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REVIEW

Risk Factors for Poor Outcomes Among Patients with Extensively Drug-Resistant Tuberculosis (XDR-TB): A Scoping Review

Karan Varshney
Beverly Anaele
Matthew Molaei
Rosemary Frasso
Vittorio Maio

College of Population Health, Thomas Jefferson University, Philadelphia, PA, USA

Abstract: In recent years, there has been an upsurge in cases of drug-resistant TB, and strains of TB resistant to all forms of treatment have begun to emerge; the highest level of resistance is classified as extensively drug-resistant tuberculosis (XDR-TB). There is an urgent need to prevent poor outcomes (death/default/failed treatment) of XDR-TB, and knowing the risk factors can inform such efforts. The objective of this scoping review was to therefore identify risk factors for poor outcomes among XDR-TB patients. We searched three scientific databases, PubMed, Scopus, and ProQuest, and identified 25 articles that examined relevant risk factors. Across the included studies, the proportion of patients with poor outcomes ranged from 8.6 to 88.7%. We found that the most commonly reported risk factor for patients with XDR-TB developing poor outcomes was having a history of TB. Other risk factors were human immunodeficiency virus (HIV), a history of incarceration, low body mass, being a smoker, alcohol use, unemployment, being male, and being middle-aged. Knowledge and understanding of the risk factors associated with poor outcomes of XDR-TB can help policy makers and organizations in the process of designing and implementing effective programs.

Keywords: drug-resistant, tuberculosis, risk factors, compliance, adherence, XDR-TB

Introduction

An estimated 1.7 billion people are currently infected with Mycobacterium tuberculosis,[1] the causative agent of tuberculosis (TB). TB was the leading cause of mortality from a single pathogen in 2018, with the bacterium being the attributed caused of approximately 1.5 million deaths worldwide.[2]

Successful treatment of TB is crucial to both curing the individual patient and reducing the transmission of Mycobacterium tuberculosis in the community. First-line treatment includes combination of chemotherapy, such as isoniazid, rifampicin, pyrazinamide, and ethambutol.[3] However, A major issue is the widespread prevalence of drug-resistant TB (DR-TB). At least 5% of all global cases of TB have some form of drug-resistance, that is, resistance to at least one first-line anti-TB drug.[4] Multi-drug resistant TB (MDR-TB) is defined as resistance to at least two first-line anti-TB drugs, isoniazid and rifampin,[2] and extensively drug-resistant TB (XDR-TB) is defined as resistance to isoniazid and rifampin, as well as any fluoroquinolone and any Group A TB drug (the most potent second-line drugs, and include levofloxacin, bedaquiline, linezolid, and moxifloxacin).[5] Pre-

Correspondence: Karan Varshney
College of Population Health, Thomas Jefferson University, 901 Walnut Street, 10th Floor, Philadelphia, PA, 19107, USA
Tel +1 604-359-6721
Email karan.varshney@students.jefferson.edu

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extensively drug-resistant TB (pre-XDR-TB) is defined as resistance to isoniazid and rifampin, as well as any fluoroquinolones.[5]

Drug-susceptible TB (DS-TB) is tuberculosis that is susceptible to all forms of standard treatment, and is normally treated with isoniazid, rifampin, pyrazinamide, and ethambutol.[6,7] Compared to patients with DS-TB, patients with drug-resistant strains of TB have considerably longer treatment regimens (regimens can be as long as 18–24 months for resistant strains compared to the standard 6-month regimen for non-resistant strains in DS-TB patients) which are more costly (treatment for XDR-TB can cost more than 25 times that of standard treatment [$494,000 USD compared to $17,000 USD][8]), and the negative side-effects of the drugs are more severe. Due to the difficulties associated with treatment, patients with DR-TB have higher default rates for treatment compared to those with DS-TB.[9,10]

Concerns about drug-resistant infections have been on the rise in recent years, with TB cases resistant to all available forms of treatment among the most worrisome. The first reported cases were described in Italy and Germany in 2007.[11] Additional reports of cases came from Iran in 2009, followed by India in 2012, and South Africa in 2013.[12–14] Since the emergence of these initial cases, it is not clearly understood how many more cases, which are resistant to all forms of treatment, have emerged.

Cases that have been identified as XDR-TB comprise an estimated 5.4% of all cases of DR-TB, or approximately 0.3% (5.1 million) of all global cases of TB.[15] However, cases of XDR-TB may be greatly underestimated because some patients may receive care in the private sector and because many individuals living in under-resourced settings never receive a diagnosis or treatment.[16,17]

The outlook for new antimicrobial drugs against XDR-TB is grim. Despite the urgent need, only minimal, new classes of antibiotics have been created in recent years. Antibiotics, such as those needed to treat TB, have a very low economic return, and so pharmaceutical companies devote only limited amounts of resources to their development.[18] Moreover, there are sizeable additional costs, along with other difficulties, associated with distributing drugs to regions experiencing XDR-TB. Lastly, once XDR-TB becomes prevalent in an area, it holds the potential to spread—as is the case with any drug-resistant disease or infection—with catastrophic consequences.[19–21]

XDR-TB incidence has been rising in recent years.[22] Furthermore, it has been demonstrated that XDR-TB patients have poorer outcomes (death/treatment default/failure) at rates much higher than those of non-XDR-TB patients.[23] Considering the extent of this issue, controlling XDR-TB is a very important global health priority. To better address this global health issue, more information is needed about the risk factors for poor outcomes associated with this infection. A review on the risk factors for XDR-TB that analyzed the literature published from 2006 to 2010 found that risk factors for developing XDR-TB included immigration status, HIV coinfection, alcoholism, having previously been infected with TB, and having pre-XDR-TB;[15] however, the authors noted that the literature was quite limited and that a more thorough investigation of possible risk factors is needed.[15] While a recent systematic review has focused on the risk factors for poor outcomes among DR-TB, minimal detail was given regarding risk factors specifically for XDR-TB.[24] Therefore, the purpose of this scoping review was to provide information on risk factors associated with poor outcomes for patients with XDR-TB.

Methods

Two reviewers (KV and BA) independently searched PubMed, Scopus and ProQuest, with the workflow following the "Preferred Items for Systematic Review and Meta-Analyses extension for Scoping Reviews" (PRISMA-ScR) guidelines.[25,26] All searches were conducted on July 10, 2020. As this review expands on a systematic review conducted in 2014 by Flor de Lima and Tavares, which analyzed risk factors for XDR-TB in studies published up to June 2010,[15] our searches were restricted to articles published after June 2010.

The most highly resistant forms of TB have been described in the literature in a number of different ways, aside from XDR-TB. These include: total drug-resistant TB,[27,28] totally drug-resistant TB,[11–14] (TDR-TB), super extensively drug-resistant TB (SXDR-TB or super XDR-TB),[12,29] extra extensively drug-resistant TB (XXDR-TB),[11,30] pan-resistant TB,[36,37] pan drug-resistant TB (PDR-TB),[30–33,38,39] untreatable TB,[34,35,40] untreatable drug-resistant TB,[36,37] incurable TB,[20,41] and incurable drug-resistant TB.[42,43] The term extremely drug-resistant TB has also, in some cases, been given the same abbreviation as extra extensively drug-resistant TB (XXDR-TB),[38,42] and, in others, the same as abbreviation as extensively drug-resistant TB (XDR-TB)[39,40] In order to account for this variation in terminology, all of these terms were included as search terms in our review. Additionally, our search terms referred to population-level factors and individual-level factors, as well as outcomes. Complete search terms are listed in Table 1.

Eligible settings included any region in the world where there have been recorded instances of XDR-TB. For the review process, the two reviewers screened potential articles for eligibility based on title, abstract, keywords, and date of publication. Duplicates were removed and all remaining full-text articles were then assessed. Data were extracted from each study if they satisfied the following inclusion criteria: (1) had a longitudinal design, (2) were originally published in English, (3) provided an analysis of population-level and/or individual-level risk factors, (4) provided stratified data for patients with poor outcomes (death/default/failed treatment) despite initial treatment, (6) described the prevalence of at least one of the levels of resistance described in Table 1, and (7) included at least 10 patients who ended up with poor outcomes. There was no registered study protocol for this review.

Data collection and extraction was conducted by utilizing the process from Flor de Lima and Tavares[15] as a framework. From all included studies, we extracted data on study characteristics, such as: country, data source, study design, sampling method, proportion of XDR-TB cases compared to total cases of TB, and the proportion of patients with poor outcomes. Thereafter, we extracted data on patient characteristics related to the outcome of interest, including sex, age, comorbidities, history of TB, and additional relevant factors identified in the individual study. These additional factors included, but were not limited to smoking status, race, adverse events during treatment, and body mass index (BMI).

Study quality was assessed using the Joanna Briggs Institute's (JBI) critical appraisal tools.[44] Study metrics that were assessed included reliability of exposure measurement, strategies to deal with confounding factors, validity of outcome measures, follow-up completion and loss of follow-up, and appropriateness of statistical of analyses. Following the approach taken in a number of different reviews,[45–47] the JBI tools were modified to provide a total score based on the number of yes/no responses on an eleven-item scale for cohort studies, and ten-item scale for case-control studies, and were depicted graphically thereafter. Quality assessment scores are shown in Supplementary Tables 1 and 2.

Table 1 Search Terms by Category*

Population	OR	Individual	AND	Outcomes
"Risk Factors"[Mesh] OR "Sociological Factors"[Mesh] OR "Socioeconomic Factors"[Mesh] OR "Social Determinants of Health"[Mesh] OR "Epidemiologic Factors"[Mesh] OR "Biological Variation, Population"[Mesh] OR "Genetics, Population"[Mesh]		"Biological Variation, Individual"[Mesh] OR "Genetics, Behavioral"[Mesh] OR "Health Risk Behaviors"[Mesh] OR "Patient Compliance"[Mesh] OR "Medication Adherence"[Mesh] OR "HIV Infections"[Mesh] OR "Emigration and Immigration"[Mesh] OR "Poverty"[Mesh] OR "Guideline Adherence"[Mesh] OR "Disease Susceptibility"[Mesh] OR "Coinfection"[Mesh]		"Extensively Drug-Resistant Tuberculosis" OR "Extremely Drug-Resistant Tuberculosis" OR "Extensively Drug-Resistant Tuberculosis" OR "Extremely Drug-Resistant Tuberculosis" OR "Extra Extensively Drug-Resistant Tuberculosis" OR "Super Extensively Drug-Resistant Tuberculosis" "Totally Drug-Resistant Tuberculosis" OR "Total Drug-Resistant Tuberculosis" OR "Pan-Resistant Tuberculosis" OR "Pan Drug-Resistant Tuberculosis" OR "Pan Drug Resistant Tuberculosis" OR "Untreatable Tuberculosis" OR "Untreatable Drug-Resistant Tuberculosis" OR "Incurable Tuberculosis" OR "Incurable Drug-Resistant Tuberculosis" OR "XDRTB" OR "TDRTB" OR "XDR TB" OR "XXDR TB" OR "TDR TB" OR "XDR-TB" OR "XXDR-TB" OR "SXDR TB" OR "PDRTB" OR "PDR TB" OR "SXDR-TB" "SXDR TB" OR "SXDRTB"

Notes: *Mesh term used for PubMed, and its equivalent used for Scopus and ProQuest.

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Results

The initial searches produced 2825 articles. After removal of duplicates, 2150 remained, 1922 of which were excluded after screening by title and abstract. Of the 228 articles that remained, 25 articles[48–72] met eligibility requirements and were included in the final review. The complete workflow is listed in Figure 1.

The study characteristics for the 25 articles that were reviewed are described in Table 2. The 25 articles provided data from 11 countries. One article provided data from four countries,[48] whereas the other 24 articles each provided data from a single country only. Twelve articles focused on South Africa,[53,55,56,60,62–67,70,71] four focused on China,[50,61,69,72] four on Latvia,[48,59] four on Estonia,[48,52] four on Russia,[49,68] and one on each of the following countries: India,[57] Pakistan,[58] Brazil,[51] Lithuania,[48] Romania,[48] and Georgia.[5454]

Of the articles included, 16 were retrospective cohort analyses,[49–52,54–61,64–67] eight were prospective cohort analyses,[46–50,62,63,68–70] and one was a case-control study.[55] Twelve studies focused only on XDR-TB patients,[49,50,54,60,62–67,70,71] whereas the other 13 also included MDR-TB patients.-[48,51–53,61,68,69,72] Total number of patients ranged from 67–3270. The proportion of patients with poor outcomes ranged from 8.6%-88.7% across the studies.

Quality assessment scores are shown in Figure 2. Out of 11 points total, the average score across cohort studies was 8.0 (range 6–10). The score for the single case-control study was 8 out of 10. The most frequent study limitations were insufficient follow-up time, a lack of strategies to describe and address incomplete follow-up, and a lack of appropriate statistical analyses.

All of the articles described used the term extensively drug-resistant TB, and its associated abbreviations. Two of the articles also utilized other terms and abbreviations to describe the highest levels of resistance in the patient population.[57,65] Pietersen et al used the

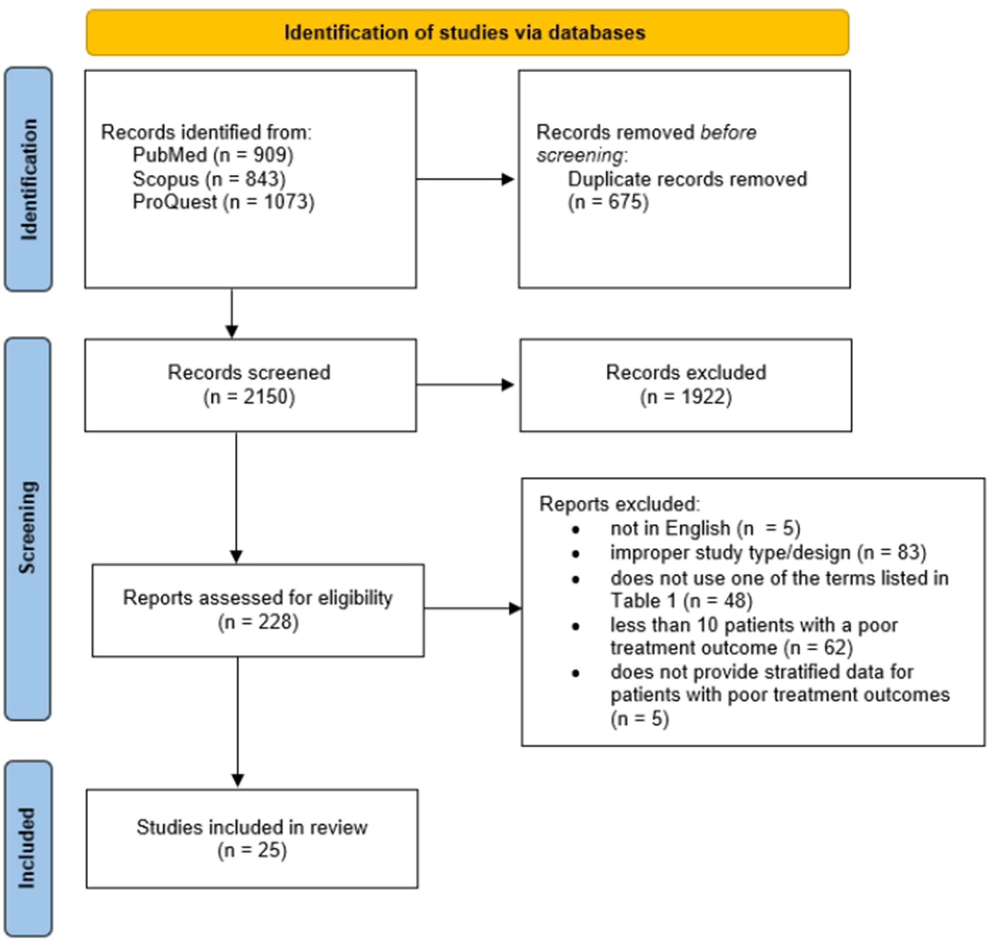

Figure 1 Study selection flow diagram.

Notes: PRISMAfigureadaptedfromPage MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.CreativeCommons.[26]

Table 2 Study, Region, and Participant Characteristics for Included Articles

Study	Country	Data Source	Study Design	Proportion of XDR Patients with Poor Outcomes (%)	XDR-TB Patients (% of Total)	Quality Score
Balabanova et al (2016)[48]	Latvia, Lithuania, Estonia, Romania	MDR and XDR TB patients at Lung Hospital at Tartu University (Estonia), National Tuberculosis and Infectious Diseases University Hospital in Vilnius (Lithuania), Clinic of Tuberculosis and Lung Diseases at Riga East University hospital (Riga, Latvia), and Marius Nasta Institute of Pneumology (Bucharest, Romania)	Prospective cohort study	227/737 (30.8%)*	81 (11.0%)	8/11
Balabanova et al (2011)[49]	Russia	Two separate cohorts from Samara with data from TB patients' register, and chart reviews (only the second cohort was included for this review): 1)Non MDR-TB and MDR-TB patients in a pilot DOTS-programme, from the civilian and prison sectors 2)XDR-TB patients, all of whom were civilians	Prospective cohort study	53/92 (57.6%)	92 (100%)	7/11
Bei et al (2018)[50]	China	XDR-TB patients in 4 TB care centers across China (Changsha Central Hospital, Wuhan Treatment Center, the Third People's Hospital of Hengyang, and the Second People's Hospital of Chenzhou)	Prospective cohort study	20/67 (29.9%)	67 (100%)	7/11
Bhering, Duarte and Kritski (2019)[51]	Brazil	MDR and XDR-TB patients in Rio de Janeiro; data from Tuberculosis Surveillance System	Retrospective cohort study	1005/2269 (44.3%)*	140 (6.2%)	9/11
Blöndal et al (2012)[52]	Estonia	Tuberculosis patients across Estonia via the Tuberculosis Registry Database	Retrospective cohort study	82/211 (38.9%)	43 (20.4%)	10/11
Chingonzoh et al (2018)[53]	South Africa	Laboratory confirmed DR-TB patients of patients 18 years old and above across Eastern Cape Province; data from Electronic DR-TB Register (EDRWeb) by the South African National TB Programme	Retrospective cohort study	1445/3729 (38.8%)	763 (20.5%)	7/11
Frank et al (2019)[54]	Georgia	XDR-TB patients across Georgia; data from National TB program, medical charts, interviews, and national Georgian death registry	Retrospective cohort study	71/111 (67.0%)	111 (100%)	8/11
Gandhi et al (2012)[55]	South Africa	MDR and XDR-TB patients in from the district hospital Tugela Ferry, KwaZulu-Natal; data from medical records	Case-control study	189/262 (72.1%)	139 (53.1%)	8/10
Gandhi et al (2010b)[56]	South Africa	MDR and XDR-TB patients in Tugela Ferry, South Africa; data came from medical records	Retrospective cohort study	498/639 (77.9%)	374 (58.5%)	7/11
James et al (2011)[57]	India	MDR and XDR-TB suspected patients in a tertiary care hospital in Vellore, Tamil Nadu; data came from medical records	Retrospective cohort study	21/177 cases (11.9%)	45/177 (25.4%)	6/11
Javaid et al (2018)[58]	Pakistan	MDR and XDR-TB patients who received care the MDR-TB unit in Peshawar, Khyber Pakhtunkhwa province	Retrospective cohort study	129/535 (24.1%)*	26 (4.9%)	9/11
Kuksa et al (2014)[59]	Latvia	MDR and XDR-TB patients across Latvia; data from national TB registry	Retrospective cohort study	564/1779 (31.7%)	133 (6.7%)	10/11

(*Continued*)

Table 2 (Continued).

Study	Country	Data Source	Study Design	Proportion of XDR Patients with Poor Outcomes (%)	XDR-TB Patients (% of Total)	Quality Score
Kvasnovsky et al (2011)[60]	South Africa	XDR-TB patients in hospitals of Eastern Cape Province, South Africa	Retrospective cohort study	95/206 (46.1%)	206 (100%)	10/11
Liu et al (2011)[61]	China	MDR and XDR-TB patients from the 309 hospital in Beijing	Retrospective cohort study	280/576 (48.6%)	48 (8.3%)	8/11
O'Donnell et al (2013)[62]	South Africa	Chart records from XDR patients admitted to a public TB referral hospital in KwaZulu-Natal	Retrospective cohort study	89/114 (78.1%)	114 (100%)	6/11
O'Donnell et al (2015)[63]	South Africa	Newly diagnosed adult XDR-TB patients in a public TB hospital in KwaZulu-Natal	Retrospective cohort study	49/216 (22.7%)	216 (100%)	8/11
Olayanju et al (2018)[64]	South Africa	Patients with laboratory-confirmed XDR-TB admitted to the Brooklyn Chest Hospital in Cape Town, Western Province	Prospective cohort study	168/272 (61.8%)	272 (100%)	9/11
Pietersen et al (2014)[65]	South Africa	XDR-TB patients from 3 XDR tuberculosis facilities: Brooklyn Chest Hospital (Cape Town, Western Cape), Gordonia Hospital (Upington, Northern Cape), Sizwe Tropical Diseases Hospital (Johannesburg, Gauteng Province)	Prospective cohort study	93/107 (86.9%)	107 (100%)	8/11
Pietersen et al (2015)[66]	South Africa	Case records of XDR-TB patients at two TB facilities in Western and Northern Cape Provinces	Retrospective cohort study	93/178 (52.2%)	178 (100%)	7/11
Shean et al (2013)[67]	South Africa	Case records of laboratory-confirmed XDR-TB patients across three XDR-TB treatment centers located in Gauteng, Northern Cape, and Western Cape	Retrospective cohort study	55/115 (47.8%)	55 (100%)	7/11
Shin et al (2010)[68]	Russia	Patients who began MDR-TB treatment at the Tomsk Oblast TB Treatment Services facility in Russia's Western Siberia	Retrospective cohort study	210/608 (34.5%)	34 (5.6%)	7/11
Tang et al (2013)[69]	China	MDR and XDR-TB HIV-negative patients in 5 hospitals across China (Shanghai Pulmonary Hospital, Guangzhou Chest Hospital, Hangzhou Red Cross Hospital, Tianjin Haihe Hospital and Henan Infectious Hospital)	Retrospective cohort study	346/1662 (20.8%)*	169 (10.2%)	6/11
Te Riele et al (2019)[70]	South Africa	Patients with an XDR-TB diagnosis at the Brooklyn Chest Hospital in Cape Town	Prospective cohort study	86/97 (88.7%)	97 (100%)	8/11
Yuengling et al (2018)[71]	South Africa	Adult XDR-TB patients at a TB referral hospital in KwaZulu-Natal, South Africa	Prospective cohort study	72/105 (68.6%)	105 (100%)	10/11
Zhang et al (2018)[72]	China	MDR-TB and XDR-TB patients from six regions in Zhejiang province: Hangzhou, Huzhou, Jiaxing, Lishui, Quzhou, and Shaoxing	Prospective cohort study	148/537 (27.6%)*	19 (3.5%)	10/11

Notes: *Presented as MDR and XDR-TB patients with poor outcomes/Total MDR and XDR-TB patients if stratification for XDR-TB patients' poor outcomes was not conducted in study.

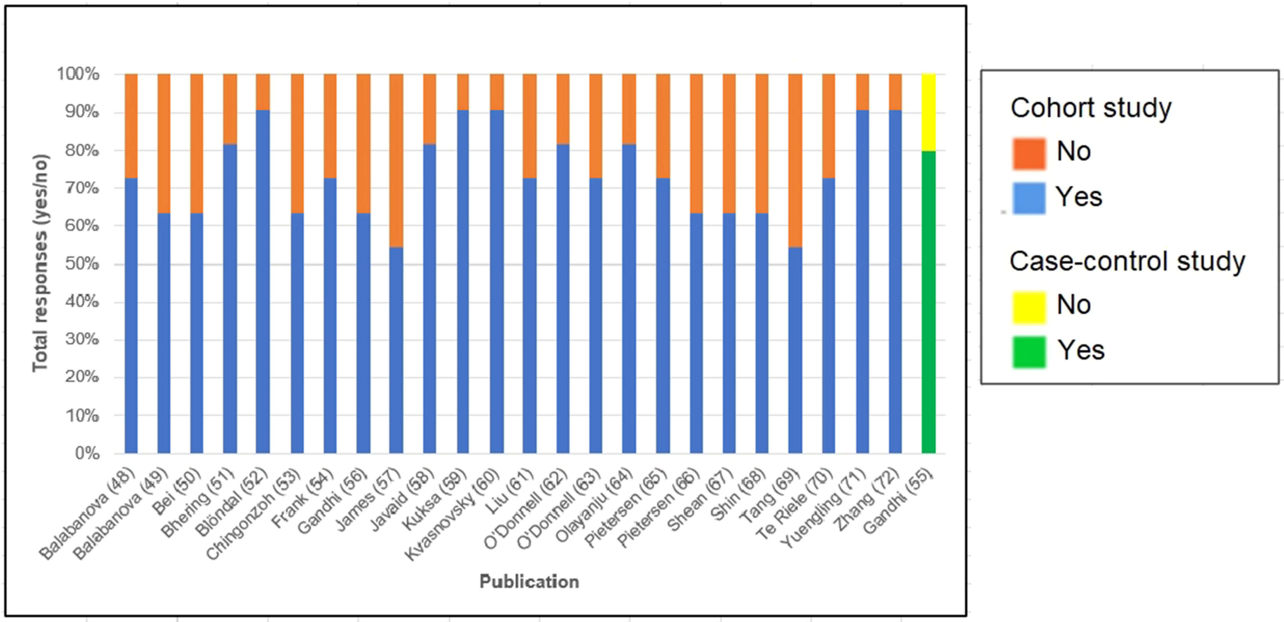

Figure 2 Quality assessment score by study with the Joanna Briggs Institute's Tools.

term totally drug-resistant TB,[65] and James et al used TDR-TB and XXDR-TB.[57]

Table 3 lists the risk factors for poor outcomes among patients in the included studies. A history of TB was consistently found to increase risk of poor outcomes among XDR-TB patients. In a number of the studies reviewed, nearly all patients who had a poor outcome had been undergoing retreatment for TB after having previously failed treatment/defaulted treatment/been cured. One study found that 90.5% of patients with poor outcomes were retreatment cases.[69] A different study found that 93.0% of patients with poor outcomes had a history of TB.[68] In another study, all 45 patients with XDR-TB/TDR-TB had a reported history of TB.[57]

Evidence from a wide array of contexts showed that the presence of HIV increases risk for poor outcomes, and in the three studies with the highest proportions of this comorbidity, 79.6%,[62] 82.7,[56] and 82.9%[55] of patients had both poor outcomes and HIV. The studies with the highest proportion of cases of HIV were from South Africa. The few studies that completed stratification based on whether patients were HIV-positive and were receiving antiretroviral therapies (ARTs) consistently found that risk of death was considerably higher among people with HIV who did not receive ARTs compared to those who did.[56,60,64,71]

Aside from HIV, findings related to comorbidities were limited. Eight of the 25 studies included an analysis of diseases/health issues other than HIV.[49–51,54,58,61,69,70] Comorbidities included in these studies were: diabetes,-[51,54,61,69,70] hepatitis,[54,61,89] chronic obstructive pulmonary disease (COPD),[61,69] abnormal liver function,[61] low albumin,[69] and hypertension.[61] The total proportions of patients with comorbidities in these studies were generally relatively low, with the exception of two studies.[54,69] In the first of these two studies, 26.8% of patients with poor outcomes had hepatitis C virus.[54] In the second study, 30.3% of patients with poor outcomes had low albumin levels, and 18.8% had diabetes.[69]

Findings related to age were mixed, although the majority of the studies that analyzed age as a potential risk factor showed that individuals approximately 30–45 years of age were at the highest risk for poor outcomes,[48,53–56,58,59,61,70,71] or that differences among age groups were minimal.[49,63–65,68] Studies that included patients under 18 years of age indicated that young patients comprise a relatively low proportion of patients with poor outcomes.[48,58,59,61]

In 15 of the 25 articles, men were more likely than women to be at risk for mortality, default, and/or treatment failure.[48–52,54,59–61,64,65,69–72] Some studies varied greatly in the number of men and women included, with several studies having a considerably higher proportion of male participants with poor outcomes,[48,54,59,61,72] and others having considerably higher women.[54,56,58,62]

The studies identified a number of other risk factors. Alcohol abuse was described in three studies;[54,59,68] and two of these studies each included individuals who were regular consumers of alcohol and had TB with poor

Table 3 Characteristics of Patients with XDR-TB and Having Poor Outcomes

Study	Country/ City	XDR-TB Patients with PO/Total XDR-TB Patients* (%)	Males/Females	Ages in Years (Range)	Comorbidities	History of TB	Additional Features
Balabanova et al (2016)[48]	Estonia/ Tartu, Lithuania/ Vilnius, Latvia/Riga, Romania/ Bucharest	227/737 (30.8%)*	195/32	15–29: 13 30–39: 37 40–49: 62 50–59: 72 60+: 43	HIV-positive: 10 Condition other than HIV: 22	Retreatment case: 148 92 had an unsuccessful treatment outcome in the past 56 had a successful treatment outcome in the past	149 resided in an urban setting 78 resided in a rural setting 173 were unemployed 152 were smokers 212 had only pulmonary (ie non extrapulmonary) TB 28 were smear positive at diagnosis 31 were not smear positive at diagnosis
Balabanova et al (2011)[49]	Russia/ Samara	53/92 (57.6%)	Exact numbers not specified Female HR in comparison to males: 0.67, 95% CI: 0.37–1.22	Exact numbers not specified Greater than 40 years HR in comparison to those 40 and below: 1.01, 95% CI: 0.98–1.03	Exact numbers not specified HIV-positive HR in comparison to HIV-negative: 1.23, 95% CI: 0.49–3.11 Median survival time for HIV-positive patients was 185 days, compared to 496 days for HIV-negative patients	Exact numbers not specified Treatment history HR in comparison new patients: 1.54, 95% CI: 0.37–6.34	
Bei et al (2018)[50]	China/ Chuzhishi, Wuhan, Hengyan, Chenzhou	20/67 (29.9%)	Exact numbers not specified aHR for male sex (univariable analysis): 1.32, 95% CI: 0.44–3.96	Exact numbers not specified aHR for age>50 years: 2.40, 95% CI: 0.84–6.85	Cases combined with underlying diseases (exact numbers not specified) aHR: 3.48, 95% CI: 1.30–9.36	Exact numbers not specified: aHR for retreatment cases (univariable analysis): 0.43, 95% CI: 0.17–1.08	aHR for patients with BMI < 18.5 kg/m^2: 4.52, 95% CI: 1.31–15.65 aHR for patients with smoking history: 4.67, 95% CI: 1.66–3.16

Bhering, Duarte and Kritski (2019)[51]	Brazil/Rio de Janeiro (no particular city)	1005/2269 (44.3%) *	Exact numbers not specified Male univariable analysis aOR: 1.11 95% CI: 0.93–1.23 Male multivariable analysis aOR (for default only): 1.42, 95% CI: 1.08–1.87	Exact numbers not specified 40+ multivariable analysis aOR: 1.32, 95% CI: 1.06–1.66	Exact numbers not specified HIV positive multivariable analysis aOR: 1.60, 95% CI: 1.05–2.43 Diabetes multivariable analysis aOR: 0.72, 95% CI: 0.53–0.98 Other comorbidities multivariable analysis aOR (for default only): 0.39, 95% CI: 0.22–0.67 Other comorbidities multivariable analysis aOR (for death only): 2.03, 95% CI: 1.36–3.01	Exact numbers not specified Previous MDR-TB treatment multivariable analysis aOR: 2.35, 95% CI: 1.79–3.09	XDR-TB patients with poor outcomes multivariable analysis aOR (in comparison to MDR-TB patients): 4.71, 95% CI: 2.67–8.33 Afro-Brazilian patients with poor outcomes multivariable analysis aOR: 1.33, 95% CI: 1.05–1.67 Drug using patients with poor outcomes multivariable analysis aOR: 1.78, 95% CI: 1.15–2.75 Smoking patients with poor outcomes multivariable analysis aOR (default only): 1.66, 95% CI: 1.06–2.61 Individualized treatment regimen with poor outcomes (compared to standard regimen) univariable analysis aOR: 1.56, 95% CI: 1.31–1.86 Unemployed patients with poor outcomes univariable analysis aOR: 1.60, 95% CI: 1.28–2.00
Blöndal et al (2012)[52]	Estonia (no particular city)	20/43 (46.5%)	Exact numbers not specified. Male aHR: 3.61, 95% CI: 1.42–9.15	Not specified.	Not specified.	Exact numbers not specified. History of previous anti-tuberculosis treatment aHR: 3.96, 95% CI: 1.94–8.07	Birth outside of Estonia aHR: 1.91, 95% CI: 1.03–3.53 Second line drugs not stopped due to side effects aHR: 0.38, 95% CI: 0.16–0.90
Chingonzoh et al (2018)[53]	South Africa/ Eastern Cape Province (city not specified)	463/763 (60.7%)	218/245	18–29: 125 30–44: 224 45–59: 103 60+: 11 Median (IQR): 36 (29–44)	HIV-positive: 324 HIV-positive and on ART treatment: 318 Compared to those who were HIV-negative, those coinfected with HIV and on ART had an aIRR of 1.1, 95% CI: 1.0–1.3, and those coinfected with HIV and not on ART had an aIRR of 1.8, 95% CI: 1.5–2.2	History of TB with 1st line drugs as treatment: 194 History of TB with 2nd line drugs as treatment: 209	376 initiated treatment at a DR-TB hospital 62 initiated treatment at a community level site
Frank et al (2019)[54]	Georgia (no particular city)	71/111 (67.0%)	56/15	Exact numbers not specified Median age: 39.0, IQR: 29.8–51.9	Hepatitis C Virus: 19 HIV-positive: 2 Diabetes mellitus: 6	41	38 patients with poor outcomes had reported tobacco use (OR for PO: 4.75, 95% CI 1.83–12.31) 32 patients with poor outcomes had reported alcohol use (OR for PO: 2.29, 95% CI: 0.95–5.49) 31 patients with poor outcomes had a history of incarceration (OR for poor outcomes: 8.27, 95% CI: 2.32–29.52)

(*Continued*)

Table 3 (Continued).

Study	Country/ City	XDR-TB Patients with PO/Total XDR-TB Patients* (%)	Males/Females	Ages in Years (Range)	Comorbidities	History of TB	Additional Features
Gandhi et al (2012)[55]	South Africa/ Tugela Ferry	111/139 (79.9%)	54/57	Exact numbers not specified Median (IQR): 35 (29–43)	HIV-positive: 92	Previous TB treatment (any): 82	73 had a positive sputum smear (HR: 0.91, p=0.80) 20 (out of 92 HIV-positive) were on ART (HR for those HIV-positive and on ART: 0.34, p=0.009) 64 had been hospitalized within the last year (HR: 2.04, p=0.002) 17 patients with <50 CD4 cells/ mm^3 (compared to those with > 200 CD4 cells/m^3, HR: 4.46, p=0.01) 22 patients with 51–200 CD4 cells/mm^3 (compared to those with > 200 CD4 cells/m^3, HR: 2.34, p=0.15)
Gandhi et al (2010b)[56]	South Africa/ Tugela Ferry	310/374 (83%). Medical records only available for 139 XDR-TB patients	61/78	Median (IQR): 34 (29–42)	HIV-positive: 115 Receiving ARTs at time of TB diagnosis: 25 (22% of HIV positive)	Any previous TB treatment: 96 (69%) Previous TB treatment in the prior year: 78 (56%)	41 (30%) of XDR-TB patients had a presence of extrapulmonary TB Mortality was highest in the first 30 days after sputum collection. Median survival time after sputum collection for XDR-TB patients was 28.5 days, 95% CI, 20–34; P < 0.0001.
James et al (2011)[57]	India/Vellore	Not specified for XDR TB patients; 21/177 cases reported as resistant to all forms of available treatment (reported as XXDR-TB and TDR-TB – though these 2 terms were used interchangeably)	Exact numbers not specified	Exact numbers not specified	Out of 86 consenting to test for HIV, 0 had the virus	All (45; 100%) cases of XDR-TB and TDR TB had history of anti-TB drug use 12 (57.1%) of TDR TB cases had previously used second-line drugs. Mean duration of past anti-TB treatment for TDR TB cases (months): Mean: 25.38, SD: 25.73; p=0.770) TDR-TB cases had been given a mean of 4.10, SD: 3.87, p = 0.185 treatment regimens in the past	Smoking history was more common among those with non-resistant TB (40.0%) compared to those with DR TB (27.0%), with p=0.132
Javaid et al (2018)[58]	Pakistan/ Peshawar	129/535 (24.1%)*	62/67	<18: 15 18–40: 69 41–60: 30 60+: 15	Comorbidities (any): 6	History of TB: 120 Previous use of second line drugs: 28	108 patients resided in a rural area 106 patients were married 17 patients were unemployed 23 patients were housewives

Kuksa et al (2014)[59]	Latvia (no particular city)	63/133 (47.4%)	48/15	< 18: 1 18–34: 18 35–54: 41 55+: 3	HIV-positive: 8	Retreatment after first treatment regimen: 12 Previous failure/default on MDR-TB treatment: 20 Relapse after MDR-TB treatment: 10	36 patients with alcohol abuse had PO: RR: 1.2, 95% CI: 0.9–1.4 46 patients that were smear-positive at the start of treatment had poor outcomes (RR: 1.9, 95% CI: 1.2–2.8) 23 patients with poor outcomeswere ex-prisoners (RR: 2.0, 95% CI: 1.4–2.7)
Kvasnovsky et al (2011)[60]	South Africa/ Eastern Cape Province (city not specified)	86/206 (41.8%)	Exact numbers not specified Male aOR: 1.2, 95% CI: 0.6–2.4 Comparison of HIV negative patients with HIV-positive patients not on HIV treatment: Male aOR: 1.1, 95%: 0.5–2.4	Exact numbers not specified <25 vs 25–42 years aOR: 3.5, 95% CI: 1.3–9.6 <25 vs >42 years old aOR: 2.2, 95% CI: 0.8–6.5 Comparison of HIV negative patients with HIV-positive patients not on HIV treatment: <25 vs 25–42 years aOR: 3.6, 95% CI: 1.2–10.3 <25 vs >42 years old aOR: 1.3, 95% CI: 0.4–3.8	Exact numbers not specified HIV status aOR: 1.2, 95% CI: 0.5–2.6 Comparison of HIV negative patients with HIV-positive patients not on HIV treatment: HIV status aOR: 2.5, 95% CI: 1.0–6.3	Exact numbers not specified Previous MDR-TB episode aOR: 1.3, 95% CI: 0.4–4.3 Comparison of HIV negative patients with HIV-positive patients not on HIV treatment: Previous MDRT TB episode aOR: 2.3, 95% CI: 0.6–8.7	65 XDR-TB diagnosed patients died before treatment Smear positive at treatment start aOR for patients with PO: 2.0, 95% CI: 1.0–4.1 Comparison of HIV negative patients with HIV-positive patients not on HIV treatment: Smear positive at treatment start aOR for patients with PO: 2.2, 95% CI: 1.0–5.0
Liu et al (2011)[61]	China/Beijing	34/48 (70.8%)	28/8	0–14: 1 15–29: 10 30–44: 13 45–59: 2 60–74: 6 75+: 2	Diabetes mellitus: 1 COPD: 8 Abnormal liver function: 8 Hepatitis: 1 Hypertension: 4	25	24 patients were migrants 31 patients with poor outcomes were reported to have resistance to more than 5 drugs 31 patients with poor outcomes had 4 or more years of TB disease 20 patients with poor outcomes not receiving 3 or more drugs, whereas only 2 survived (OR: 8.57, 95% CI: 1.65, 44.43) 28 patients with poor outcomes had smear-positivity at onset, whereas only 5 survived (OR: 6.72, 95% CI: 1.47, 30.76)

(Continued)

Table 3 (Continued).

Study	Country/ City	XDR-TB Patients with PO/Total XDR-TB Patients* (%)	Males/Females	Ages in Years (Range)	Comorbidities	History of TB	Additional Features
O'Donnell et al (2013)[62]	South Africa/ KwaZulu-Natal	49/216 (22.7%)	16/33 Female aHR: 1.83, 95% CI: 0.96–3.49	Exact numbers not specified. Age aHR (per every 5 years): 1.18, 95% CI: 1.02–1.37	HIV-positive: 39 HIV-positive on ART: 24 HIV-positive aHR: 1.85, 95% CI: 0.65–5.26	History of TB treatment: 46 Does not have a history of TB treatment aHR: 0.97, 95% CI: 0.23–4.03	Capreomycin provided as treatment: 38. Capreomycin provided as treatment aHR: 1.68, 95% CI: 0.83–3.41
O'Donnell et al (2015)[63]	South Africa/ KwaZulu-Natal	89/114 (78.1%) note: stratified data only available for 49 patients who died	22/27 Female aHR: 0.95, 95% CI: 0.51–1.77	<36: 25 36+: 24 <36 HR: 1.03, 95% CI: 0.59–1.80	HIV-positive: 36 HIV-positive aHR: 1.30, 95% CI: 0.61–2.78	History of TB treatment: 38 History of TB treatment aHR: 1.28, 95% CI: 0.45–3.65	Adverse event during treatment: 23 Adverse event during treatment HR: 1.02, 95% CI: 0.58–1.79
Olayanju et al (2018)[64]	South Africa/ Cape Town	168/272 (61.8%)	Exact numbers not specified. Male aHR: 1.08, 95% CI: 0.76–1.52	Exact numbers not specified. Age HR: 1.00, 95% CI: 0.97, 1.03	Exact numbers not specified. HIV-positive aHR: 1.51, 95 CI: 1.06–2.15 HIV-positive on ART aHR: 1.31, 95% CI: 0.44–2.91	Exact numbers not specified. History of TB treatment (all patients) aHR: 1.08, 95% CI: 0.69–1.68 History of TB treatment (HIV-positive patients) aHR: 1.29, 95% CI: 0.65–2.54	Weight <50 kg aHR: 1.96, 95% CI: 1.38–2.78 Bedaquiline provided as treatment aHR: 0.14, 95% CI: 0.06, 0.30 Any aminoglycosides provided as treatment aHR: 4.10, 95% CI: 1.87, 8.97
Pietersen et al (2014)[65]	South Africa/ Cape Town, Upington, Johannesburg	93/107 (86.9%)	Exact numbers not specified Male HR: 1.48, 95% CI: 0.58–3.78 Male HR among those HIV-positive: 0.76, 95% CI: 0.21–2.82	Exact numbers not specified Age at time of diagnosis HR: 0.99, 95% CI: 0.95–1.04 Age at time of diagnosis among those HIV-positive HR: 0.95, 95% CI: 0.89–1.01	Exact numbers not specified HIV infection HR: 1.48, 95% CI: 0.50–4.39	Exact numbers not specified Net sputum culture conversion ratio for those with no history of MDR-TB compared to those with a history of MDR-TB: 10.21, 95% CI: 2.64–39.38 Among those with HIV, no history of MDR-TB HR: 1.61, 95% CI: 0.37–6.96	1 reported case of totally drug-resistant tuberculosis Increased resistance was associated with Beijing genotype of disease (OR: 2.66, 95% CI: 1.18–17.35)
Pietersen et al (2015)[66]	South Africa/ Northern and Western Cape Provinces (cities not specified)	93/178 (52.2%)	Not specified.	Not specified	HIV-positive OR: 2.90, 95% CI: 1.34–6.30	Not specified	Weight (kg) OR: 0.935, 95% CI: 0.902–0.969 Capreomycin rrs resistance (A1401G mutation) OR: 0.59, 95% CI: 0.21–1.65 Provision of Co-amoxicillin/ clavulanic acid as treatment OR: 3.1, 95% CI: 1.4–6.6

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Shean et al (2013)[67]	South Africa/ Gauteng, Northern Cape, Western Cape (cities not specified)	55/115 (47.8%)	Not specified	Not specified	Not specified	Exact numbers not specified. History of MDR-TB aHR: 2.91, 95% CI: 1.16–7.35	Grade 3–5 adverse event aHR (note: reference is Grade 0–2 adverse event):1.43, 95% CI: 0.67–3.05 6 month culture conversion aHR: 0.10, 95% CI: 0.01–0.747
Shin et al (2010)[68]	Russia/ Tomsk	29/34 (85.3%)	Exact numbers not specified. Male sex aHR: 0.37, 95% CI: 0.17–0.81	Exact numbers not specified. Age aHR: 1.01, 95% CI: 0.17–0.81	Exact numbers not specified. HIV-positive HR: 3.11, 95% CI: 0.43–22.71	Exact numbers not specified. Prior TB treatment with a second-line injectable aHR: 3.65, 95% CI: 1.81–7.37 Prior TB treatment with a quinolone HR: 3.31, 95% CI: 1.61–6.79	Started in TB hospital HR: 2.28, 95% CI: 1.11–4.68 Alcohol use during treatment HR: 1.58, 95% CI: 0.80–3.11 Baseline bilateral and cavitary lesions aHR: 3.47, 95% CI: 1.32–9.14
Tang et al (2013)[69]	China/ Shanghai Guangzhou, Hangzhou, Tianjin, and Henan	346/1662 (20.8%)*	225/121	<45: 151 (43.6%) 45–65: 131 (37.9%) 65+: 64 (18.5%)	Diabetes: 65 COPD: 37 Chronic hepatitis: 30 Tumor: 10 Hepatic dysfunction: 39 Low albumin: 105	Retreatment case: 313 Duration of previous anti-TB treatment: <1 year: 83 1+ year: 263	147/169 of XDR-TB patients had PO (OR of poor outcomes for XDR-TB patients: 13.37, 95% CI: 6.75–26.50) 172 had a BMI of <18.5 174 had a BMI of 18.5+ (OR for poor outcomes: 2.19, 95% CI: 1.37–3.48) 77 (had the highest level of education as primary school 204 had the highest level of education as middle school 55 had the highest level of education as undergraduate 120 were peasants 135 were workers 91 had some other occupation
Te Riele et al (2019)[70]	South Africa/ Cape Town	86/97 (88.7%) note: stratified data only available for 64 patients	40/24	Median (IQR): 35 (27–45)	Diabetes mellitus: 5 HIV-positive: 31	History of DR TB: 38	Median weight (kg) (IQR): 50 (44–58)
Yuengling et al (2018)[71]	South Africa/ KwaZulu-Natal Province (city not specified)	72/105 (68.6%)	Exact numbers not specified Female aHR: 0.71, 95% CI: 0.38–1.34	Exact numbers not specified <36 aHR: 0.72, 95% CI: 0.37–1.38	HIV-positive: 46 HIV not on ART aHR (ref: HIV-negative): 4.68, 95% CI: 1.16–18.94 HIV on ART aHR (ref: HIV-negative): 1.59, 95% CI: 0.69–3.48	Any TB history aHR: 4.76, 95% CI: 0.65–34.95 History of MDR-TB treatment aHR (univariate analysis): 1.21, 95% CI: 0.65–2.24	An analysis of factors associated with favorable outcomes was conducted, and no other variables were found to be significantly associated with favorable outcomes

(Continued)

Table 3 (Continued).

Study	Country/ City	XDR-TB Patients with PO/Total XDR-TB Patients* (%)	Males/Females	Ages in Years (Range)	Comorbidities	History of TB	Additional Features
Zhang et al (2018)[72]	China/ Hangzhou, Huzhou, Jiaxing, Lishui, Quzhou, and Shaoxing	148/537 (27.6%)*	105/43	<30: 21 30–60: 80 >60: 47	Exact numbers not specified	Relapse patients: 60 Treatment after failure/ default: 69 Other patients previously treated: 7 Previously treated with 1st line drugs only: 92 Previously treated with 2nd line drugs: 50	32 had individualized treatment 100 had standardized treatment 65 had adverse events during treatment 90 had unknown level of baseline resistance patterns 122 were not hospitalized prior to treatment 92 were farmers

Notes: *Presented as MDR and XDR-TB patients with poor outcomes/Total MDR and XDR-TB patients as stratification for XDR-TB patients' poor outcomes was not conducted in study.

Abbreviations: TB, tuberculosis; DR-TB, drug-resistant tuberculosis; MDR-TB, multi-drug resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis; pre-XDR-TB, pre-extensively drug-resistant tuberculosis; DS-TB, drug-susceptible tuberculosis; USD, United States dollar; HIV, human immunodeficiency virus; PRISMA-ScR, Preferred Items for Systematic Review and Meta-Analyses extension for Scoping Reviews; JBI, Joanna Briggs Institute; BMI, body mass index; ARTs, anti-retroviral therapies; DOT, directly observed therapy; EDRWeb, Electronic Drug-Resistant Tuberculosis Register; COPD, chronic obstructive pulmonary disease; OR, odds ratio; HR, hazard ratio; CI, confidence interval; aHR, adjusted hazard ratio; aOR, adjusted odds ratios; SD, standard deviation; kg, kilograms; IQR, interquartile range; ACF, active case finding; IPU, integrated practice units.

outcomes.[54,59] A history of smoking was reported in four studies.[50,51,54,57] In one of these studies, individuals with a smoking history had an adjusted hazard ratio of 4.67 (95% CI: 1.66–13.16) in comparison to those who had never smoked.[50] Another study had fairly similar results, with smokers having an odds ratio (OR) for poor outcomes of 4.75 (95% CI: 1.83–12.31).[54] Two studies analyzed history of incarceration as a risk factor, and in both of these studies, former prisoners had higher odds for poor outcomes compared to those who were not former prisoners.[54,59] In one of these studies, former prisoners had a relative risk of 2.0 (95% CI: 1.4–2.7),[59] and in the other study, former prisoners had an OR of 8.27 (95% CI: 2.32–29.52).[54] In two studies, low body mass was associated with higher odds of poor outcomes.[50,69] The adjusted hazards ratio for patients of a BMI less than 18.5 kg/m^2 in a study involving 20 patients with poor outcomes was 4.52 (95% CI: 1.31–15.65),[50] and the OR in another was 2.19 (95% CI: 1.37–3.48).[69]

Although socioeconomic status was not directly analyzed as a risk factor in any of the 25 studies reviewed, several studies did analyze other measures related to socioeconomic status. In one study, 76.2% were unemployed,[48] and in another 13.2% were unemployed.[58] A third study showed that unemployed patients had 1.60 odds of poor outcomes compared to those who were employed (95% CI: 1.28–2.00).[51] One study analyzed educational attainment and found that 22.2% of patients with poor outcomes had primary school as their highest level of education and 59.2% with poor outcomes had middle school as their highest level of education.[69]

Various other factors associated with poor outcomes that emerged in individual studies included having extrapulmonary TB,[56] being a migrant,[52,61] having a Beijing genotype of disease,[65] being treated with clavulanic acid,[66] residing in a rural area,[48,58] being of African descent,[51] illicit drug-use,[51] having had adverse reactions to TB treatment,[52,63,67,72] being a farmer,[72] and initiating treatment at a hospital rather than a community-level site.[53,68] Based on the limited evidence, it was not possible to determine if these were risk factors XDR-TB.

Discussion

While at least 123 countries across the globe have reported the existence of XDR-TB,[80] the majority of the studies in this review (16 of the 25 studies) were conducted either in South Africa or China. Globally, approximately half of the cases of MDR-TB occur in India, Russia, and China and XDR-TB was reported to be prevalent in India as far back as in 2012.[13,81] However, only one study from India,[57] and two from Russia[49,68] were eligible for this review. It is therefore strongly recommended that more studies be conducted in India and Russia on risk factors for poor outcomes of XDR-TB.

In our review, it was found that a number of different factors have been shown to increase the risk for poor outcomes among XDR-TB patients. These include a previous history of TB, alcoholism, smoking, low BMI, unemployment, as well as being male, formerly incarcerated, and middle-aged.

Our review has also shown that certain comorbidities consistently increase the risk for poor outcomes by XDR-TB. In particular, HIV appears to be a risk factor, especially when untreated. These findings may explain why many of the studies included in this review were from South Africa, a country with the highest number of people living with HIV in the world.[79] It is also plausible that socioeconomic status and quality of care served as confounders in this relationship, though these factors were infrequently analyzed in the studies included in this review. A number of studies in this review also showed evidence that diabetes is a risk factor for poor outcomes among XDR-TB patients.[51,54,61,69,70]

There are notable similarities between the findings of our review, and those of prior reviews on risk factors for mortality from other forms of DR-TB, as well as DS-TB. While previous reviews on DS-TB have had conflicting findings,[82,83] HIV with advanced immunosuppression, non-infective comorbidities, alcohol use, and substance misuse have been identified as possible risk factors for mortality among DS-TB patients.[82,83] Furthermore, similar to our findings, a previous review by Alemu et al[24] showed that, among DR-TB patients, risk factors for mortality included being male, having HIV, clinical complications, and having diabetes or any other comorbidity.

Considering the risk for poor outcomes of coinfected HIV-positive patients, regardless of the level of drug-resistance, there is a clear need to focus on increasing access to care among this demographic. Settings that are endemic with both TB and HIV will require scaling up of resources to ensure that patients are treated for both diseases concurrently. As well, any type of comorbidity increases a TB patient's risk for poor outcomes at all levels of drug-resistance, and this may be because TB both increases risk for other comorbidities and complicates management of pre-existing conditions.[84] This further emphasizes the importance of ongoing efforts, such as the World Health Organization's End TB strategy, to focus on management of comorbidities among TB patients.[84] We hence recommend that future research be conducted on the possible relationship between XDR-TB and HIV, as well as diabetes and other comorbidities.

In contrast with previous reviews on risk factors for TB mortality,[24,82,83] our review showed that there is strong evidence indicating that a previous history of TB is a risk factor for poor outcomes. Notably, all 25 studies reviewed included a proportion of individuals who previously underwent treatment for TB and died as a result of XDR-TB infection. While previous reviews on TB mortality have shown that, as age increases, risk for death also increases,[24,82,83] our review instead demonstrated that those most commonly aged 30–45 were at a greater risk. Former prisoners, smokers, those with low BMI, and those with COPD were found to be at an elevated risk for poor outcomes in our review, which was not shown to be the case for patients with DS-TB/other forms of DR-TB in previous reviews.[24,82,83]

As rates of poor outcomes among XDR-TB patients were shown to be exceedingly high in a number of included studies, it is important to consider the risk factors for developing XDR-TB alongside risk factors for XDR-TB poor outcomes. In their systematic review on factors for developing XDR-TB, Flor de lima and Tavares[15] found that previous TB treatment, prior TB treatment length, having had pre-XDR-TB in the past, being an immigrant, alcoholism, HIV co-infection, and being male all served as major risk factors. It was also found that XDR-TB was less likely to occur in older individuals, and there was limited evidence that being a prisoner, having had cancer, or diabetes increased risk.[15]

Our findings show that there are numerous important similarities between risk for developing XDR-TB, and for having poor outcomes. Therefore, it is critical that health interventions which focus on addressing outcomes for XDR-TB patients also concurrently prioritize preventative efforts against XDR-TB. The exceedingly high rates of poor outcomes among XDR-TB patients further highlights this importance.

The consistency of the finding that prior treatment of TB contributes to risk of both to developing XDR-TB, and to having poor outcomes with XDR-TB, highlights the need for efforts to ensure that patients consistently adhere to treatment. To date, efforts to improve adherence have focused on directly observed therapy (DOT) and DOT Plus for DR-TB. These programs are effective in ensuring that patients complete their treatment regimens, and they need to be continued and potentially scaled up. However, these programs may not be enough to reduce escalation of XDR-TB.

In order to address issues of patient adherence to TB treatment, an array of additional solutions is needed. More health facilities that offer complete care, and are located closer to the place of residents of patients, are needed. Patients undergoing lengthy treatment regimens may also require transportation to care facilities, or perhaps delivery services. Though the evidence regarding the positive impacts of home delivery of TB treatment is limited,[85] home delivery for treatment of other diseases has been shown to be impactful.[86,87]

Patients may need support so that they can cope with the severe physical and psychological side effects from drug regimens used to treat the most resistant strains of TB.[10,73,74] Mental health care, including counselling, therapy, and prescribing of appropriate psychiatric treatment, can help patients deal with the treatment side-effects as well as with issues related to a lack of social support.[75,76] The usage of integrated practice units (IPUs), which involve the usage of mental health services within TB facilities in the form of counselling sessions, has been shown to both improve mental health symptoms and increase TB treatment adherence rates.[88] Scaling up of IPUs may therefore be an effective intervention for TB patients.

Reducing costs to patients and removing financial constraints for TB treatment is also critical to improving adherence rates,[75–78] as numerous studies in this review have shown that individuals with low educational/socioeconomic standing tend to have worse outcomes.[48,51,58,69] Lowering catastrophic costs, which are high expenses due to TB that exceed a certain threshold of total household income,[89] will be crucial. Active case finding (ACF), a strategy utilizing approaches such as house-to-house outreach to find TB patients before they show major signs of illness,[90] has shown promise as an intervention that can lower transmission rates,[90] improve health outcomes,[90,91] and reduce catastrophic costs for TB patients.[90,92] ACF hence have the potential to serve as interventions that can contribute to prevention efforts and reduce the likelihood of poor outcomes by early detection, while also lowering financial burdens for patients. Cash transfer and microfinance programs, which have been implemented to address numerous health issues, may also have a role in improving TB outcomes for impoverished patients.[93]

While a number of the findings of our review are comparable to the previously mentioned review on risk factors for developing XDR-TB by Flor de Lima and Tavares,[15] there are also important differences that need to be emphasized. In contrast to their findings, it is worth reiterating that this review showed that comorbidities greatly increase one's risk for poor outcomes, as does smoking, low BMI, being formerly incarcerated, and being immunocompromised. Our review also emphasizes that adverse reactions to XDR-TB drugs may increase one's risk for poor outcomes after developing XDR-TB, though more research is required. These differing findings indicate that the aforementioned factors may have a measurable impact on XDR-TB outcomes, but not necessarily for developing XDR-TB. More research is therefore needed to better understand the extent to which certain factors have on influence on developing XDR-TB, compared to an influence on patient outcomes.

Further investigation of the possible relationship between smoking and poor outcomes is also needed, and more explicit guidelines may be needed to advise DR-TB patients against smoking. An additional notable finding was that individuals who were most at risk of poor outcomes from XDR-TB were approximately 30–45 years of age. A possible explanation of why TB was more deadly for this relatively younger group, rather than for older individuals, is that they may be more likely to participate in risky behaviors and less likely to completely adhere to the arduous treatment regimen, perhaps due to financial constraints. It is worth further analyzing the role of age in future research.

This review included 25 studies from an array of geographic locations and cultural contexts, which increases the robustness of the overall findings. A number of these studies had relatively large sample sizes, with some incorporating thousands of individuals, thereby also increasing the robustness of the findings. Overall, the findings of the review provide avenues for future research and important insights to guide the development of policies and clinical guidelines.

Among the limitations to this review are the inconsistencies and variations in the way the articles reported results, making it difficult to compare the results of the different studies. Large confidence intervals across numerous findings require the usage of caution when interpreting results. There were also inherent limitations in terms of determining temporality. It is not known whether the mutable factors had occurred before diagnosis of TB, or simply before the patient died.

Conclusion

XDR-TB patients have a high risk for mortality overall. Our review highlights a number of important risk factors for poor outcomes including being a smoker, being a former prisoner, being middle-aged, being coinfected with HIV, and having a previous history of TB. These findings contribute to the literature by further emphasizing the urgency of ensuring that TB patients adhere to antimicrobial treatment until the pathogen is completely cleared, particularly among high-risk groups. As well, the findings indicate a need for future research to better understand other possible risk factors such as adverse events during treatment, specific comorbidities, and being an immigrant. In consideration of the enormity of the threat that XDR-TB poses, there is a very strong need for action to be taken.

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