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CONTRIBUTING FACTORS LINKED TO THE INCREASED RISK OF MULTI-DRUG-RESISTANT TUBERCULOSIS IN PAKISTAN, META-ANALYSIS.

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ABSTRACT

BACKGROUND: One of the most important public health issues related to tuberculosis (TB) is the growing problem of multidrug-resistant TB (MDR-TB), especially in high-burden countries like Pakistan. MDR-TB is defined as tuberculosis caused by strains which are resistant to at least two of the most used first-line treatments for TB. There are many factors supporting the emergence and spread of MDR-TB in Pakistan including socio-economic status, healthcare infrastructure, treatment compliance levels, and even population movement. **OBJECTIVE:** This aim of this meta-analysis is looking into demographic details along with previous treatment history, somatic illnesses, surrounding environment, and other relevant factors to assess their contribution towards the development and progression of MDR-TB in Pakistan. **METHODS:** We reviewed literature published from 2000 to 2024. The studies included in this meta-analysis featured both cross-sectional and cohort designs of varying sample sizes. Multiple databases related to medicine and public health were searched for relevant articles. Information including age, sex, education, job title, previous tuberculosis management, other existing health illnesses, and their housing conditions were gathered. **RESULTS:** The most significant risk factors are a history of treatment for TB, low educational level, poor compliance with treatment, lack of employment, and close contact with MDR-TB patients. The most affected age group is 20 to 40 years, with an almost equal predominance of males. The most common reported comorbidities are diabetes, CKD, and HIV, that also raise the risk of developing MDR-TB. Moreover, crowded living arrangements and restricted healthcare access were identified as prominent drivers of the problem**. CONCLUSION:** This meta-analysis calls for complete strategies to address MDR-TB in Pakistan. It is essential to counteract socio-economic disparities, enhance TB medication adherence, and enhance household screening and prevention measures to manage the transmission of MDR-TB efficiently. Public health activities should target high-risk populations, especially those with a past history of TB infection or comorbid conditions.

KEY WORDS: MDR TB, Pakistan, comorbidities, risk factors, public health.

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INTRODUCTION

Around 10 million people worldwide were afflicted with tuberculosis (TB) in 2020 alone, making it a significant public health concern (World Health Organization [WHO][1]. Although the disease is curable and treatable, managing and eliminating it has become more difficult due to the emergence of drug-resistant strains, particularly multidrug-resistant tuberculosis (MDR-TB). TB that is resistant to at least isoniazid and rifampicin, the two most potent first-line anti-TB drugs, is known as MDR-TB[2]. Nearly 500,000 people worldwide received a diagnosis of MDR-TB in 2020, and the disease claimed 230,000 lives1. Poor or insufficient treatment protocols, noncompliance with recommended medicine, and inadequate infection control methods are the main causes of the global rise in MDR-TB[3]. Pakistan has one of the highest rates of tuberculosis (TB) in the world. According to the WHO Global TB Report, Pakistan has about 520,000 new cases of TB and 32,000 instances of multidrug-resistant TB (MDR-TB) annually, placing it fifth in the world for total TB cases. The nation's alarmingly high rate of MDR-TB poses a serious threat to both the healthcare sector and public health. In Pakistan, a considerable portion of TB cases remain misdiagnosed, and MDR-TB is a major contributing factor to these cases being missed. Despite being a global concern, the effects of MDR-TB are particularly severe in low- and middle-income countries (LMICs) like Pakistan because of a lack of adequate healthcare infrastructure, restricted access to medical treatment, and economic difficulties[5]. Drug resistance is made more likely by the drawn-out and frequently insufficient treatment regimens. Significant treatment challenges arise from multidrug-resistant tuberculosis (MDR-TB), which calls for a second-line drug regimen that is more expensive, less effective, and hazardous than first-line drugs6. In Pakistan, where the healthcare system is already under a lot of stress, these difficulties make managing MDR-TB even more difficult.

The rising incidence of MDR-TB in Pakistan is caused by a number of reasons, such as prior TB treatment experiences, irregular medication compliance, co-occurring infections with other illnesses, and socioeconomic problems like poverty, malnourishment, and low literacy. In addition, a lack of community awareness about TB and its appropriate treatment further intensifies the problem[7]. This advent affords a complete evaluate of the danger elements related to MDR-TB in Pakistan and discusses the consequences for public fitness techniques geared toward fighting the disease.

A number one risk aspect for the improvement of MDR-TB is preceding TB treatment, especially while treatment is incomplete, interrupted, or insufficient. Studies display that sufferers who fail to stick to the whole direction of TB remedy or get hold of insufficient drug regimens are at better danger of growing resistance[8]. This is mainly authentic in Pakistan, in which the care is frequently suboptimal, and sufferers might also additionally prevent taking medicines after they experience better, now no longer knowing the significance of completing the whole routine to save the drug resistance[9]. In Punjab, the prior treatment of tuberculosis (TB) represents one of the most significant risk factors for the emergence of multidrug-resistant tuberculosis (MDR-TB) in Pakistan[7]. Research indicates that individuals with a history of incomplete TB treatment face a considerably higher likelihood of being diagnosed with MDR-

TB. The study highlighted the necessity for improved monitoring of TB patients to ensure complete adherence to treatment protocols. Unfinished treatment is common in Pakistan, especially because of the logistical difficulties in distributing medications, the lack of access to healthcare in remote areas, and the lack of patient education about the need of finishing the course of treatment[10]. MDR-TB development and transmission are strongly influenced by socioeconomic conditions. Many Pakistani MDR-TB patients have poor treatment outcomes, which are largely caused by low levels of education, poverty, unemployment, and substandard living conditions[5]. The significance of appropriate TB treatment7 is frequently not understood by those with less knowledge, which results in non-compliance and the emergence of drug resistance[9]. others who live in densely populated regions, particularly in urban slums, are at a higher risk of contracting multi-drug resistant tuberculosis (MDR-TB) because they share living conditions with others who may have active TB. The disease is more likely to spread in these settings due to inadequate ventilation, poor sanitation, and restricted access to healthcare. Additionally, many patients are unable to afford the necessary medications due to the significant cost burden of TB treatment, particularly for the second-line treatments needed for MDR-TB4. Furthermore, the socioeconomic aspects of TB therapy in Pakistan are strongly influenced by gender. Cultural traditions and a lack of healthcare resources can make it difficult for women, especially in rural areas, to get healthcare. Additionally, they are usually assigned home duties, which may delay their diagnosis and treatment[12]. Patients with multidrug-resistant tuberculosis (MDR-TB) often have diabetes mellitus, chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD). These coexisting diseases are associated with poor treatment outcomes and increased mortality rates[14]. For instance, because diabetes and its treatments both depress the immune system, people with diabetes may find it difficult to get rid of the infection[15]. These comorbidities' confluence with MDR-TB emphasizes the difficulties in treating people with several underlying medical conditions.

Furthermore, because HIV-positive individuals are more likely to develop drug-resistant tuberculosis due to compromised immune systems, HIV infection is a serious concern with relation to MDR-TB4. Co-infections of HIV and TB have been shown to significantly increase the risk of acquiring MDR-TB and make treatment more difficult[10].

Inadequate living circumstances exacerbate the socioeconomic barriers that contribute to the spread of MDR-TB. Poor cleanliness, inadequate ventilation, and crowded living arrangements create the ideal environment for the spread of tuberculosis[11]. These problems are particularly prevalent in rural areas and urban slums where there are limited resources for TB prevention programs and healthcare access. The risk of developing MDR-TB is significantly higher for those who live with MDR-TB patients[16]. The transmission of MDR-TB has been found to be significantly influenced by the distribution of the disease within families, especially in crowded households. Therefore, in order to successfully manage the spread of MDR-TB, it is essential to improve living circumstances, guarantee better sanitation, and promote tuberculosis infection control methods in high-risk situations. There are several challenges facing Pakistan's healthcare system that make it difficult to diagnose and treat

MDR-TB. The Directly Observed Treatment, Short-course (DOTS) strategy has been adopted nationwide, although there are still implementation problems, particularly in rural areas[10]. In addition to the problems of limited access to diagnostic resources, inadequate patient monitoring, and medicine shortages, the healthcare system often faces hurdles in treating drug-resistant tuberculosis cases.

Another challenge facing Pakistan is the high cost of second-line drugs required for the treatment of MDR-TB. For many people attempting to finish their recommended therapy, the cost of these drugs and the lack of insurance for TB treatment present a major obstacle[17]. Financial aid for TB treatment has been made possible through foreign assistance and public-private sector collaboration, but these resources are insufficient to meet the current need.

The emergence and spread of MDR-TB in Pakistan is a complex public health concern that is impacted by a number of variables, including socioeconomic level, treatment compliance, access to healthcare, and the existence of other medical conditions. reducing these challenges requires a multifaceted approach that includes improving treatment adherence, reducing socioeconomic disparities, raising awareness of tuberculosis, and improving healthcare infrastructure. Although Pakistan continues to fight MDR-TB, the impact of this deadly disease might be lessened with concerted efforts and well-coordinated actions.

METHODOLOGY

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) standards were followed in this meta-analysis. Several important databases, including PubMed, Scopus, Google Scholar, PakMediNet, and publications from the WHO regional offices, were thoroughly searched. The search encompassed studies published from January 2000 to March 2024, utilizing a mix of keywords such as "MDR-TB," "drug-resistant tuberculosis," "Pakistan," "risk factors," "comorbidities," and "treatment outcomes."

Inclusion and Exclusion Criteria: The studies incorporated in this meta-analysis fulfilled the following requirements: they were conducted in Pakistan; used cross-sectional, case-control, or cohort study designs; reported on risk factors or the prevalence of multidrug-resistant tuberculosis (MDR-TB); were published in English; and had a minimum participant count of 50. Excluded from the analysis were case reports, review articles, editorials, and conference abstracts lacking full text. Additionally, studies that did not define MDR-TB using standard diagnostic criteria, or those focusing exclusively on pediatric or extrapulmonary TB without specific MDR-TB stratification, were omitted.

Two independent reviewers screened titles and abstracts for relevance. Full texts of selected articles were reviewed, and data were extracted using a structured form. Extracted variables included study location, year, design, sample size, age, gender, education, occupation, prior TB history, comorbidities (e.g., diabetes, HIV), and environmental or social risk factors.

Quality assessment was conducted using the Newcastle-Ottawa Scale for observational studies. Data were synthesized descriptively due to heterogeneity in study designs and outcome measures. Where applicable, odds ratios (OR) with 95% confidence intervals (CI) were extracted or calculated to quantify associations.

RESULTS

The meta-analysis compiled data from over 20 Pakistani studies on MDR-TB, encompassing more than 9,000 patients. A key demographic observation was the higher prevalence of MDR-TB among males, with male-to-female ratios commonly ranging from 1.2:1 to 1.7:1, indicating possible occupational and behavioral exposure differences. Young adults aged 20 to 40 years represented the most affected age group, reflecting the vulnerability of the working population due to higher social interaction and possible immunological factors. A striking majority of patients had a history of previous TB treatment, with rates ranging from 58% to 87% across various studies, suggesting that previous inadequate or incomplete treatment is a major contributor to drug resistance.

Socioeconomic factors played a substantial role; over 70% of patients came from low-income households, and more than 70% had received only primary or no formal education, limiting their access to care and awareness about adherence. Regarding occupation, a majority were manual laborers or unemployed, reflecting the role of poor working and living conditions in disease transmission and treatment failure. Overcrowded living conditions, reported in 60–75% of cases, and household contact with known TB or MDR-TB patients (40–55%) were major transmission factors.

Comorbid conditions such as diabetes mellitus, chronic kidney disease, COPD, and HIV were present in 22–36% of cases, significantly complicating treatment outcomes and increasing susceptibility. Treatment non-adherence was another recurring theme, reported in 35–45% of cases, often due to lack of patient education, side effects, and social stigma. Genetic studies identified rpoB gene mutations in up to 88% of patients, confirming widespread rifampicin resistance and supporting the need for molecular testing like GeneXpert.

Additional findings revealed that treatment default due to migration, socioeconomic stress, or lack of systemic support was documented in 20–40% of patients, directly contributing to resistance development. Healthcare access issues, including inconsistent drug supply, poor transport infrastructure, and lack of trained staff, further impeded treatment continuity. Lastly, drug resistance testing revealed that over 90% of MDR-TB patients were resistant to both rifampicin and isoniazid, necessitating urgent policy implementation for second-line drug use, DOTS-plus expansion, and preventive strategies.

DISCUSSION

Multidrug-resistant tuberculosis (MDR-TB) remains a critical public health challenge in Pakistan, one of the 30 high MDR-TB burden countries identified by the World Health Organization[18]. The current study explored multiple risk factors contributing to the increased prevalence of MDR-TB, consistent with findings from other national and international studies.

One of the strongest predictors of MDR-TB identified in this study was a history of previous TB treatment, particularly among patients who had experienced treatment failure or default[19]. This is consistent with WHO's Global TB Report which attributes more than 80% of MDR-TB cases globally to inadequate or incomplete prior treatment[2].

Socioeconomic determinants such as low income, poor education, and unemployment were significantly associated with MDR-TB[11,15]. These factors likely contribute to delays in seeking care, poor treatment adherence, and limited access to diagnostic services[20,21].

Gender disparities were also evident, with a slightly higher prevalence of MDR-TB among males. This may reflect occupational exposure

and lifestyle factors such as smoking, which is more common among men in Pakistan[10, 22].

Table: Summary of Associated Risk Factors for MDR-TB in Pakistan

Risk Factor	Description	Prevalence Range (%)	Supporting Studies
Previous TB Treatment	History of incomplete, failed, or irregular TB treatment	58% – 87%	Ullah et al., Javaid et al., Ahmad, Mughul et al.
Male Gender	Higher incidence in males due to exposure and access patterns	55% – 70%	Khan et al., Javaid et al., Ullah et al.
Age (20–40 years)	Most cases in young adults, likely due to high exposure and mobility	45% – 65%	Aslam et al., Hayat et al.
Low Socioeconomic Status	Poverty, inadequate housing, and poor nutrition	70% – 80%	Rajput & Memon, Hayat et al.
Low Education Level	Illiteracy or primary education leads to poor treatment understanding	65% – 75%	Ahmad, Rameen et al., Rajput & Memon
Unemployment/Manual Labor	Limited resources and exposure to poor environments	60% – 70%	Javaid et al., Hayat et al.
Household Contact with MDR-TB	Close contact increases transmission risk	40% – 55%	Aslam et al., Rameen et al.
Overcrowding	Poor housing conditions enable rapid spread of infection	60% – 75%	Rajput & Memon, WHO (2013), Ahmad
Comorbidities (DM, HIV, CKD, COPD)	Immunosuppressive conditions worsen outcomes and resistance	22% – 36%	Hayat et al., Javaid et al.
Treatment Non-Adherence	Skipping doses, stopping treatment early	35% – 45%	Javaid et al., Khalid et al.
Drug Resistance Gene (rpoB mutation)	Rifampicin resistance gene found in MDR-TB patients	85% – 88%	Mughul et al.
Treatment Default/Interruption	Migration, stigma, or poor follow-up	20% – 40%	Ullah et al., WHO (2018)
Limited Access to Healthcare	Geographic and systemic barriers to diagnosis and treatment	Qualitative	WHO reports, Guardian report
Poor Infection Control Practices	Weak surveillance, delayed diagnosis, and improper isolation	Qualitative	WHO (2018), Javaid et al.
Over-the-counter Drug Use	Self-medication and unregulated antibiotic access	Qualitative	Financial Times Report (2024)

However, other studies have reported varying gender patterns, suggesting the need for gender-sensitive TB control programs[23].

Age group analysis showed that individuals between 20–40 years were disproportionately affected by MDR-TB. This is consistent with regional studies[16,24] indicating that young adults—likely to be economically active—may be at increased risk due to frequent mobility and exposure in workplaces or congested urban settings.

Poor treatment adherence was another strong risk factor[25,26]. Patients often discontinue therapy due to long treatment duration, adverse drug effects, or inadequate counselling by healthcare workers[5]. The issue is compounded by an unregulated pharmaceutical sector, where over-the-counter availability of antibiotics encourages self-medication and resistance development[27].

Clinical comorbidities such as diabetes mellitus, HIV, and chronic kidney disease were also significantly associated with MDR-TB[15]. Diabetes, in particular, impairs immune response, leading to poor treatment outcomes, while HIV co-infection complicates TB management and increases drug resistance[28].

Urban-rural disparities were apparent, with urban dwellers exhibiting higher MDR-TB

prevalence, possibly due to increased population density, housing congestion, and limited infection control[11,16]. However, rural areas may be underrepresented due to limited access to diagnostic centers.

From a molecular perspective, it have highlighted genetic mutations (e.g., rpoB gene) as indicators of rifampicin resistance, reinforcing the importance of molecular diagnostics like GeneXpert for early detection[29].

Pakistan's national TB control efforts have made progress, yet challenges persist. According to, nearly 27,000 estimated MDR-TB cases occur annually in Pakistan, but fewer than 50% are enrolled in proper treatment programs[1]. This gap is partly due to systemic issues such as poor surveillance, shortage of trained staff, and inadequate follow-up mechanisms[10].

Mass awareness campaigns, enhanced DOTS (Directly Observed Treatment, Short-course) implementation, and integration of TB services with primary care are essential for improving adherence and early detection[9]. Furthermore, contact tracing and screening among household contacts—especially in high-burden communities—can help curb community transmission[16].

Finally, the need for operational research, robust public-private partnerships, and policy-level reforms cannot be overstated. A multifaceted approach targeting both biomedical and social determinants is vital for containing the MDR-TB epidemic in Pakistan[17,21,].

CONCLUSION

This meta-analysis highlights critical risk factors contributing to MDR-TB in Pakistan, including prior TB treatment, poor adherence, comorbidities, and socio-environmental challenges. Targeted public health strategies are needed to address these issues—focusing on early detection, improved treatment compliance, and support for high-risk groups. Strengthening healthcare access, especially in underserved areas, and addressing socio-economic disparities will be essential to curb the spread of MDR-TB and improve long-term disease control.

LIMITATIONS

This meta-analysis has several limitations. Study design variability and inconsistent sample sizes hinder comparability. Key data such as gender, comorbidities, and occupation were often missing. Rural regions were underrepresented, and publication bias may have favored positive findings. Genetic mutation data (e.g., *rpoB, katG*) were inconsistently reported. The study period (2002–2024) includes shifts in treatment protocols. Language barriers may have excluded local non-English studies. Lack of patient-level data limited deeper analysis, and behavioral factors like stigma and health-seeking behavior were poorly covered.

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