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Factors contributing to multidrug-resistant tuberculosis among sputum culture-positive pulmonary tuberculosis patients in Indonesia: A cross-sectional study

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ABSTRACT

Objective: To analyze the risk factors associated with multidrug-resistant tuberculosis (MDR-TB) as a first national survey in Indonesia.

Methods: This national coverage cross-sectional study was conducted from 2017 to 2018. The study subjects were selected using a multi-stage probability random sampling method. MDR-TB is tuberculosis caused by bacteria resistant to at least isoniazid and rifampicin. The dependent variable was MDR-TB. Independent variables included age, sex, education, employment status, place of residence, history of living with TB patients, and the number of household members. Univariate and multivariate logistic regression models were used to analyze the risk factors associated with MDR-TB. All the data were analyzed using STATA V.14.0 (Stata Corp LLC, College Station, TX).

Results: This study found the MDR rate was 109/3 234 (3.4%) among positive pulmonary TB patients. More than twice as many patients had MDR re-treatment (74/3 234, 2.3%), compared to 35/3 234 (1.1%) who had new TB diagnoses or were getting initial treatment. After adjusting for employment status, individuals with a prior history of tuberculosis treatment were found to have significantly higher odds of developing MDR-TB, with an odds ratio of 7.22 (95% *CI* 3.87-13.44).

Conclusions: Increasing attention should be paid to these patients to prevent MDR-TB, and MDR-TB transmission is an urgent challenge for controlling TB worldwide. Early detection of MDR-TB is a critical part of TB control programs.

KEYWORDS: Multi-drug resistance; Tuberculosis; Risk factors; Indonesia

1. Introduction

Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium* (*M.*) *tuberculosis*, a significant global health problem. According to the Global Tuberculosis Report 2024, an estimated 10.8 million people fell ill with TB worldwide in 2023. There were

Summary

Question: What are the factors contributing to multidrug-resistant tuberculosis among patients with pulmonary tuberculosis exhibiting positive sputum.

Findings: The cross-sectional study found 3.4% individuals with positive pulmonary TB were multidrug resistant. After adjusting for employment status (*OR* 1.46; 95% *CI* 0.96–2.21), individuals with a prior history of tuberculosis treatment were found to have significantly higher odds of developing multidrug-resistant tuberculosis (MDR-TB), with an odds ratio of 7.22 (95% *CI* 3.87–13.44).

Meaning: Increasing attention should be paid to the initial patiens TB treatment to prevent MDR-TB.

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an estimated 1.25 million deaths among HIV-negative people in 2023. Indonesia contributes 10% of the estimated TB cases, which is 1 090 000, and ranks second globally after India. Moreover, the number of deaths caused by tuberculosis was 125 000 in Indonesia[1]. Drug-resistant TB (DR-TB) is the main challenge of the WHO Global TB Program due to its high risk of relapse, treatment failure, prolonged transmission of the bacilli, and death[2,3]. Incomplete treatments are driving the development of multidrug-resistant tuberculosis (MDR-TB), defined as TB resistant to at least isoniazid and rifampicin. These two drugs are considered first-line drugs for the treatment of individuals with drug-susceptible TB disease[4]. Increasing MDR-TB incidence is one of the many factors explaining the resurgence of the global TB epidemic. Global estimates of tuberculosis incidence have risen by approximately 800 000 cases over the past four years, compared to 2019[5].

Multidrug-resistant TB often occurs in individuals with failed repeated irregular treatment with standard short-course and relapse regimens, representing a source of relapse and refractory treatment. Patients with MDR-TB are practically incurable by standard first-line TB drugs[6-8]. The occurrence of MDR-TB possibly involves many different factors such as race, socioeconomic situation, culture, lifestyle, epidemiology, medical condition, and detection techniques. Therefore, identifying risk factors for MDR-TB is critical. Multiple investigations examining risk factors for MDR-TB have been carried out in several countries, including Indonesia[9,10].

Traditional treatment for multidrug/rifampicin-resistant tuberculosis (MDR/RR-TB) is lengthy, associated with severe adverse events, and complicated. Non-adherence, treatment interruption, and loss to follow-up are common consequences, making loss to follow-up a significant obstacle to TB control[11,12]. Incomplete and insufficient treatment regimens can contribute to the development of antimicrobial resistance. Earlier detection requires access to care and rapid diagnostic tools, which may be limited in many areas. MDR-TB treatment can be challenging due to adherence and tolerability issues. Recent evidence suggests that MDR-TB is an important contributor to post-TB lung disease[13,14].

A better understanding of treatment-related factors associated with an elevated risk of recurrent tuberculosis after cure is urgently needed to optimize MDR tuberculosis therapy and reduce recurrence and transmission[15]. Therefore, we conducted this analysis to identify associated factors for multidrug-resistant (rifampicin and isoniazid) TB resistance (new cases and retreated cases) among pulmonary patients in Indonesia based on the drug-resistant TB survey from 2017 to 2018.

2. Methods

2.1. Sample size

Using the simple random sampling formula from WHO[16] and Indonesian data (N=195 451), as well as the parameters Z=1.96 (with α =5%), estimated proportion to be MDR (p=1.9%), and precision 0.7% (d=0.007), a minimum sample size of n=1 450 smear positive cases in this study was obtained.

$$n = \frac{N \times Z^2_{\alpha/2} \times p \times (1-p)}{d^2 \times (N-1) + Z^2_{\alpha/2} \times p \times (1-p)}$$

Because this study used a cluster sampling design, the sample size was corrected with a design effect (Deff), resulting in a Deff is 1.5, the required final sample size is 2 175.

Additional 20% for compensation loss of sample due to not enough sputum and contamination the samples size required to achieve the survey objective is 2 610 new cases of smear-positive pulmonary TB. TB cases with retreatment (relapse, return after treatment, interruption, treatmen failure) registered at selected healthcare facilities will also be collected and examined along with specimens from new TB cases. This will increase the number of participating patients by 15%. This bring the total sample size to 3 002.

2.2. Study design and participants

Researchers selected participants from 70 health facilities across 40 districts or cities in 12 Indonesian provinces. The population in the survey consisted of smear-positive TB patients in selected health facilities, with a total sample of 3 234. The details included 2 608 (80.6%) new cases and 626 (19.4%) cases of retreatment. Data for this paper comes from the 2017-2018 National Antituberculosis Drug Resistance Survey. The study used a cross-sectional design with stratified multi-stage cluster sampling. The sampling frame was all new smear-positive pulmonary TB cases from all regions in Indonesia. Sample selection was systematically performed in stages, using probability proportional to size at the provincial, district/city, and health facility levels. An eligible population was the target population of selected health facilities that met the inclusion and exclusion criteria. The inclusion criteria were all smear-positive TB patients of any age, as well as new cases or cases of TB retreatment diagnosed during the data collection period. The exclusion criteria were cases of extrapulmonary TB and those that had received treatment for more than one week during the data collection period (Figure 1).

The dependent variables are MDR-TB patients (new TB cases and retreatment TB cases). New cases/initial treatment refers to patients who have never received treatment for TB before or have been on anti-TB treatment for less than four weeks. Retreatment cases refer to patients who have previously received treatment for any form of TB[17]. The independent variables predicted to affect MDR-TB occurrence based on the available survey data were age (grouped into two: <45 years and ≥45 years), sex (female and male), education

(junior high school and below, and senior high school), employment status (working and not working), place of residence (district and city), having lived with TB patients (yes and no), and the number of household members (≤4 persons and >4 persons). Ever smoked (yes and no), and treatment for TB history (yes and no)[18].

2.3. Data analysis

Researchers performed univariate analysis to describe the frequency distribution and proportion of all study variables, with a focus on respondents' characteristics and sociodemographic data. Variables with a *P*-value< 0.25 in the bivariate analysis were included in the multivariate model, along with variables considered clinically or theoretically relevant. The final model was constructed using backward stepwise selection, retaining variables with $P<0.05$ or those functioning as confounders—that is, variables whose removal altered the odds ratio (*OR*) by 10% or more[19]. The objective of multivariate analysis is to identify the most influential factors in the occurrence of MDR-TB. Data analysis was conducted using STATA 14.0 (StataCorp LLC, College Station, TX).

2.4. Ethics statement

This research has received ethical approval from the Health

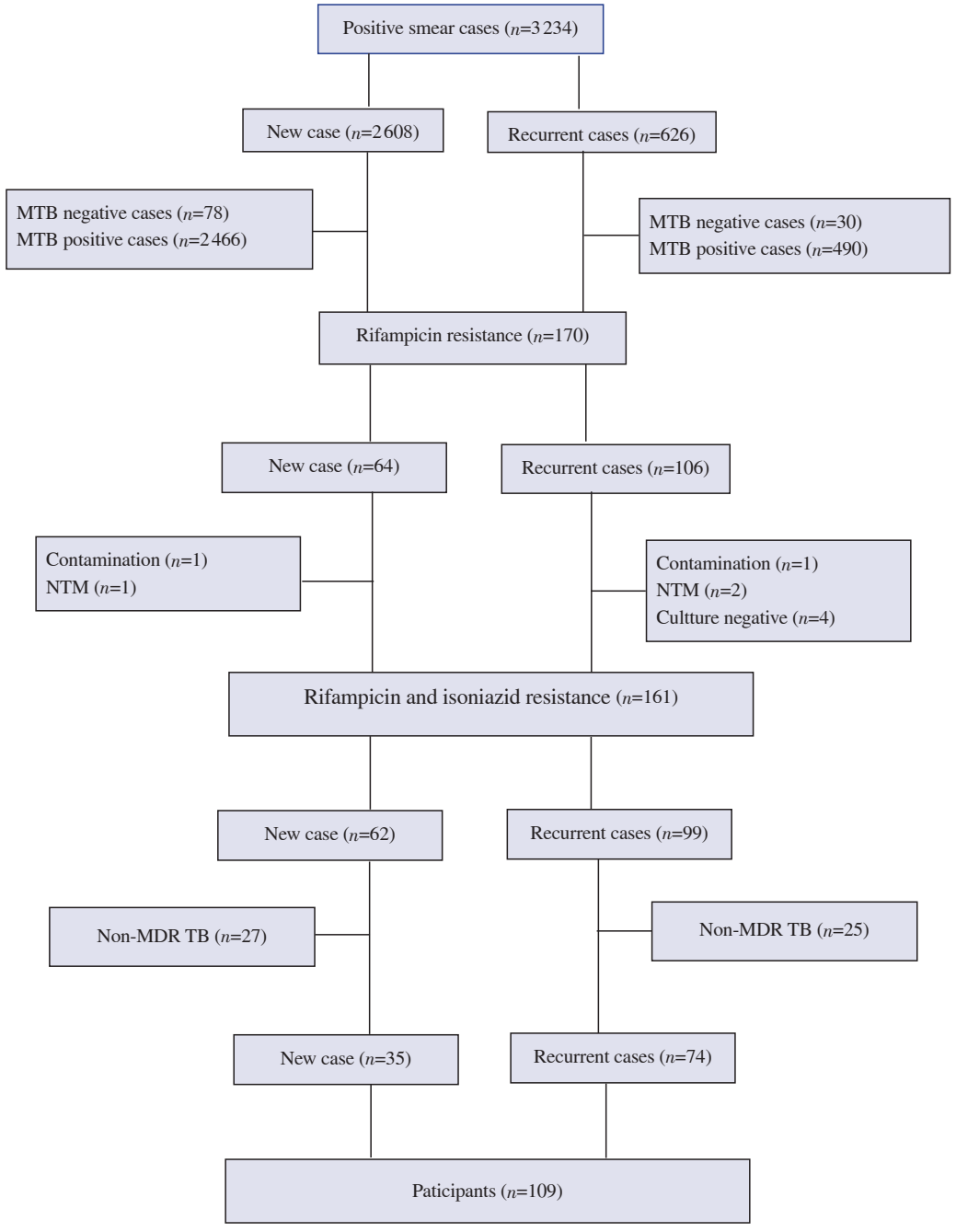

Figure 1. Patients inclusion flowchart. MTB: *Mycobacterium tuberculosis*, NTM: Nontuberculous mycobacteria.

Research Ethics Commission of the Health Research and Development Agency with letter number LB. 5.2/KE 2545/2016 dated July 28, 2016. This is secondary data analysis, so ethical clearance is no longer needed. Written informed consent was obtained before the interview, and all participants signed it. All enumerators were trained to avoid bias in information. All identity details of the survey participants were kept confidential.

3. Results

The total number of cases examined by X-pert MTB/Rif during the survey was 3 234 cases of positive smear. After the X-Pert MTB/Rif examination, it was found that there were 170 cases of rifampicin resistance. Subsequently, culture examination indicated 161 cases positive for rifampicin resistance. Following this, a drug susceptibility testing examination was conducted on the 161 cases to observe resistance to INH, resulting in 109 cases identified as MDR-TB and 52 cases as non-MDR TB. This study found the MDR rate was 109/3 234 (3.4%) among positive pulmonary TB patients. The rate of patients with MDR retreatment outcomes was 74/3 234 (2.3%), more than twice that of TB new cases or those receiving initial treatment, which was 35/3 234 (1.1%) (Figure 1).

This study includes smear-positive TB patients diagnosed according to the International Standards for Tuberculosis Care or national TB control guidelines. It also includes children under 15 years of age who meet the same criteria. Eligible cases include new or retreatment cases (such as relapse, treatment failure, return after interruption, or chronic cases) diagnosed during the data collection period at a health facility. Exclusion criteria include extrapulmonary TB cases and patients who had received TB treatment for more than one week at the time of data collection.

Table 1 illustrates that individuals aged 45 and above have a higher likelihood of MDR-TB, with a total of 57 cases (3.93%), compared to those below 45 years old, totaling 52 cases (2.92%). This association is not significant, with a *P*-value of 0.09 and an odds ratio (*OR*) of 1.37 (95% *CI* 0.94-1.98). Regarding sex demographics, males are more predisposed to MDR-TB, constituting 66 cases (3.21%) compared to females (43 cases, 3.66%), although not statistically significant with a *P*-value of 0.424 and an *OR* of 1.11 (95% *CI* 0.83-1.49).

Furthermore, in terms of education, individuals with a junior high school education or below has a higher likelihood of experiencing MDR-TB, totaling 68 cases (3.31%), compared to those with a

Table 1. Bivariate analysis of factors associated with MDR-TB and non-MDR-TB.

Variable	*N*	Non-MDR, *n* (%)	MDR, *n* (%)	*OR* (95% *CI*)	*P*-value
Age group, years					
<45	1 782	1 730 (97.08)	52 (2.92)	1	
≥45	1 452	1 395 (96.07)	57 (3.93)	1.37 (0.94-1.98)	0.09
Sex					
Male	2 059	1 993 (96.79	66 (3.21)	1.11 (0.83-1.49)	0.42
Female	1 175	1 132 (96.34)	43 (3.66)	1	
Education					
Junior high school	2 053	1 985 (96.69)	68 (3.31)	1.01 (0.63-1.61)	0.96
Senior high school	1 181	1 140 (96.53)	41 (3.47)	1	
Employment status					
Not working	1 499	1 457 (97.20)	42 (2.80)	1	
Working	1 735	1 668 (96.14)	67 (3.86)	1.42 (0.98-2.04)	0.06
Ever lived with a TB patient?					
No	2 765	2 671 (96.60)	94 (3.40)	1	
Yes	469	454 (96.80)	15 (3.20)	0.93 (0.58-1.48)	0.75
Prior TB treatment					
No	2 578	2 537 (98.41)	41 (1.59)	1	
Yes	656	588 (89.63)	68 (10.37)	7.17 (3.87-13.29)	<0.001
Number of household members					
≤4 persons	1 733	1 673 (96.54)	60 (3.46)	1	
>4 persons	1 501	1 452 (96.74)	49 (3.26)	1.07 (0.60-1.93)	0.77
Ever smoking					
No	1 431	1 379 (96.37)	52 (3.63)	1	
Yes	1 803	1 746 (94.84)	57 (3.16)	0.89 (0.64-1.22)	0.44
Place of residence					
Regency (rural)	1 895	1844 (97.31)	51 (2.69)	1	
City (urban)	1 339	1281 (95.67)	58 (4.33)	1.64 (0.96-2.78)	0.06

MDR: multi-drug resistance tuberculosis; Non-MDR: non multi-drug resistance tuberculosis.

senior high school education or higher, reaching 41 cases (3.47%), while not statistically significant with a *P*-value of 0.96 and *OR* of 1.01 (95% *CI* 0.63-1.61). Regarding employment status, individuals who are employed are more prone to TB-MDR, totaling 67 cases (3.86%) compared to unemployed individuals, constituting 42 cases (2.80%), although statistically not significant with a *P*-value of 0.06 and an *OR* of 1.42 (95% *CI* 0.98-2.04).

Individuals who have previously lived with TB patients have a lower likelihood of contracting TB-MDR, totaling 15 cases (3.20%), compared to those who have never lived with TB patients, totaling 94 cases (3.40%), while not statistically significant with a *P*-value of 0.745 and an *OR* of 0.93 (95% *CI* 0.58-1.48). Conversely, individuals with a history of TB treatment are at a higher risk of MDR-TB, totaling 68 cases (10.37%) compared to those who have never undergone TB treatment, constituting 41 cases (1.59%). This association is significant, with a *P*-value of <0.001 and an *OR* of 7.17 (95% *CI* 3.87-13.29).

Considering the number of household members, individuals residing with more than four individuals tend to have a slightly lower risk of TB MDR, totaling 49 cases (3.26%), compared to those living with less than five individuals, constituting 60 cases (3.46%), although not statistically significant with a *P*-value of 0.772 and an *OR* of 1.07 (95% *CI* 0.60-1.93). Furthermore, in terms of smoking habits, individuals with a history of smoking have a lower likelihood of MDR-TB, totaling 57 cases (3.16%), compared to non-smokers, constituting 52 cases (3.63%), although not statistically significant with a *P*-value of 0.44 and *OR* of 0.89 (95% *CI* 0.64-1.22). Lastly, regarding residential areas, individuals residing in cities are more likely to contract MDR-TB, totaling 58 cases (4.33%), compared to those living in district areas, constituting 51 cases (2.69%), although not statistically significant with a *P*-value of 0.063 and an *OR* of 1.64 (95% *CI* 0.96-2.78).

Based on the final results of the multivariate analysis in Table 2, treatment TB history was found to be significantly associated with experiencing MDR-TB after adjusted by working variable. Individuals who had been treated for TB have a higher risk of MDR-TB (*OR* 7.22, 95% *CI* 3.87-13.44) compared to those who have never been treated for TB (Table 2).

Table 2. Multivariate logistic regression analysis of multi-drug resistence tuberculosis (MDR-TB) with full and fixed model.

Variable	Full model a*OR (95% CI)*	*P*-value	Fixed model a*OR (95% CI)*	*P*-value
Age				
<45	1			
≥45	1.38 (0.92-2.07)	0.11	-	-
Sex				
Male	1			
Female	1.34 (0.69 - 2.59)	0.33	-	-
Education				
Junior high school or lower	1			
Senior high school	1.04 (0.63 - 1.69)	0.18	-	-
Employment status				
Not working	1		1	
Working	1.74 (1.02 - 2.93)	0.04	1.46 (0.96-2.21)	0.070
Ever lived with a TB patient				
No	1			
Yes	0.76 (0.47 - 1.23)	0.24		
Treatment TB history				
No	1		1	
Yes	7.07 (3.96 - 12.61)	<0.01	7.22 (3.87-13.44)	<0.001
Number of household members				
≤4	1			
>4	1.01 (0.53-1.89)	0.98	-	-
Ever smoking				
No	1			
Yes	0.87 (0.47 - 1.60)	0.63	-	-
Place of residence				
Regency (rural)	1			
City (urban)	1.40 (0.89 - 2.19)	0.13	-	-

All variables with *P*<0.25 in the bivariate analysis were included in the full multivariable logistic regression model. Backward elimination was then applied to remove non-significant variables while assessing potential confounding effects, with the goal of identifying the most efficient final model (fixed model). a*OR* : adjusted Odds Ratio, *CI*: Confidence Interval; MDR-TB: multidrug-resistant tuberculosis.

4. Discussion

MDR was due to the failed repeated irregular treatment with standard short-course and relapse regimens, representing a source of relapse; refractory treatment is practically incurable by standard first-line TB drugs[9,20]. This study analyzes risk factors for MDR representation in Indonesia, marking the first national survey of its kind. Our study revealed that prevalence of MDR of Indonesia was 3.4% (109/3 234). Similarly, the first national survey of tuberculosis drug resistance in the Lao People's Democratic Republic revealed a retreatment multi-drug resistance rate of 4.1% (2/49), while the rate for initial treatment was 1.2% (11/897)[17]. A study in Nigeria revealed that the prevalence of MDR-TB among the fifty-seven isolates was 10.5%. Previously treated and new cases had a prevalence of 7.0% and 3.5% MDR-TB, respectively[21].

Our study found that a treatment TB history was significantly associated with experiencing MDR-TB, 7.22 times higher than that of initially treated patients. Several studies demonstrated a significant association between tuberculosis treatment history—including relapse, treatment failure, and treatment dropout—and the incidence of MDR-TB. The use of Gene-Xpert testing revealed that over 60% of patients with a history of TB treatment exhibited rifampicin resistance, indicative of MDR-TB. These findings suggest that non-adherence to prescribed treatment regimens, incomplete therapy, and interruptions in treatment significantly contribute to the development of drug-resistant strains of *M. tuberculosis*. Consequently, enhancing patient adherence through targeted education and consistent monitoring is crucial to reducing the incidence and transmission of MDR-TB[22]. Use of separated TB drugs taken improperly and without DOTS supervision increases the risk of treatment failure and MDR-TB development, whereas FDC (fixed dose combination) regimens aligned with pharmacokinetic guidelines and proper supervision may mitigate resistance emergence and improve treatment outcomes[23].

A study in China in 2023 also revealed that 395 tuberculosis patients with positive sputum tuberculosis culture concluded that retreatment is the most significant risk factor for the occurrence of multidrug resistance in tuberculosis. The multidrug resistance rate in re-treated patients is 3.764 times higher than that of initially treated patients[24]. A systematic review and meta-analysis in Ethiopia of 18,908 tuberculosis patients across 24 studies showed an overall pooled prevalence of MDR-TB of 10.78% (95% *CI* 4.74%–16.83%). Moreover, there was a big difference in drug resistance rates between initial treatment (2.64%) and retreatment (11.54%)[25].

Similarly, Badgeba *et al.* in southern Ethiopia found that a history of previous TB treatment was a significant risk factor for MDR-TB, with affected patients being 11.8 times more likely to develop drug resistance compared to those without prior treatment. This association may be attributed to factors such as inappropriate treatment regimen, poor adherence, or issues with drug availability, all of which contribute to the emergence of resistance[26].

In a cross-sectional study conducted by Mansoori *et al.*, prior tuberculosis treatment history was found to be significantly associated with the development of drug-resistant TB, including multidrug-resistant or MDR-/RR-TB and any drug-resistant TB (ADR-TB). Among the 1 083 TB patients included in the study, 156 individuals (19.5%) reported a history of previous anti-TB treatment. Statistical analysis revealed that previously treated patients were approximately twice as likely to develop MDR-/RR-TB compared to new TB cases. These findings align with WHO estimates, which indicate that 18%–21% of patients with a prior TB treatment history are at risk of developing drug resistance. The authors emphasized that inadequate prior treatment plays a central role in the emergence of secondary resistance, which may result from poor adherence to therapy, inappropriate drug regimens, irregular drug supply, and insufficient treatment supervision. These results underscore the need for strengthened treatment monitoring and tailored interventions for previously treated individuals to prevent the development and transmission of resistant TB strains[1,27].

Similar findings were reported by Kusumandari *et al.* in a study conducted at RSUD Prof. Dr. Margono Soekarjo, Indonesia, which demonstrated a significant association between prior TB treatment history and the incidence of MDR-TB. Among 62 patients diagnosed with drug-resistant TB, the majority belonged to the newly diagnosed group (61.2%) and relapse cases (30.6%), with *P*-values of 0.037 and 0.022, respectively. The analysis revealed that new TB cases had a 7.33 times higher risk, while relapse cases had a 3.79 times higher risk of developing MDR-TB compared to other categories. These findings suggest that primary infection with drug-resistant *Mycobacterium tuberculosis* strains and reinfection due to poor treatment adherence are critical contributors to the increasing prevalence of MDR-TB. This highlights the need for strengthened surveillance and targeted interventions, particularly for new and previously treated TB patients, to curb the transmission of resistant strains[28].

Furthermore, our results showed that the development of MDR-TB could be influenced by employment status. Several studies have shown a significant relationship[29,30]. Variables with a *P*-value > 0.05 can still be included if they are a significant confounder[31]. In a dataset with a small sample size, the *P*-value may not be significant due to a lack of statistical power. However, this does not always mean that the variable is not practically or clinically important[32]. The *P*-value should not be used exclusively for decision-making, and the clinical or practical context should be considered[33]. The importance of considering models that have theoretical support and improve the overall accuracy of the model, even though certain variables are not significant[34].

Previous TB treatment is a well-established risk factor for

MDR-TB. Recent evidence also highlights the significant role of employment status in influencing treatment adherence and the development of resistance. Both formal and informal employment have been linked to MDR-TB, particularly in settings involving high mobility, limited job security, or occupational exposure. Informal workers, including migrants and daily wage laborers, as well as health care workers, face elevated risks due to frequent treatment interruptions and increased exposure. These findings underscore the need to consider occupational factors in TB control strategies[27,35,36].

A study in China identified some MDR risk factors, such as unemployment status and smoking[29,30]. In contrast, our study found that patients with a history of employment have an association with MDR. In addition to working informally (construction, labour, *etc.*), high mobilization may also be a cause of this, especially among the productive ages. This difference may be due to differences in access to TB services, socio-economic variables, and the level of awareness about adherence to first-line TB treatment, as rural communities have poor adherence to treatment, which likely leads to MDR-TB[37].

Finally, timely and standardized treatment and management of newly diagnosed tuberculosis patients are crucial in preventing the development of drug-resistant tuberculosis. Medical institutions should improve relevant regulations and systems[38]. Moreover, establish a new tuberculosis monitoring system, such as the application of artificial intelligence in diagnosis and prediction of drug resistance in pulmonary tuberculosis[39,40]. Medication adherence is crucial, so healthcare providers should intensify their efforts to educate and motivate patients to take their medications consistently. The effectiveness of TB treatment and prevention in Indonesia is strongly correlated with having had appropriate TB treatment training, had one to five years of work experience, and having adequate knowledge[41,42].

The limitation of the study is that the design is cross-sectional, so the temporal relationship of several independent variables with the dependent variable cannot be ascertained. The independent variables were assessed based on interviews with patients. Consequently, the patients might be subjected to recall bias. There are limitations to the variables analyzed, which means we have not yet been able to explore other factors that might contribute to MDR-TB.

Considering these findings, increasing attention should be paid to these patients for more efficient TB control to prevent MDR-TB. Early detection of MDR-TB is a critical part of the TB control program. Another crucial aspect is finding an effective and accurate treatment for new or initial cases of TB. MDR-TB transmission is an urgent challenge for controlling TB worldwide.

Conflict of interest statement

There is no conflict of interst.

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Authors' contributions

Conceptualization: DBL and JI; Design: DBL, IT, and KLT; Definition of intellectual content: DBL, MHH, SI, and MAN; Literature search, manuscript preparation, manuscript editing, and manuscript review: All authors; Clinical studies and data acquisition: DBL, KLT, MHH; Data analysis: DBL, JI, IT, MAN and KLT; Statistical analysis: DBL, JI, IT, KLT, MAN and SI; Guarantor: DBL and JI.

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