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ORIGINAL ARTICLE

IDENTIFYING RISK FACTORS FOR THE SPREAD OF DRUG-RESISTANT TUBERCULOSIS IN LAMPUNG IN 2023: A CASE-CONTROL STUDY

Analisis Faktor Risiko Penyebaran Tuberkulosis Resisten Obat di Provinsi Lampung Tahun 2023

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ABSTRACT

Background: Drug-resistant tuberculosis (DR-TB) is a growing health concern in Lampung, where the low rate of DR-TB case detection and high treatment failure rates emphasize the necessity of identifying risk factors to strengthen control measures for DR-TB. **Purpose:** This study aimed to identify the dominant risk factors for the spread of drug-resistant tuberculosis among patients in Lampung Province in 2023. **Methods:** Using a case-control study design, the research utilized secondary data from the Tuberculosis Information System (SITB) Lampung Province. A total sampling method was employed, with 126 respondents in the case group and a 1:1 ratio, making the total sample size 252 respondents. Data matching was done for gender and age variables. Statistical analysis included univariate, bivariate chi-square, and multivariate logistic regression tests. **Results:** Univariate analysis showed that 57.90% of respondents were male, 57.90% were in the at-risk age group, 58.30% were employed, 81.30% did not have diabetes (DM) comorbidity, 97,20% did not have HIV comorbidity, 67,50% had no prior TB treatment history. Bivariate analysis indicated significant associations with occupation (p-value 0.04), DM comorbidity (p-value 0.02), and treatment history (p-value 0.00). Gender, age, and HIV comorbidity showed no significant associations. The multivariate analysis showed a significant effect of the TB treatment history variable (p-value 0.00, OR=9.04) and the HIV comorbidity variable (p-value 0.03, OR= 0.08). **Conclusion:** TB treatment history is the dominant factor that can affect the spread of drug-resistant tuberculosis in Lampung Province in 2023. Future researchers are encouraged to focus on studying the types of treatment failures.

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ABSTRAK

Latar Belakang: *Tuberkulosis resisten obat (TB-RO) merupakan masalah kesehatan yang berkembang di Lampung, di mana rendahnya tingkat deteksi kasus TB RO dan tingginya tingkat kegagalan pengobatan menekankan perlunya mengidentifikasi faktor risiko untuk memperkuat langkah-langkah pengendalian TB-RO.* ***Tujuan:*** *Penelitian ini bertujuan untuk mengidentifikasi faktor risiko dominan penyebaran tuberkulosis resisten obat di antara pasien di Provinsi Lampung pada tahun 2023.* ***Metode:*** *Menggunakan desain studi kasus-kontrol, penelitian ini menggunakan data sekunder dari Sistem Informasi Tuberkulosis (SITB) Provinsi Lampung. Metode total sampling digunakan, dengan 126 responden pada kelompok kasus dan rasio 1:1, sehingga jumlah sampel sebanyak 252 responden. Pencocokan data dilakukan untuk variabel jenis kelamin dan usia. Analisis statistik yang dilakukan meliputi uji univariat, bivariat chi-square, dan regresi logistik multivariat.* ***Hasil:*** *Analisis univariat menunjukkan bahwa 57,90% responden berjenis kelamin laki-laki, 57,90% berada pada kelompok usia berisiko, 58,30% bekerja, 81,30% tidak memiliki komorbiditas diabetes (DM), 97,20% tidak memiliki komorbiditas HIV, 67,50% tidak memiliki riwayat pengobatan TB. Analisis bivariat menunjukkan adanya hubungan yang signifikan antara pekerjaan (p-value 0,04), komorbiditas DM (p-value 0,02), dan riwayat pengobatan (p-value 0,00). Jenis kelamin, usia, dan komorbiditas HIV tidak menunjukkan hubungan yang signifikan. Analisis multivariat menunjukkan adanya pengaruh yang signifikan dari variabel riwayat pengobatan TB (p-value 0,00, OR=9,04) dan variabel komorbiditas HIV (p-value 0,03, OR= 0,08).* ***Simpulan:*** *Riwayat pengobatan TB merupakan faktor dominan yang dapat mempengaruhi penyebaran TB resisten obat di Provinsi Lampung pada tahun 2023. Peneliti selanjutnya disarankan untuk fokus mempelajari jenis-jenis kegagalan pengobatan.*

INTRODUCTION

Drug-resistant tuberculosis (DR-TB) is caused by spontaneous mutations in the chromosomes of Mycobacterium tuberculosis (Mtb), leading to resistance against anti-tuberculosis drugs, with a tiny proportion of mutated Mtb in patients who have never received treatment, as TB treatment kills sensitive bacteria. At the same time, mutant strains multiply, causing resistance, which occurs in new patients who have never been treated or received anti-tuberculosis drugs for less than one month and in previously treated patients who received treatment for more than one month, including those with treatment failure, relapse, or those who discontinued medication (1). In 2021, the WHO reported 10.6 million TB cases worldwide, with 6,4 million receiving treatment. Indonesia ranked second after India, with approximately 969.000 TB cases in 2020. WHO established an eradication strategy known as Directly Observed Therapy Short-Course (DOTS) because TB is becoming more and more uncontrollable in some countries due to the high number of patients who experience treatment failure, particularly those who test positive for acid-resistant bacteria (BTA). However, the program still faces numerous challenges (2).

Expected to have 24.666 cases of DR-TB in 2022, while national DR-TB case-finding coverage in Indonesia reached only 50.80% by 2022, well below the 70% target, and Lampung Province recorded 106 cases of O-TB in 2022, accounting for 0.43% of the national total, with TB-RO case-finding coverage at just 17% and a treatment success rate of 58% (3). When the mycobacterium tuberculosis bacteria cannot be treated with multiple first-line medications, at least isoniazid and rifampicin, the two most effective types of OAT (anti-tuberculosis drugs) are used. MDR-TB cases are a specific type of TB that is resistant to these medications. The medication is an anti-tuberculosis medication (4).

The emergence of Mycobacterium tuberculosis strains resistant to anti-tuberculosis drugs (OAT) exacerbates the situation, complicating treatment

and control, as the spread of drug-resistant TB (DR-TB) is influenced by factors such as socioeconomic status, behaviour, comorbidities like diabetes and HIV, and other sociodemographic factors (1). Gender, age, marital status, education, employment, smoking habits, alcohol consumption, and drug abuse increase the risk of DR-TB transmission, while its prevalence is higher among individuals with low socioeconomic status, poor access to healthcare, and irregular treatment (5). This study is essential for identifying the risk factors for DR-TB spread in Lampung Province and developing more effective disease control strategies.

METHODS

This research applied a case-control design with a retrospective method in its observational analysis. This study used secondary data from the Tuberculosis Information System data of the Lampung Provincial Health Office. The data in this study were taken from January to December 2023. The place of this research was conducted at the Lampung Provincial Health Office.

Participants in this study had a TB diagnosis at the Lampung Provincial Health Office in 2023. The case population in this study were all patients diagnosed with drug-resistant tuberculosis (TB) at the Lampung Provincial Health Office in 2023, totalling 126 cases. The control population in this study were all patients diagnosed with TB at the Lampung Provincial Health Office in 2023, totalling 17,363 cases.

In this study, non-probability sampling was used with a total sampling technique. Where all populations from the case group were sampled in this study, this study used a 1:1 ratio between the case and control groups. The number of samples in the case group was 126, and the control group was 126, so the total was 252. In the control group, adjustments were made to the case group based on age and gender.

This study examined independent variables, including gender (male and female), age (at-risk: >40 years, and not at-risk: <40 years), occupation (working and not working), comorbidities such as diabetes mellitus (present and absent) and HIV (present and absent), and history of TB treatment (present and absent). The dependent variable was the spread of drug-resistant tuberculosis, classified into drug-resistant TB patients and positive TB patients.

This study utilized univariate analysis, bivariate analysis with the chi-square test to examine the relationship between two variables based on the odds ratio (OR) value, and multivariate analysis using multiple logistic regression, with data processed through IBM SPSS version 26.

The Research Ethics Committee of Malahayati University has issued a certificate of ethical clearance for this study (4398/EC/KEP-UNMAL/VI/2024).

RESULTS

The majority of responders were male, as many as 146 people (57.90%), at-risk age group (<40 years) as many as 146 people (57.90%), working status as many as 147 people (58.30%), did not have DM comorbidities as many as 205 people (81.30%), did not have HIV comorbidities as many as 245 people (97.20%) and did not have a history of TB treatment as many as 170 people (67.50%) (See Table 1).

Table 1
Frequency Distribution of Respondents based on Gender, Age, Job, Comorbidity DM, Comorbidity HIV, Treatment History TB and Spread of Drug-Resistant Tuberculosis in Lampung Provincial Health Office in 2023

Variable	n	%
Gender		
Man	146	57.90
Woman	106	42.10
Age		
Risk (> 40 years)	146	57.90
Nor risk (≤ 40 years)	106	42.10
Job		
Working	147	58.30
Not working	105	41.70
Comorbidity DM		
Yes	47	18.70
No	205	81.30
Comorbidity HIV		
Yes	7	2.80
No	245	97.20
TB treatment history		
Yes	82	32.50
No	170	67.50
Spread TB		
TB-RO	126	50
TB-positive	126	50
Total	252	100%

According to Table 2, The results of the bivariate analysis revealed several key factors influencing the spread of DR-TB. There was no significant association between gender (p-value = 1.00) and age (p-value = 0.89) with the spread of DR-TB. However, there was a significant correlation between employment and the spread of DR-TB (p-value = 0.04); the odds ratio (OR) for working respondents was 1.74, meaning they were 1.74 times more likely to have been exposed to DR-TB. The spread of DR-TB was also shown to be significantly correlated with the comorbidity of diabetes mellitus (DM) (p-value = 0.02), with an OR of 2.24, suggesting that DM raises the risk of DR-TB spread. On the other hand, there was no significant association between the spread of DR-TB and the presence of HIV (p-value=0.12). Additionally, a history of TB treatment was strongly linked to the spread of DR-TB (p-value=0.00), with an OR of 8.40, meaning those with a history of TB treatment are 8,40 times more likely to develop DR-TB. However, the confidence in these findings is low due to the wide gap between the upper and lower values of the confidence interval.

Table 2
Results of Bivariate Analysis of Risk Factors with Spread of Drug-Resistant Tuberculosis in Lampung Provincial Health Office in 2023

Risk Factors		Spread Drug-resistant Tuberculosis				p-value	OR 95%CI
		Drug-resistant TB		TB-positive			
		n	%	n	%		
Gender	Male	73	57.90	73	57.90		
	Female	53	42.10	53	42.10	1.00	
	Total	126	100	126	100		
Age	Risk (> 40 years)	74	58.70	72	57.10		
	Nor risk (≤ 40 years)	52	41.30	54	42.90	0.89	
	Total	126	100	126	100		
Job	Working	82	65.10	65	51.60		
	Not working	44	34.90	61	48.40	0.04	1.74 (1.05-2.90)
	Total	126	100	126	100		
Comorbidity DM	Yes	31	24.60	16	12.70		
	No	95	75.40	110	87.30	0.02	2.24 (1.15-4.35)
	Total	126	100	126	100		
Comorbidity HIV	Yes	1	0.80	6	4.80		
	No	125	99.20	120	95.20	0.12	
	Total	126	100	126	100		
TB treatment history	Yes	67	53.20	15	11.90		
	No	59	46.80	111	88.10	0.00	
	Total	126	100	126	100		

Table 3
Multivariate Test Results with Multiple Logistic Regression Tests

Variable	B	p-value	OR	95%CI	
				Lower	Upper
TB treatment history	2.20	0.00	9.04	4.60	17.77
Comorbidity DM	0.59	0.11	1.80	0.86	3.78
Comorbidity HIV	-2.45	0.03	0.08	0.09	0.85
Constant	0.36	0.76	1.43		

According to Table 3, the variables that significantly affect the spread of DR-TB are TB treatment history and HIV comorbidity, while DM comorbidity acts as a confounding variable. This analysis model explains 28.60% of the variance in the tested variables, with the remaining variation influenced by other untested factors. The analysis results show that the OR for TB treatment history is 9.04, showing that respondents with a history of failed TB treatment, treatment discontinuation,

nonstandard treatment, or relapse have a 9,049 times higher risk of spreading O-TB after adjusting for HIV and DM. Meanwhile, the OR for HIV comorbidity is 0.08, suggesting that respondents with HIV have an 11,627 times lower risk of developing O-TB compared to those without HIV after controlling for TB treatment history and DM.

DISCUSSION

The gender variable and the incidence of MDR-TB did not significantly correlate (p=0.09). Gender and the incidence of MDR-TB did not significantly correlate (p=0.13) (6). The outcomes of research by Mehari et al (7) conducted in Tigray Regional State from 2015 to 2016 showed that the incidence of MDR-TB did not correlate with gender (p=0.87). The outcomes of the research above are not in line with research by Sutrisna and Rahmadani (8), where gender is related to the incidence of MDR-TB (p = 0.03). The relationship between gender and the spread of drug-resistant tuberculosis (TB) is still a controversial topic with mixed research results. Several studies show a significant relationship between gender and the spread of drug-resistant tuberculosis (TB), with men being diagnosed with drug-resistant tuberculosis (TB) more often than women (9). Other studies did not find a significant relationship between gender and the spread of drug-resistant tuberculosis (TB). Factors contributing to differences in research results include differences in research methodology, differences in research populations, biological factors of respondents such as differences in the immune system and differences in hormones and behavioral and social factors (6).

From the results of the research above, it was found that more male patients were found than female. It has been demonstrated through epidemiology that men and women differ in terms of infectious disease, disease progression, incidence, and TB-related deaths. The progression of the disease varies between men and women, with women tending to experience more severe symptoms upon arrival at the hospital and often seeking medical help later than men. The humiliation and shame that women experience more than men may be connected to this. Women are more likely to worry about being shunned by their surroundings and family because of their condition (7).

Likewise, research conducted by Aristiana and Wartono (10) did not find a significant relationship between age and MDR-TB (p=0.78). The outcomes of the research above contradict research by Mehari et al (7), which was conducted in Tigray Regional State from 2015 to 2016. The findings indicated that the incidence of MDR-TB was correlated with age (p=0.04). The results of the research above are not in line with research by Sutrisna and Rahmadani (8), where age is related to the incidence of MDR-TB (p = 0.01).

The relationship between age and the spread of drug-resistant tuberculosis (TB) is still a controversial topic with mixed research results. Other studies show a significant relationship between age and the spread of drug-resistant tuberculosis, with children and the elderly being more at risk of being diagnosed with drug-resistant tuberculosis (TB) than adults of productive age. Other studies did not find a significant relationship between age and the spread of drug-resistant tuberculosis (7).

Several theories explain why children and the elderly are more susceptible to drug-resistant tuberculosis (TB) (than adults of reproductive age. Children have underdeveloped immune systems, so they are more easily infected with TB bacteria and may be exposed to TB bacteria more often, especially if they live with infected adults (10). Older people experience a decline in their immune system as they age (11), more often have comorbidities such as diabetes and heart disease which increase the risk of drug-resistant tuberculosis (TB), and may have old TB infections which can be reactive and become a source of drug-resistant tuberculosis (TB) transmission. Meanwhile, adults of productive age have a more muscular immune system, so they are better able to fight TB infection and have lower exposure to TB bacteria than children and the elderly (12).

People with strong immune systems, even in at-risk age groups, may be able to fight TB infection and not develop drug-resistant tuberculosis (TB). Exposure to TB bacteria, where the level of exposure to TB bacteria also influences the risk of drug-resistant tuberculosis (TB). People in at-risk age groups who are not frequently exposed to TB bacteria may have a lower risk of drug-resistant tuberculosis (TB), even if they have other risk factors. The body's capacity to fight infection can be enhanced, and the immune system can be strengthened by a healthy nutritional state (13). On the other hand, people in at-risk age groups with good nutritional status may have a lower risk of drug-resistant tuberculosis (TB). Behaviors that increase the risk of exposure to TB bacteria, such as smoking and living in crowded and poorly

ventilated environments, can increase the risk of drug-resistant tuberculosis (TB). People in the at-risk age group who do not have these risky behaviors may have a lower risk of drug-resistant tuberculosis (TB) (14).

Low income will affect daily needs, including obtaining adequate health services. A low economic level is an obstacle for clients in reaching health service facilities. Also, TB clients need high nutrition levels during TB healing (15). In terms of activities related to work and the TB RO incident, work is an activity done for financial gain. A person may be exposed to a disease due to work-related environmental variables. Drivers, laborers, pedicab drivers, and others who work in unfavorable environments are more likely to contract drug-resistant tuberculosis (TB) than those who work in offices (12).

In TB patients who suffer from DM and swallow anti-tuberculosis drugs with high blood sugar levels, it can cause anti-tuberculosis drug absorption problems so that the effectiveness of anti-tuberculosis drugs decreases, which results in anti-tuberculosis drug resistance. DM patients who experience TB infection will find it difficult to control blood sugar levels. High blood sugar levels in DM sufferers can increase the growth and replication of TB bacteria, including drug-resistant strains. DM sufferers with TB have a higher risk of failing TB treatment, which can lead to the development of drug-resistant tuberculosis (TB). DM increases the risk of TB 1,5 to 7,8 times compared to non-DM. The dual disease condition of TB-DM can reduce the body's immunity in TB patients. It can increase RO TB cases. In DM patients, it is suspected that neutrophil's phagocytic and bactericidal activity is impaired, and the number of T lymphocytes decreases. Host defense against mycobacterium infection decreases (13). From the results of the research above, researchers believe that DM sufferers with TB have a higher risk of failing TB treatment, which can lead to the development of drug-resistant tuberculosis (TB). DM sufferers may experience more severe side effects from TB medication, which may cause them to stop taking the medication before completing treatment (14).

People with HIV who are infected with TB (HIV-TB coinfection) have a higher risk of developing drug-resistant tuberculosis (TB) compared to people without HIV. This is caused by several factors, including high replication of HIV in people with HIV-TB coinfection, which can accelerate the mutation of TB bacteria, thereby increasing the risk of drug resistance. Low CD4 levels in HIV-TB sufferers are an indicator of a weak immune system, so TB bacteria grow more easily and are resistant to drugs (16).

Several factors can cause the absence of a relationship between HIV history and the spread of drug-resistant tuberculosis (TB), such as a healthy immune system, where people with a strong immune system, even though they are infected with HIV, may be able to fight TB bacteria effectively and prevent the development of drug-resistant tuberculosis (TB) (17). Genetic polymorphisms where certain genetic factors can influence a person's susceptibility to HIV and TB. People with certain genetic variations that protect against HIV or TB may be less at risk of developing these diseases (18). The sample of people living with HIV who experienced drug-resistant tuberculosis (TB) was insufficient to be said to be related in statistical analysis (14).

There is a relationship between previous treatment history and the incidence of TB RO (p-value=0.00). In line with research conducted by Lema in 2016, respondents who had a history of TB treatment had a 3.3 more significant chance of developing MDR TB compared to respondents who had no history of TB treatment. Previous treatment that failed, stopped, or relapsed has a greater risk of developing drug-resistant tuberculosis (TB). Patients who have swallowed anti-tuberculosis drugs with inappropriate management develop TB germs' immunity to anti-tuberculosis drugs. There are patients with drug-resistant tuberculosis (TB) who have never undergone anti-tuberculosis drug treatment before or are new cases (13).

The occurrence of TB-RO in these patients is likely due to a history of previous close contact with TB-RO sufferers or the patient was not honest in providing information regarding previous treatment. The patient has completed treatment, but the patient is diagnosed with TB again, influenced by several factors such as a decreased immune system, poor nutrition, and contact with TB sufferers (18).

TB treatment that does not comply with standards such as incorrect dosage, changing times for swallowing medication and stopping swallowing medication is an indication of irregularity in taking medication and is a risk of resistance to 1st line anti-tuberculosis drugs. Irregular medication intake during previous TB treatment can be caused by the patient being bored of taking medication for an extended period and feeling burdened, misunderstanding information

regarding dosage and rules for taking anti-tuberculosis drugs (17). Stop taking anti-tuberculosis drugs due to side effects, lack of family support in motivating, providing encouragement and lack of attention in providing care if complaints occur that make the patient decide to stop taking medication, lack of patient motivation and negative stigma about TB disease (18).

Treatment history is closely related to drug resistance. Mutations in the M. tuberculosis gene result in resistance to anti-tuberculosis drugs. Inadequate drug therapy doses can cause the emergence of mutations, especially when combined with non-compliance with anti-tuberculosis drug intake. Drug-resistant tuberculosis (TB) patients who do not complete treatment, whether due to drug withdrawal, inappropriate treatment, or other factors, are at high risk of transmitting resistant TB bacteria to other people (19).

One factor contributing to the spread of drug-resistant tuberculosis (TB) is treatment failure, which is impacted by the patient's immune system, socioeconomic status, length of therapy, and compliance and regularity in seeking treatment. Treatment that is interrupted or not by DOTS standards also causes drug-resistant tuberculosis (TB). Compared to managing non-resistant TB, managing drug-resistant TB is more complicated and demands more outstanding care (20).

People who do not follow TB treatment properly have a much greater chance of spreading drug-resistant tuberculosis (TB) compared to those who undergo treatment regularly (21). When TB treatment is not completed, or the drug dosage is not appropriate, TB bacteria can mutate and become resistant to the drugs used. This makes TB treatment more difficult and increases the risk of drug-resistant tuberculosis (TB). Individuals with TB who are not treated adequately can transmit TB bacteria to other people, including drug-resistant TB bacteria. Incomplete treatment can cause disease recurrence and increase the risk of death (13).

Several factors that need to be considered include DM and HIV, which can weaken the immune system, making the body more susceptible to TB bacterial infection and having more difficulty fighting it (22). This can slow down the recovery process, increase the risk of relapse, and increase the risk of drug-resistant tuberculosis (TB) treatment failure. Patients with DM and HIV who are undergoing drug-resistant tuberculosis (TB) treatment are at higher risk of experiencing complications such as hyperglycemia (high blood sugar levels) in DM patients, severe drug side effects, kidney failure, and opportunistic infections in HIV patients (13).

Research Limitations

The study used secondary data to examine risk factors for the spread of ocular tuberculosis in Lampung Province in 2023 with a sample of 252 pulmonary TB patients, which had various shortcomings, such as the researchers had no control over the caliber of secondary data used in this investigation. Erroneous, lacking, or inconsistent data could impact the analysis's findings. The study's small sample size (252 respondents) could also impact the analysis's statistical power and dependability. To identify minor effects and validate the results of this investigation, bigger sample sizes may be required. Notwithstanding its shortcomings, this study offers important insights into the risk factors for the 2023 development of ocular tuberculosis in Lampung Province.

CONCLUSION

TB treatment history is the dominant factor that can affect the spread of drug-resistant tuberculosis in Lampung Province in 2023. Future researchers are encouraged to focus on studying the types of treatment failures (e.g., drug withdrawal, inappropriate treatment) and their link to the spread of O-TB, as well as analyze the transmission patterns of O-TB concerning treatment history and other risk factors.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the research, authorship, or publication of this article

AUTHOR CONTRIBUTIONS

KA: Conceptualization, methodology, data curation, analysis, and writing-original draft. AF: methodology, writing review, and editing. NM: methodology, writing review, and editing. KA: manuscript review and proofreading, FE: manuscript review and proofreading.

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