developing renal sequelae, including end-stage renal failure.[106] Moreover, comorbidities including DM and hypertension negatively impact on the patient's immune response, precipitate treatment failure.[107] It could be also due to the high cost and complexity of diagnosing renal sequelae in LICs and LMICs countries.

A high prevalence of neurological sequelae was reported among patients with a high prevalence of DM. A possible reason could be that DM causes endothelial dysfunction, inflammation, platelet aggregation, and vascular smooth muscle cell dysfunction, which leads to atherosclerosis, which in turn can impact neurological outcomes.[108] The prevalence of musculoskeletal sequelae significantly differed by HIV status. This could be due to the high prevalence of HIV among patients with XDR-TB (>50% prevalence in 75% of studies) than patients with MDR-TB (>50% in none of the studies).

Patients with MDR and XDR-TB developed sequelae during or post-TB treatment due to either the nature of the second-line drugs or the disease itself. MDR-TB by itself causes active lesions of the parenchymal (infiltration, cavitations, consolidations, and glass opacity) that further cause extensive tissue damage by the long duration of the disease compared to DS-TB.[3] The dominant cavities and consolidations in MDR- and XDR-TB occurred following a failure of post-TB treatment.[2] Unhealed cavities, in turn, cause new cavities and consolidations in patients with MDR-TB.[2] Bronchiectasis, a non-lung parenchymal morphology, is a dilation of multiple bronchi resulting from the course of active lesions of post-pulmonary TB and affects the surrounding structures such as bronchus and bronchioles.[109] Non-active parenchymal lesions (fibrosis, calcification, and atelectasis) are common post-MDR-TB sequelae in patients with DR-TB. It causes the reactivation of active TB in the long run and leads to recovery.[2,3] Therefore, we can conclude that respiratory sequelae are mainly caused by the disease progression and not a drug-related problems.

On the other hand, aminoglycosides such as Amikacin, Capreomycin, and Kanamycin are the common causes of hearing sequelae among patients with MDR-and XDR-TB.[110] For instance: a previous study showed that Kanamycin-based regimens were associated with a higher risk of hearing loss.[4,111] WHO 2018 report recommended the replacement of aminoglycoside agents with less toxic agents such as Bedaquiline-based regimens to minimise permanent hearing loss.[89] This evidence supports our hypothesis aminoglycoside agents cause hearing-related sequelae, and it is possible to conclude that hearing sequelae is mainly drug-related sequelae.

In the current study, patients with XDR-TB were at a higher risk of developing visual sequelae compared with patients with MDR-TB. The higher prevalence of visual sequelae among patients with XDR-TB could be because of higher doses and longer durations of linezolid, it is a well-known cause of optic neuropathy among patients with MDR-TB.[112] Similarly, patients with MDR-TB were at a higher risk of developing neurological sequelae due to the drug linezolid. Its effect increases with the dose and duration of treatment. As a result, patients with DR-TB were at a higher risk of neurological and visual sequelae. For instance, reducing linezolid dose from 600 to 300 g reduced the risk of neurological abnormalities and improved treatment outcomes.[113] This finding strengthens our hypothesis of both neurological and visual sequelae are more drug-related sequelae. However, the effect of linezolid on neurological sequelae among patients with MDR- and XDR-TB needs further study. In general, neurological sequelae are irreversible and patient's quality of life through functional, mental, and social impairment.[91,114]

Adequate and standardised monitoring of patients with MDR- and XDR-TB during and after the completion of treatment will be necessary to minimise the burden of physical sequelae. DR-patients with TB are declared cured or completed based on clinical, smear, and radiological examinations.[1] However, there is a lack of follow-up and support for patients with MDR-TB and XDR-TB after the completion of their treatment. Therefore, policymakers, planners, researchers, and clinicians need to work collaboratively to decrease the burden of long-term physical sequelae after the completion of their treatment. Preparing standard monitoring guidelines, expanding the availability of objective tools, and discussions with stakeholders on the management of post-MDR-TB sequelae will reduce the burden of physical sequelae.

Secondly, creating awareness of physical sequelae among clinicians and patients will be necessary to ensure the provision of integrated care during and after the completion of treatment. Thirdly, the ministries of health of each country should implement a strategy to build skills and systems for long-term care for patients. Finally, the scaling-up of a rehabilitation centre and tools (hearing aids, vision aids, and wheelchairs) will play a vital role. LICs and LMICs countries need international support to manage the high costs associated with patient care with long-term sequelae.

This study has some important limitations. The first limitation was the presence of high heterogeneity between included studies. We investigated the sources of heterogeneity by conducting a sub-group analysis for each of the outcomes. Secondly, each study used different methodologies or tools for outcome ascertainment. This will lead to errors in estimates of the prevalence of physical sequelae. Thirdly, since more than 50% of studies did not report the dose and type of DR-TB regimen, it wasn't possible to determine drug-specific sequelae among patients with DR-TB. The study lacks information on whether the sequelae developed because of the DR-TB drugs or the disease itself. Fourthly, it is impossible to assess the severity of sequelae as there isn't reported data on the severity of sequelae. The existing publication bias will under or overestimate the overall finding. As a result, it could affect the representativeness of the study. The study also lacks information on what fraction of patients had been previously treated for TB as included studies reported previously treated cases of TB, MDR-TB, and XDR-TB combined.

This systematic review found that long-term physical sequelae such as respiratory, hearing, musculoskeletal, neurological, renal, hepatic, and visual sequelae were common among survivors of MDR- and XDR-TB. There were significant differences in the prevalence of sequelae between patients with MDR- and XDR-TB. There is a substantial need for incorporating post-MDR-TB and XDR-TB treatment surveillance into the current programmatic management of MDR-TB to early detect and prevent post-treatment sequelae, and for health systems to be supported and strengthened to be able to provide appropriate ongoing care to patients after cessation of TB treatment.

Contributors

TYA, ACAC, and KAA conceptualised the study. TYA, ACAC, HFW, and KAA performed data curation. TYA and KAA carried out the statistical analysis and accessed and verified the data. TYA wrote the first draft of the manuscript with input from ACAC and KAA. All authors reviewed the final draft of the manuscript for intellectual content. All authors had full access to the data and had final responsibility for the decision to submit for publication.

Data sharing statement

Data will be available upon request from the corresponding author.

Declaration of interests

All authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.101900.

References

1 World Health Organization. *WHO consolidated guidelines on drug-resistant tuberculosis treatment*. World Health Organization. 2019; Geneva, License: CC BY-NC-SA 3.0 IGO.

2 Zahirifard S, Bakhshayeshkaram M. The radiological spectrum of pulmonary multidrug-resistant tuberculosis in HIV-negative patients. *Iran J Radiol*. 2003;1(3&4):161–166.

3 Icksan AG, Napitupulu MRS, Nawas MA, Nurwidya F. Chest X-ray findings comparison between multi-drug-resistant tuberculosis and drug-sensitive tuberculosis. *J Nat Sci Biol Med*. 2018;9(1):42–46.

4 Nizamuddin S, Khan FA, Khan AR, Kamaal CM. Assessment of hearing loss in multi-drug resistant tuberculosis (MDR-TB) patients undergoing aminoglycoside treatment. *Int J Res Med Sci*. 2015;3(7):1734–1740.

5 Alene KA, Clements ACA, McBryde ES, et al. Sequelae of multidrug-resistant tuberculosis: protocol for a systematic review and meta-analysis. *BMJ Open*. 2018;8(2):e019593.

6 Alene KA, Clements AC, McBryde ES, et al. Mental health disorders, social stressors, and health-related quality of life in patients with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *J Infect*. 2018;77(5):357–367.

7 Byrne AL, Marais BJ, Mitnick CD, et al. Chronic airflow obstruction after successful treatment of multidrug-resistant tuberculosis. *ERJ Open Res*. 2017;3(3):00026-2017.

8 van Kampen SC, Wanner A, Edwards M, et al. International research and guidelines on post-tuberculosis chronic lung disorders: a systematic scoping review. *BMJ Glob Health*. 2018;3(4): e000745.

9 Amaral AF, Coton S, Kato B, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. *Eur Respir J*. 2015;46(4):1104–1112.

10 Akkara S, Shah A, Adalja M, Akkara A, Rathi A, Shah D. Pulmonary tuberculosis: the day after. *Int J Tuberc Lung Dis*. 2013;17(6): 810–813.

11 Godoy MD, Mello FC, Lopes AJ, et al. The functional assessment of patients with pulmonary multidrug-resistant tuberculosis. *Respir Care*. 2012;57(11):1949–1954.

12 Garg RK, Somvanshi DS. Spinal tuberculosis: a review. *J Spinal Cord Med*. 2011;34(5):440–454.

13 Jain A. Tuberculosis of the spine: a fresh look at an old disease. *J Bone Joint Surg Br*. 2010;92(7):905–913.

14 Tahaoğlu K, Törün T, Sevim T, et al. The treatment of multidrug-resistant tuberculosis in Turkey. *N Engl J Med*. 2001;345(3): 170–174.

15 Zhang J, Herdman T, Saunders M, et al. Rising burden of visual and auditory disability in patients after tuberculosis therapy in Peruvian slums. *Int J Infect Dis*. 2018;73(Suppl):348–349.

16 Gunasekeran DV, Gupta B, Cardoso J, Pavesio CE, Agrawal R. Visual morbidity and ocular complications in presumed intraocular tuberculosis: an analysis of 354 cases from a non-endemic population. *Ocul Immunol Inflamm*. 2018;26(6):865–869.

17 Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis*. 2009;9(3):153–161.

18 Ettehad D, Schaaf HS, Seddon JA, Cooke GS, Ford N. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis*. 2012;12(6): 449–456.

19 Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. *Clin Infect Dis*. 2010;51(1):6–14.

20 Alene KA, Wangdi K, Colquhoun S, et al. Tuberculosis related disability: a systematic review and meta-analysis. *BMC Med*. 2021; 19(1):1–19.

21 Uplekar M, Weil D, Lonnroth K, et al. WHO's new end TB strategy. *Lancet*. 2015;385(9979):1799–1801.

22 Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1.

23 Wells G, Shea B, O'Connell D, et al. *Newcastle-Ottawa quality assessment scale cohort studies*. 2014.

24 Appana D, Joseph L, Paken J. An audiological profile of patients infected with multi-drug resistant tuberculosis at a district hospital in KwaZulu-Natal. *S Afr J Commun Disord*. 2016;63(1): e1–e12.

25 Arnold A, Cooke GS, Kon OM, et al. Adverse effects and choice between the injectable agents amikacin and capreomycin in multidrug-resistant tuberculosis. *Antimicrob Agents Chemother*. 2017;61(9).

26 Atif M, Bashir A, Ahmad N, Fatima RK, Saba S, Scahill S. Predictors of unsuccessful interim treatment outcomes of multidrug resistant tuberculosis patients. *BMC Infect Dis*. 2017;17(1):655.

27 Baghaei P, Tabarsi P, Dorriz D, et al. Adverse effects of multidrug-resistant tuberculosis treatment with a standardized regimen: a report from Iran. *Am J Ther*. 2011;18(2):e29–e34.

28 Buziashvili M, Mirtskhulava V, Kipiani M, et al. Rates and risk factors for nephrotoxicity and ototoxicity among tuberculosis patients in Tbilisi, Georgia. *Int J Tuberc Lung Dis*. 2019;23(9): 1005–1011.

29 Cheng N, Wu S, Luo X, et al. A comparative study of chest computed tomography findings: 1030 cases of drug-sensitive tuberculosis versus 516 cases of drug-resistant tuberculosis. *Infect Drug Resist*. 2021;14:1115–1128.

30 Dayyab F, Iliyasu G, Ahmad B, Habib A. Early safety and efficacy of linezolid-based combination therapy among patients with drug-resistant tuberculosis in North-western Nigeria. *Int J Mycobacteriol*. 2021;10(2):129–135.

31 de Jager P, van Altena R. Hearing loss and nephrotoxicity in long-term aminoglycoside treatment in patients with tuberculosis. *Int J Tuberc Lung Dis*. 2002;6(7):622–627.

32 Dela AI, Tank NKD, Singh AP, Piparva KG. Adverse drug reactions and treatment outcome analysis of DOTS-plus therapy of MDR-TB patients at district tuberculosis centre: a four year retrospective study. *Lung India*. 2017;34(6):522–526.

33 Fatima S, Syeda MF, Adla N, Devi R. Ambispective study of adverse drug reactions in multi-drug resistant tuberculosis patients in Warangal, Telangana. *Lung India: official organ of Indian Chest Society*. 2021;38(4):330–337.

34 Gao JT, Du J, Wu GH, et al. Bedaquiline-containing regimens in patients with pulmonary multidrug-resistant tuberculosis in China: focus on the safety. *Infect Dis Poverty*. 2021;10(1):32.

35 Geerligs WA, Van Altena R, De Lange WCM, Van Soolingen D, Van Der Werf TS. Multidrug-resistant tuberculosis: long-term treatment outcome in The Netherlands. *Int J Tuberc Lung Dis*. 2000;4(8):758–764.

36 Gualano G, Mencarini P, Musso M, et al. Putting in harm to cure: drug related adverse events do not affect outcome of patients receiving treatment for multidrug-resistant Tuberculosis. Experience from a tertiary hospital in Italy. *PLoS One*. 2019;14(2):e0212948.

37 Harouna SH, Ortuno-Gutierrez N, Souleymane MB, et al. Short-course treatment outcomes and adverse events in adults and children-adolescents with MDR-TB in Niger. *Int J Tuberc Lung Dis*. 2019;23(5):625–630.

38 Hong H, Dowdy DW, Dooley KE, et al. Risk of hearing loss among multidrug-resistant tuberculosis patients according to cumulative aminoglycoside dose. *Int J Tuberc Lung Dis*. 2020;24(1):65–72.

39 Huerga H, Bastard M, Kamene M, et al. Outcomes from the first multidrug-resistant tuberculosis programme in Kenya. *Int J Tuberc Lung Dis*. 2017;21(3):314–319.

40 Isaakidis P, Cox HS, Varghese B, et al. Ambulatory multi-drug resistant tuberculosis treatment outcomes in a cohort of HIV-infected patients in a slum setting in Mumbai, India. *PLoS One*. 2011;6(12):e28066.

41 Jain K, Desai M, Solanki R, Dikshit RK. Treatment outcome of standardized regimen in patients with multidrug resistant tuberculosis. *J Pharmacol Pharmacother*. 2014;5(2):145–149.

42 Jones J, Mudaly V, Voget J, Naledi T, Maartens G, Cohen K. Adverse drug reactions in South African patients receiving bedaquiline-containing tuberculosis treatment: an evaluation of spontaneously reported cases. *BMC Infect Dis*. 2019;19(1):544.

43 Kashongwe IM, Mawete F, Mbulula L, et al. Outcomes and adverse events of pre- and extensively drug-resistant tuberculosis patients in Kinshasa, Democratique Republic of the Congo: a retrospective cohort study. *PLoS One*. 2020;15(8):e0236264.

44 Keshavjee S, Gelmanova IY, Shin SS, et al. Hepatotoxicity during treatment for multidrug-resistant tuberculosis: occurrence, management and outcome. *Int J Tuberc Lung Dis*. 2012;16(5):596–603.
45 Kuaban C, Noeske J, Rieder HL, Ait-Khaled N, Abena Foe JL, Trebucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. *Int J Tuberc Lung Dis*. 2015;19(5):517–524.
46 Li D, He W, Chen B, Lv P. Primary multidrug-resistant tuberculosis versus drug-sensitive tuberculosis in non-HIV-infected patients: comparisons of CT findings. *PLoS One*. 2017;12(6):e0176354.
47 Matambo R, Takarinda KC, Thekkur P, et al. Treatment outcomes of multi drug resistant and rifampicin resistant Tuberculosis in Zimbabwe: a cohort analysis of patients initiated on treatment during 2010 to 2015. *PLoS One*. 2020;15(4):e0230848.
48 Merid MW, Gezie LD, Kassa GM, Muluneh AG, Akalu TY, Yenit MK. Incidence and predictors of major adverse drug events among drug-resistant tuberculosis patients on second-line anti-tuberculosis treatment in Amhara regional state public hospitals; Ethiopia: a retrospective cohort study. *BMC Infect Dis*. 2019; 19(1):286.
49 Modongo C, Sobota RS, Kesenogile B, et al. Successful MDR-TB treatment regimens including amikacin are associated with high rates of hearing loss. *BMC Infect Dis*. 2014;14:542.
50 Muñoz-Torrico M, Cid-Juárez S, Gochicoa-Rangel L, et al. Functional impact of sequelae in drug-susceptible and multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis*. 2020;24(7):700–705.
51 Murniati M, Handayani D, Isbaniah F. Two-years biannual evaluation of drug-resistant tuberculosis patients completing their treatment at persahabatan general hospital jakarta. *Respir Sci*. 2020;1(1):15–32.
52 Nair D, Velayutham B, Kannan T, et al. Predictors of unfavourable treatment outcome in patients with multidrug-resistant tuberculosis in India. *Public Health Action*. 2017;7(1):32–38.
53 Nuwagira E, Stadelman A, Baluku JB, et al. Obstructive lung disease and quality of life after cure of multi-drug-resistant tuberculosis in Uganda: a cross-sectional study. *Trop Med Health*. 2020;48:34.
54 Olayanju O, Esmail A, Limberis J, Gina P, Dheda K. Linezolid interruption in patients with fluoroquinolone-resistant tuberculosis receiving a bedaquiline-based treatment regimen. *Int J Infect Dis*. 2019;85:74–79.
55 Onur ST, Ortakoylu MG, Iliaz S, Alkan F. Treatment outcome and mortality among geriatric patients diagnosed with multiple-drug resistant tuberculosis: a comparative analysis from a tertiary referral center. *Haseki Tip Bulteni*. 2021;59(5):377–380.
56 Padayatchi N, Bionghi N, Osman F, et al. Treatment outcomes in patients with drug-resistant TB-HIV coinfection treated with bedaquiline and linezolid. *Int J Tuberc Lung Dis*. 2020;24(10): 1024–1031.
57 Piparva KG, Jansari G, Singh AP. Evaluation of treatment outcome and adverse drug reaction of directly observed treatment (DOT) plus regimen in multidrug-resistant tuberculosis (MDR-TB) patients at district tuberculosis centre Rajkot. *Perspect Clin Res*. 2018;9(4):165–169.
58 Piubello A, Harouna SH, Souleymane MB, et al. High cure rate with standardised short-course multidrugresistant tuberculosis treatment in Niger: No relapses. *Int J Tuberc Lung Dis*. 2014;18(10): 1188–1194.
59 Prasad R, Singh A, Srivastava R, Hosmane GB, Kushwaha RAS, Jain A. Frequency of adverse events observed with second-line drugs among patients treated for multidrug-resistant tuberculosis. *Indian J Tuberc*. 2016;63(2):106–114.
60 Ramma L, Ibekwe TS. Cochleo-vestibular clinical findings among drug resistant Tuberculosis Patients on therapy-a pilot study. *Int Arch Med*. 2012;5:3.
61 Rehman S, Munir MK, Iqbal R, Saeed MS, Aasim M. Long term follow up of multi drug resistance tuberculosis patients after 3-4 Years of starting second line anti tubercular drugs. *Ann King Edw Med Univ Lahore Pakistan*. 2017;23(3):328–334.
62 Sabur NF, Brar MS, Wu L, Brode SK. Low-dose amikacin in the treatment of multidrug-resistant tuberculosis (MDR-TB). *BMC Infect Dis*. 2021;21(1):254.
63 Sagwa E, Mantel-Teeuwisse AK, Ruswa N, et al. The burden of adverse events during treatment of drug-resistant tuberculosis in Namibia. *South Med Rev*. 2012;5(1):6–13.
64 Sagwa EL, Ruswa N, Mavhunga F, Rennie T, Leufkens HGM, Mantel-Teeuwisse AK. Comparing amikacin and kanamycin-induced hearing loss in multidrug-resistant tuberculosis treatment under programmatic conditions in a Namibian retrospective cohort. *BMC Pharmacol Toxicol*. 2015;16:36.
65 Sagwa EL, Ruswa N, Mavhunga F, et al. Renal function of MDR-TB patients treated with kanamycin regimens or concomitantly with antiretroviral agents. *Int J Tuberc Lung Dis*. 2017;21(12):1245–1250.
66 Satti H, McLaughlin MM, Omotayo DB, et al. Outcomes of comprehensive care for children empirically treated for multidrug-resistant tuberculosis in a setting of high HIV prevalence. *PLoS One*. 2012;7(5):e37114.
67 Schnippel K, Berhanu RH, Black A, et al. Severe adverse events during second-line tuberculosis treatment in the context of high HIV Co-infection in South Africa: a retrospective cohort study. *BMC Infect Dis*. 2016;16(1):593.
68 Seddon JA, Thee S, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in children treated for multidrug-resistant tuberculosis. *J Infect*. 2013;66(4):320–329.
69 Seid Y, Ketema B, Yilma M, Desalegn Z. Severe adverse effects associated with multidrug resistant tuberculosis medications among patients attending alert hospital, Ethiopia. *Ethiop Med J*. 2019;57(1):49–58.
70 Shah NP, Pyakurel P, Khanal M, et al. High success and low recurrence with shorter treatment regimen for multidrug-resistant tb in Nepal. *Public Health Action*. 2021;11:38–45.
71 Sharma V, Bhagat S, Verma B, Singh R, Singh S. Audiological evaluation of patients taking kanamycin for multidrug resistant tuberculosis. *Iran J Otorhinolaryngol*. 2016;28(86): 203–208.
72 Shastri U, Khateeb ZF, Khan MA, Kanagokar V. Hearing in individuals enrolled for drug-resistant tuberculosis treatment: a retrospective study from a South Indian city. *Hear Bal Commun*. 2021;19(2):118–125.
73 Shean K, Streicher E, Pieterson E, et al. Drug-associated adverse events and their relationship with outcomes in patients receiving treatment for extensively drug-resistant tuberculosis in South Africa. *PLoS One*. 2013;8(5):e63057.
74 Singla N, Singla R, Fernandes S, Behera D. Post treatment sequelae of multi-drug resistant tuberculosis patients. *Indian J Tuberc*. 2009;56(4):206–212.
75 Singla R, Mallick M, Mrigpuri P, Singla N, Gupta A. Sequelae of pulmonary multidrug-resistant tuberculosis at the completion of treatment. *Lung India*. 2018;35(1):4–8.
76 Smith JP, hi NR, Shah NS, et al. The impact of concurrent antiretroviral therapy and MDR-TB treatment on adverse events (1999) *J Acquir Immune Defic Syndr*. 2020;83(1):47–55.
77 Sogebi OA, Adefuye BO, Adebola SO, Oladeji SM, Adedeji TO. Clinical predictors of aminoglycoside-induced ototoxicity in drug-resistant Tuberculosis patients on intensive therapy. *Auris Nasus Larynx*. 2017;44(4):404–410.
78 Sogebi OA, Fadeyi MO, Adefuye BO, Soyinka FO. Hearing thresholds in patients with drug-resistant tuberculosis: baseline audiogram configurations and associations. *J Bras Pneumol*. 2017;43(3):195–201.
79 Tack I, Dumicho A, Ohler L, et al. Safety and effectiveness of an all-oral, bedaquiline-based, shorter treatment regimen for rifampicin-resistant tuberculosis in high human immunodeficiency Virus (HIV) burden rural South Africa: a retrospective cohort analysis. *Clin Infect Dis*. 2021;73(9):E3563–E3571.
80 Trubnikov A, Hovhannesyan A, Akopyan K, et al. Effectiveness and safety of a shorter treatment regimen in a setting with a high burden of multidrug-resistant tuberculosis. *Int J Environ Res Public Health*. 2021;18(8):4121.
81 Vashakidze SA, Kempker JA, Jakobia NA, et al. Pulmonary function and respiratory health after successful treatment of drug-resistant tuberculosis. *Int J Infect Dis*. 2019;82:66–72.
82 Wangchuk P, Ram Adhikari T, Nima G, Dendup P. Audiological monitoring of patients undergoing multidrug resistant tuberculosis treatment at jigme dorji wangchuk national referral hospital and gidakom hospital, Bhutan. *J Clin Tuberc Other Mycobact Dis*. 2021;23:100229.
83 Yang S, Yu Y, Ji Y, et al. Multi-drug resistant spinal tuberculosis-epidemiological characteristics of in-patients: a multicentre retrospective study. *Epidemiol Infect*. 2020;148:e11.
84 Zhang Y, Wu S, Xia Y, et al. Adverse events associated with treatment of multidrug-resistant tuberculosis in China: an ambispective cohort study. *Med Sci Monit*. 2017;23:2348–2356.
85 Zubair SM, Ali MG, Irfan M. Post tuberculosis radiological sequelae in patients treated for pulmonary and pleural tuberculosis at a tertiary center in Pakistan. *Monaldi Arch Chest Dis*. 2021;92(1).

86 Oladimeji O, Adeniji-Sofoluwe AT, Othman Y, et al. Chest X-ray features in drug-resistant tuberculosis patients in Nigeria; a retrospective record review. *Medicines (Basel, Switzerland)*. 2022;9(9):46.
87 Alene KA, Wangdi K, Colquhoun S, et al. Tuberculosis related disability: a systematic review and meta-analysis. *BMC Med*. 2021;19(1):203.
88 Selimoglu E. Aminoglycoside-induced ototoxicity. *Curr Pharm Des*. 2007;13(1):119–126.
89 World Health Organization. *Rapid Communication: key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB)*. Geneva: World Health Organization; 2018.
90 WHO consolidated guidelines on tuberculosis: module 4: treatment - Drug-resistant tuberculosis treatment. *WHO guidelines approved by the guidelines review committee*. Geneva: World Health Organization; 2020.
91 Maguire G, Anstey NM, Ardian M, et al. Pulmonary tuberculosis, impaired lung function, disability and quality of life in a high-burden setting. *Int J Tuberc Lung Dis*. 2009;13(12):1500–1506.
92 Lim SA. Ethambutol-associated optic neuropathy. *Ann Acad Med Singap*. 2006;35(4):274–278.
93 Lopez-Pastorini A, Plönes T, Ludwig C, Stoelben E. Intrapulmonary aspergilloma in an old tuberculous cavity with access to the bronchial system. *Eur J Cardiothorac Surg*. 2014;46(1):144.
94 Dheda K, Booth H, Huggett JF, Johnson MA, Zumla A, Rook GA. Lung remodeling in pulmonary tuberculosis. *J Infect Dis*. 2005;192(7):1201–1209.
95 Dheda K, Chang KC, Guglielmetti L, et al. Clinical management of adults and children with multidrug-resistant and extensively drug-resistant tuberculosis. *Clin Microbiol Infect*. 2017;23(3):131–140.
96 Ravimohan S, Kornfeld H, Weissman D, Bisson GP. Tuberculosis and lung damage: from epidemiology to pathophysiology. *Eur Respir Rev*. 2018;27(147):170077.
97 Peters DH, Garg A, Bloom G, Walker DG, Brieger WR, Rahman MH. Poverty and access to health care in developing countries. *Ann N Y Acad Sci*. 2008;1136:161–171.
98 Cox V, Cox H, Pai M, Stillo J, Citro B, Brigden G. Health care gaps in the global burden of drug-resistant tuberculosis. *Int J Tuberc Lung Dis*. 2019;23(2):125–135.
99 Lazar M, Davenport L. Barriers to health care access for low income families: a review of literature. *J Community Health Nurs*. 2018;35(1):28–37.
100 Fan H, Yan Q, Coyte PC, Yu W. Does public health insurance coverage lead to better health outcomes? Evidence from Chinese adults. *Inquiry*. 2019;56:46958019842000.
101 Gulla KM, Kabra SK, Lodha R. Feasibility of pediatric non-invasive respiratory support in low- and middle-income countries. *Indian Pediatr*. 2021;58(11):1077–1084.
102 Allwood BW, Byrne A, Meghji J, Rachow A, Van Der Zalm MM, Schoch OD. Post-tuberculosis lung disease: clinical review of an under-recognised global challenge. *Respiration*. 2021;100(8):751–763.
103 Dillard LK, Martinez RX, Perez LL, Fullerton AM, Chadha S, McMahon CM. Prevalence of aminoglycoside-induced hearing loss in drug-resistant tuberculosis patients: a systematic review. *J Infect*. 2021;83(1):27–36.
104 Shahwan M, Hassan N, Shaheen RA, et al. Diabetes mellitus and renal function: current medical research and opinion. *Curr Diabetes Rev*. 2021;17(9):e011121190176.
105 Monhart V. [Hypertension and chronic renal insufficiency–chronic kidney failure]. *Vnitr Lek*. 2003;49(5):388–394.
106 Thomas PP. Changing profile of causes of chronic renal failure. *Saudi J Kidney Dis Transpl*. 2003;14(4):456–461.
107 Krishna S, Jacob JJ. Diabetes mellitus and tuberculosis. In: Feingold KR, Anawalt B, Boyce A, et al., eds. *Endotext*; 2000. South Dartmouth (MA) www.Endotext.org.
108 Soyoye DO, Abiodun OO, Ikem RT, Kolawole BA, Akintomide AO. Diabetes and peripheral artery disease: a review. *World J Diabetes*. 2021;12(6):827–838.
109 Prasad R. Multidrug and extensively drug-resistant tuberculosis management: evidences and controversies. *Lung India*. 2012;29:154–159.
110 Hong H, Dowdy DW, Dooley KE, et al. Aminoglycoside-induced hearing loss among patients being treated for drug-resistant tuberculosis in South Africa: a prediction model. *Clin Infect Dis*. 2020;70(5):917–924.
111 Ghafari N, Court R, Chirehwa MT, et al. Pharmacokinetics and other risk factors for kanamycin-induced hearing loss in patients with multi-drug resistant tuberculosis. *Int J Audiol*. 2020;59(3):219–223.
112 Park DH, Park TK, Ohn YH, Park JS, Chang JH. Linezolid induced retinopathy. *Doc Ophthalmol*. 2015;131(3):237–244.
113 Singh B, Cocker D, Ryan H, Sloan DJ. Linezolid for drug-resistant pulmonary tuberculosis. *Cochrane Database Syst Rev*. 2019;3(3):CD012836.
114 Mafukidze AT, Calnan M, Furin J. Peripheral neuropathy in persons with tuberculosis. *J Clin Tuberc Other Mycobact Dis*. 2016;2:5–11. https://doi.org/10.1016/j.jctube.2015.11.002.