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RELATIONSHIP OF DEMOGRAPHIC STATUS OF DIABETES MELLITUS IN DRUG-RESISTANT TUBERCULOSIS PATIENTS

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ABSTRACT

Background: Drug resistance tuberculosis (TB-RO) during the pandemic and the status of diabetes mellitus are considered by clinicians because affect success of therapy and the progress of the disease itself. This study aimed to analyze the relationship of demographic status of diabetes mellitus in drug-resistant tuberculosis patients.
Subjects and Method: This was a cross-sectional study conducted at Semarang Health Office, in January 2020 to October 2022. A sample of 88 patients with TB RO and diabetes mellitus were selected for this study. The dependent variable was diabetes mellitus status in TB-RO patients. The independent variables were age, health care delay, gender, and chest X-ray. The data were analyzed by chi-square test and t-test.
Results: TB-RO patients with DM status were on average older (Mean= 48.26; SD= 9.50) than TB-RO patients without DM status (Mean= 40.10; SD= 13.38), and this result was statistically significant (p <0.001). TB-RO patients with DM status had a longer average health care delay (Mean= 48.74; SD= 89.84) than TB-RO patients without DM status (Mean= 44.67; SD= 72.18), and this result was not statistically significant (p= 0.791). There was no relationship between gender (OR= 1.28; 95% CI= 0.58 to 2.79; p= 0.675) and chest X-ray (OR= 0.63; 95% CI= 0.06 to 7.17; p= 1.000) on DM status in TB-RO patients, and the results were not statistically significant.
Conclusion: TB-RO patients with DM status on average had an older age than TB patients without DM status. TB-RO patients with DM status averaged longer health care delays than TB patients without DM status. There is no relationship between gender and chest X-ray on DM status in TB-RO patients.

Keywords: healthcare delay, chest x-ray, drug-resistant tuberculosis.

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BACKGROUND

Tuberculosis is a person with airborne disease that decreases the quality of life and is caused by Mycobacterium tuberculosis (MTB) (Noviyani et al., 2021). Tuberculosis became the second infectious disease to cause death after COVID-19. The incidence of tuberculosis increased by 3.6% between 2020 and 2021.In 2021 as many as 10.6 million people suffered from tuberculosis globally with 6 million sufferers being men, 3.4 million sufferers being women and 1.2 million sufferers being children. As many as 8 countries are the largest contributors to tuberculosis cases such as India, Indonesia, China, Philippines, Pakistan, Nigeria, Bangladesh and Congo. (WHO, 2022). The COVID-19 pandemic since 2020 has

had an impact on tuberculosis services, exacerbated by its peak (delta variant) in 2021. The threat of the omicron variant in 2022 makes tuberculosis services not as optimal as they were in the year before the pandemic. There is a potential for missed cases of tuberculosis for 2 years so that increased transmission can be possible. Modeling from WHO shows that the effect of the pandemic on the incidence of tuberculosis and mortality in 2020 will increase in 2021 and beyond. The high incidence of tuberculosis in Indonesia is a priority for tuberculosis prevention and control (Khatri and Winkelman, 2022).

Diabetes mellitus is a metabolic disorder with high glucose levels because the body is unable to produce enough insulin or a low insulin response. High glucose levels cause symptoms such as frequent urination, frequent thirst and hunger. The prevalence of tuberculosis with diabetes mellitus globally is 140 per 100,000 patients. Indonesia is the country with the 4th highest position for the prevalence of diabetes mellitus and is estimated to increase in 2030. The link between active tuberculosis infections and diabetes mellitus is in the spotlight in developing countries. Diabetes mellitus increases the risk of tuberculosis 2.5 times compared to people without diabetes. Diabetes mellitus patients with high sugar levels have immunosuppression conditions because they experience a decrease in the response of Th-1, TNF-, IFN-, IL-1β, and IL-6 so that they are related to host immunity in the lungs such as the ability to adesi and phagocytosis by monocytes, macrophages and polymorphonuclear cells (PMN). This condition makes diabetics vulnerable to MTB (Bossman, 2022; Soetrisno et al., 2020). Antimicrobial resistance is one of the factors causing death from tuberculosis sufferers.

In 2020, 71% of patients diagnosed bacteriologically experienced rifampicin resistance globally. (Tiberi et al., 2022). Cases of drug-resistant tuberculosis in the city of Semarang are still the highest in Central Java. Based on data from the Semarang City Health Office, there was an increase of 128 cases in January 2017-September 2020 compared to 2013-2016 as many as 71 cases (Buryanti and Fibriana, 2021) Factors that contribute to the occurrence of drug-resistant tuberculosis are health workers, patients and tuberculosis control programs. Conditions such as side effects of first-line therapy, neglect of health workers, drug dropouts, lack of tuberculosis knowledge, stigma, and lack of family support leads to the occurrence of antimicrobial resistance. Previous studies have stated that disabilities requiring rehabilitative therapy in patients who have recovered from tuberculosis increase when experiencing drug resistance (Tiberi et al., 2022). Early detection of tuberculosis is a challenge in various regions because it requires easy access to services and fast detection tools (Febriani et al., 2021).

Xpert MTB/RIF is an early detection technology available in Indonesia. However, the technology requires the expertise of officers and the ability to collect sputum which may be difficult for some sufferers. Therefore, early detection of drug resistance is still a major problem. Currently,

health care facilities still use conventional radiological photos of the thorax for early detection, screening and surveillance of drug-resistant tuberculosis. Conventional radiological examination can be important evidence for finding the location, dimensions, and morphology of tuberculosis lesions. Conventional radiology photos can increase vigilance for health workers to suspect drug resistance in tuberculosis patients (Oladimeji et al., 2022).

The radiological picture in drug-resistant tuberculosis with diabetes mellitus that is often found is consolidation, opacity, lymphadenopathy, confluence, cavity and the spread of lesions in the pulmonary base lobes. Whereas in patients without diabetes mellitus usually infiltrate lesions in the upper lobe of the lungs. (Oladimeji et al., 2022; Soerono and Soewondo, 2019a) Factors influencing the picture have not been found in previous studies in Semarang. Therefore, the radiological picture, demographic factors such as age and gender, and healthcare delay can help early detection of drug-resistant tuberculosis in diabetes mellitus patients. This study aims to analyze the relationship of demographic factors, healthcare delay, and thoracic photo status to the status of drug-resistant tuberculosis diabetes mellitus and analyze differences in demographic factors, healthcare delay, and thoracic photo status in 2020 and 2022.

SUBJECTS AND METHOD

1. Study Design
This study is a cross-sectional study by taking data on the Tuberculosis Information System (SITB) at the Semarang City Health Office in January 2020 to October 2020 and January 2022 to October 2022.

1. Population and Sample
The data taken are data on form 03 of drug resistance tuberculosis (TB-RO). Data was edited, coding, entry, and cleaning using R Studio so that 107 samples were obtained. In 2021, no data was taken due to missing factors and data duplication.

2. Study Variable
Dependent variables such as diabetes mellitus status of TB-RO patients (yes/no). Independent variables such as radiological status (normal / abnormal) and radiological picture (atelectasis, bronchiectasis, bula, pleural effusion, fibrosis, consolidation, milier, moderately advanced, cavitation, nodules, pneumothorax, and normal), age, healthcare delay, and sex (male / female) were collected and analyzed.

3. Definition Operational of Variable
Healthcare Delay is the interval between the date of the register of suspected drug resistance and the date of start of therapy. (in Gennaro et al., 2021) Conventional Radiology Photo Thoracs is said to be normal when the size of the heart (cardiothoracic ratio < 50%, the contour of the heart is normal, there is no dilation of the pulmonary chamber, both translucent pulmonary fields with normal bronchivascular, the size of the aorta and pulmonary arteries -veins are normal, the angle of the costophrenicus is within normal limits and there is no fluid, the trachea is in the middle, hemimembrane, thorax and connective tissue in the lateral wall of the chest are normal. Photo Convencional Radiology Abnormal thorax has

several definitions including atelectasis, bronchiectasis, bula, pleural effusion, fibrosis, cavitation, consolidation, milier, moderately advanced, nodules, pneumothoraks (Singh and Tiwari, 2015; Tuddenham, 1984).

4. Study Instrument

The instrument in this study was form 03 drug resistance tuberculosis (TB-RO).

5. Data Analysis

Data analysis using SPSS (Statistical Package for the Social sciences) version 25. Descriptive statistics were carried out to analyze variable categories such as demographic factors (age and sex), radiological status, and clinical conditions (diabetes mellitus status) in the form of frequency and percentage (%). Data were also analyzed using t-test and chi-square.

RESULTS

From January to October 2020 and 2022, as many as 107 drug resistance tuberculosis patients were recorded in form 03 of the Semarang City tuberculosis information system.

Table 1. Characteristics of drug resistance tuberculosis patient data in Semarang City in January-October 2020 and 2022.

Characteristic	Category	2020 (N=88)		2022 (N=12)	
		Frequency	Percentage	Frequency	Percentage
Gender	Male	54	61%	11	58%
	Female	34	39%	8	42%
Thoracic Photographs	Atelectasis	3	3.4%	1	5.3%
	Bronchiectasis	3	3.4%	1	5.3%
	Bula	1	1.1%	0	0%
	Pleural Effusion	5	5.7%	1	5.3%
	Fibrosis	2	2.3%	0	0%
	Cavitas	55	62%	5	26%
	Konsolidasi	11	12%	5	26%
	Milier	1	1.1%	1	5.3%
	Moderatly advanced	2	2.3%	0	0%
	Nodules	2	2.3%	4	21%
	Normal	2	2.3%	1	5.3%
	Pneumothoraks	1	1.1%	0	0%
Thoracs Status	Abnormal	86	98%	18	95%
	Normal	2	2.3%	1	5.3%
Diabetic Status	Yes	39	44%	8	42%
	No	49	56%	11	58%

Table 1 shows that the median healthcare delay in 2022 is longer than in 2020 (25 days vs. 29 days). The median age of drug-resistant tuberculosis patients in 2020 and 2022 was 44.5 years and 49 years. The male sex remains dominant as a drug-resistant tuberculosis patient in 2020 and 2022 (61% vs. 58%). The predominate thoracic photo images in 2020 are kavitas (62%), consolidation (12%) and pleural effusion (5.7%) while in 2022 the domi-

nating ones are kavitas (26%), consolidation (26%), and nodules (21%). Thorax photo status in drug-resistant tuberculosis patients in 2020 and 2022 was dominated by abnormal photos (98% vs. 95%). The status of not having diabetes in drug-resistant tuberculosis patients in 2020 and 2022 still dominates between the two years (56% vs 58%).

Table 2. Data characteristics of drug resistance tuberculosis patients in Semarang City based on diabetes mellitus status.

Characteristic	Category	Without DM (N=60)		DM (N=47)	
		Frequency	Percentage	Frequency	Percentage
Gender	Male	38	63%	27	57%
	Female	22	37%	20	43%
Chest X-ray	Atelectasis	1	1.7%	3	6.4%
	Bronchiectasis	3	5.0%	1	2.1%
	Bula	1	1.7%	0	0%
	Pleural Effusion	5	8.3%	1	2.1%
	Fibrosis	1	1.7%	1	2.1%
	Cavitas	31	52%	29	62%
	Konsolidasi	8	13%	8	17%
	Milier	2	3.3%	0	0%
	Moderatly advanced	2	3.3%	0	0%
	Nodules	3	5.0%	3	6.4%
	Normal	2	3.3%	1	2.1%
	Pneumothoraks	1	1.7%	0	0%
Thoracs	Abnormal	58	97%	46	98%
Status	Normal	2	3.3%	1	2.1%

Table 2 shows that the median *healthcare delay* based on diabetes status does not differ by 26 days. The median age of drug-resistant tuberculosis patients both with no diabetes and with diabetes was 40.5 years and 49 years. The male sex remains dominant as drug-resistant tuberculosis patients with neither diabetes nor with diabetes (63% vs 57%). The photo picture of thorax in non-diabetic patients that dominated was kavitas (52%), consolidation (13%) and pleural effusion (8.3%) while in diabetic patients the dominating was cavitation (62%), consolidation (17%), nodules (6.4%), and atelectasis (6.4%). Photo status of thorax in drug resistance tuberculosis patients with neither diabetes nor with diabetes dominated abnormal photos (97% vs 98%

Table 3. Age relationship and *healthcare delay* in drug-resistant tuberculosis patients to diabetic status

Variable	Mean	SD	p-value
Age			
DM	48.26	9.50	<0.001
Without DM	40.10	13.38	
Healthcare Delay			
DM	48.74	83.84	0.791
Without DM	44.67	71.18	

Drug-resistant tuberculosis patients with DM status were averagely older (Mean=48.26; SD=9.50) compared drug-resistant tuberculosis patients without DM status (Mean= 40.10; SD= 13.38), and this result is statistically significant (p<0.001). Drug resistant tuberculosis patients with DM status experienced a longer average health care delay (Mean=48.74; SD= 83.84) compared drug-resistant tuberculosis patients without DM status (Mean= 44.67; SD= 72.18), and this result is not statistically significant (p= 0. 791).

Table 4. Association between sex and thorax photo status in drug-resistant tuberculosis patients to diabetic status

Independent Variable	OR	95%CI		p-value
		Upper Limit	Lower Limit	
Gender	1.28	0.58	2.79	0.675
Chest X-ray	0.63	0.06	7.17	1.000

Table 4 shows thatthere is no relationship between the sexes (OR= 1. 28; 95% CI= 0.58 to 2.79; p= 0.675) and chest X-ray (OR= 0.63; 95% CI= 0.06 to 7.17; p=1.000) on DM status in drug-resistant tuberculosis patients, and the results were not statistically significant.

DISCUSSION

This study aims to analyze the relationship of demographic factors (age and sex), *healthcare delay*, and thoracic photo status to drug-resistant tuberculosis diabetes mellitus status and years. Table 1 shows that the median *healthcare delay* in 2022 is longer than in 2020 (25 days vs. 29 days). Previous studies in Italy showed that median healthcare delays in 2020 and 2019 were 4-5 days ahead of Indonesia. This difference in duration is likely due to the reorganization of health facilities in overcoming COVID-19 which has an impact on the focus of services for tuberculosis patients so that it has the potential to decrease the quality of services in the detection and therapy of tuberculosis. The decrease in visits is likely due to the recommendation to minimize hospital visits to prevent the transmission of COVID-19 in acute, chronic or mildly symptomatic patients The median age of drug-resistant tuberculosis patients in 2020 and 2022 is 44.5 years and 49 years. The male sex remains dominant as a drug-resistant tuberculosis patient in 2020 and 2022 (61% vs. 58%). This study is in line with previous studies in Jambi, Indonesia that the male sex, aged 26-45 years and 46-65 years is a group of patients who are prone to drug-resistant tuberculosis. This is because these demographic factors have a high level of mobility and the high population density causes the potential for contact of tuberculosis patients to be greater. The status of not having diabetes in drug-resistant tuberculosis patients in 2020 and 2022 still dominates between the two years (56% vs 58%) (in Gennaro et al., 2021;Izhar et al., 2021).

This finding is similar to previous research in Jambi where drug-resistant tuberculosis patients dominated the status of not having diabetes mellitus. However, diabetes mellitus is associated with drug-resistant tuberculosis when compared to drug-sensitive tuberculosis. The use of rifampicin reduces the effectiveness of oral hypoglycemic drugs (OHO) so that strict

blood sugar monitoring or replacing drugs with insulin so that blood sugar regulation is better without affecting the effectiveness of anti-tuberculosis drugs. The status of hyperglycemia also affects the immunity and absorption of drugs in the gastrointestinal which has an impact on the failure of the effectiveness of the drug (Izhar et al., 2021).

The predominate thoracic photo picture in drug-resistant tuberculosis patients in 2020 is cavitation (62%), consolidation (12%) and pleural effusion (5.7%) while in 2022 the dominating ones are cavities (26%), consolidations (26%), and nodules (21%). Thorax photo status in drug-resistant tuberculosis patients in 2020 and 2022 was dominated by abnormal photos (98% vs. 95%). The findings of the thoracic photo picture of drug-resistant tuberculosis patients in this study differed from previous studies by Septa=fianty et al., where the dominant consolidation picture in drug-resistant tuberculosis patients was followed by a picture of multiple cavities and interstitial opacity. The consolidation picture is a picture of a frequent active infection of drug-resistant tuberculosis. Extensive cavitation and consolidation in the entire lung field indicates a failure of therapy or mutation of MTB that gives rise to drug resistance. The difficulty of tuberculosis drugs in penetrating avascular cavitability, which contains a lot of MTB, is suspected to be the cause of anti-tuberculosis drug resistance. Pleural abnormalities such as pleural effusion are associated with slow-type hypersensitivity reactions so that in the pleural space fluid appears due to increased activity of adenosine deaminase (Septafianty et al., 2021).

Table 4 shows that there was no statistically significant association of drug-resistant tuberculosis patient delays to diabetes mellitus status. These findings are in line with previous studies by Gennaro et al, that there was no difference in the duration of healthcare delay in tuberculosis patients to diabetic status. There is a statistically significant association in the age of drug-resistant tuberculosis patients to diabetes mellitus status. The median age of drug-resistant tuberculosis patients both with no diabetes and with diabetes was 40.5 years and 49 years. These findings are in line with previous research by Mood *et al.* (2021) where the median age of tuberculosis patients with diabetes occurs in decade 5 and tuberculosis without diabetes occurs in decade 3. In table 2 the male sex remains dominant in drug-resistant tuberculosis both with diabetes and without diabetes. There was no statistically significant association between the sexes of drug-resistant tuberculosis patients to diabetes mellitus status. These findings are also in line with previous research by Mood et al. (2021) that tuberculosis is common in men regardless of diabetic status.

The photo picture of thorax in non-diabetic patients that dominated was kavitas (52%), consolidation (13%) and pleural effusion (8.3%) while in diabetic patients the dominating was cavitation (62%), consolidation (17%), nodules (6.4%), and atelectasis (6.4%). Photo status of the thorax in drug-resistant tuberculosis patients with neither diabetes nor with diabetes is predominantly abnormal photos (97% vs 98%). This finding is in line with the study by Soerono et al, that kavitas is

becoming dominant both in diabetic patients, however, the mechanism of cavity formation in diabetic patients is still unclear and requires further research. There was no statistically significant association of thorax photo status of drug-resistant tuberculosis patients to diabetes mellitus status. This finding is different from previous research by Soerono et al, that thoracic photo status is positively correlated and very strongly with HbA1C levels. This difference in findings is due to this study not using the HbA1C parameter but diabetic status by KETB data. (Soerono and Soewondo, 2019b)

The COVID-19 pandemic may have an impact on tuberculosis services such as an increase in the duration of *healthcare delays* and an increase in the median age of drug-resistant tuberculosis patients in 2022. Male gender and thoracic photo radiological images such as cavitation dominated drug-resistant tuberculosis in 2020, 2022, and diabetes mellitus status. Diabetic status is related to the age of drug-resistant tuberculosis patients.

This study has a weakness because the data source is only from one city, limiting the findings to be generalized. The study sample is small because the data were taken within 2 years only. Long-term follow-up is required for the evaluation of this study.

AUTHOR CONTRIBUTIONS

In this study, the conception of the study is the contribution of Jessica Christanti. Data collection was carried out by the writer Jessica Christanti, Indra Adi Susianto, Nur Dian Rakhmawati, and Ririn Nurmandhani. Data analysis and interpretation was performed by Jessica Christanti. Manuscript writing, review of results and writing of the final version of the manuscript were carried out by all authors.

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