

Distribution of Rifampicin-Resistant Tuberculosis Patients based on Presumptive Drug-Resistant Tuberculosis Criteria at Dr. Hasan Sadikin Hospital 2016–2019

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Abstract

Background: Diagnosis of drug-resistant tuberculosis (DR-TB) begins with identifying presumptive DR-TB patients using Xpert MTB/RIF, as a diagnostic test to detect resistance to rifampicin. The study aimed to identify the distribution of rifampicin-resistant tuberculosis (RR-TB) patients based on presumptive DR-TB criteria at Dr. Hasan Sadikin General Hospital Bandung. Moreover, this study also explored the Xpert MTB/RIF Ct values.

Methods: This was a descriptive-retrospective study from 570 medical records of DR-TB patients collected at the Multidrug-resistant tuberculosis (MDR-TB) clinic of Dr. Hasan Sadikin General Hospital from 2016 to 2019. The inclusion criteria were suspected patients with the Xpert MTB/RIF Ct values in the very low-low and medium-high categories. Data were analyzed using frequency distribution.

Results: The most common presumptive DR-TB criteria among DR-TB patients were relapse cases (52.3%). Presumptive DR-TB criteria, with a high percentage result of medium-high Ct values, were category II treatment failure (80.9%).

Conclusion: Relapse case and category II treatment failure are presumptive DR-TB criteria, which need more attention from clinicians.

Keywords: Presumptive DR-TB criteria, tuberculosis, Xpert MTB/RIF Ct values

Introduction

Tuberculosis (TB), an infectious disease caused by *Mycobacterium tuberculosis*, is still a significant health problem in Indonesia. This disease ranks third in the world after India and China. In 2018, approximately 845,000 cases were reported in Indonesia, of which 240,000 cases were drug-resistant (DR)-TB. The high number of DR-TB makes the disease still a burden,¹ with the highest TB incidence rate in West Java Province. Dr. Hasan Sadikin General Hospital Bandung has been the primary referral for DR-TB in West Java since 2012. There are 15,393 presumptive DR-TB patients and 1,779 DR-TB patients in 2012–2019.²

Diagnosis of DR-TB begins with identifying presumptive DR-TB patients with one or more of 9 presumptive DR-TB criteria based on the Regulation of the Ministry of Health of the

Republic of Indonesia no. 67/2016.³ Xpert MTB/RIF has tested the presumptive DR-TB patients to detect the resistance. Moreover, Xpert MTB/RIF gives Ct values as a potential measure of bacterial burden.⁴ The bacterial load before treatment affects the time needed for the eradication.⁵ The information about Ct values among nine presumptive DR-TB criteria can be a reference for clinicians to focus more on specific criteria, which can result in a higher treatment success rate.

This study aimed to identify the distribution of RR-TB patients based on nine presumptive DR-TB criteria and Xpert MTB/RIF Ct values at Dr. Hasan Sadikin General Hospital Bandung.

Methods

This descriptive study collected and analyzed data from the e-TB Manager and medical

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records of the DR-TB patients in the MDR-TB clinic at Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia. The data collected was from 2016 to 2019, using the total sampling method. The inclusion criteria of this study were all medical records of DR-TB patients that had information about the patient's presumptive DR-TB criteria and Xpert MTB/RIF Ct values. Incomplete medical records were excluded. This study was approved by the Health Research Ethics Committee Universitas Padjadjaran, with Ethical clearance no. 835/UN6.KEP/EC/2020.

The nine presumptive DR-TB criteria were based on the Ministry of Health Regulation no. 67/2016. The nine criteria consisted of category II treatment failure, TB patients whose sputum remained smear-positive after three months of treatment, those with a history of non-standard treatment, and those who used quinolones or 2nd line drug injection for at least one month. Included was the category I treatment failure: TB patients whose sputum remained smear-positive after two months of treatment, relapsed, returned after default, and presumptive TB close contacts of a known DR-TB patient, and TB-human immunodeficiency virus (HIV) co-infection who was unresponsive to TB treatment. The frequency and percentage of each presumptive DR-TB criteria were calculated. Ct values were semi-quantitative, which provided results that categorized values as high ($Ct \leq 16$), medium ($16 < Ct \leq 22$), low ($22 < Ct \leq 28$), and very low

($28 < Ct \leq 38$). The categorization of Xpert MTB/RIF Ct values of each presumptive DR-TB in this study was high-medium ($Ct \leq 22$) and low-very low ($Ct > 22$). Presumptive DR-TB criteria and Xpert MTB/RIF Ct values were analyzed using descriptive statistical analysis.

Results

In total, 570 medical records on presumptive DR-TB throughout 2016–2019 were analyzed. The most common presumptive DR-TB criteria which gave a positive result for DR-TB were relapse cases (52.3%). Next, was the category I treatment failure (16.7%), and the return after default (14.0%) (Table 1). Interestingly, relapse cases had a high number in both medium-high and very low-low Ct values (Figure 1).

Xpert MTB/RIF was used to test patients, which gave Ct values that were representative of the bacterial burden. The criteria for presumptive TB-DR had a high percentage of having a high bacterial burden based on Xpert MTB/RIF Ct values (Table 2). The criteria for presumptive DR-TB with a high percentage of medium-high Ct values were category II treatment failure (80.9%). Then, the following were TB patients whose sputum remained smear-positive after two months of category I treatment (75.0%), category I treatment failure (73.6%) and relapse case (72.2%) (Table 2).

Table 1 Frequency of Patients at Dr. Hasan Sadikin General Hospital period 2016–2019 based on Presumptive DR-TB Criteria (Minister of Health Decree No. 67/2016)³

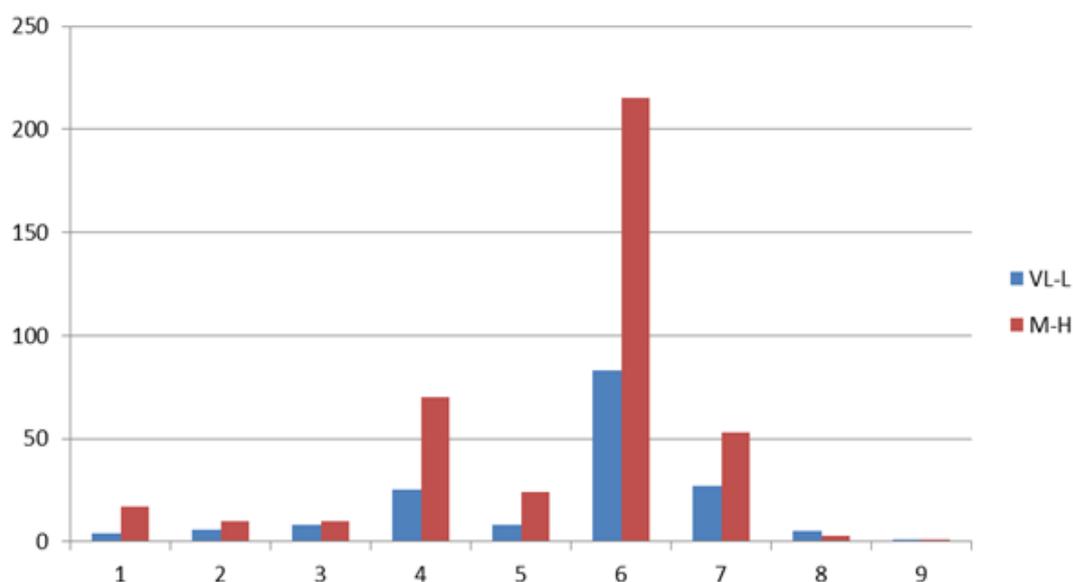
Presumptive DR-TB Criteria	DR-TB Patient (n=570)	
	n	%
1. Category II treatment failure	21	3.7
2. TB patients whose sputum remains smear-positive after 3 months of category II treatment	16	2.8
3. TB patients who have a history of non-standard treatment and use quinolones or 2 nd line drug injections for at least one month	18	3.2
4. Category I treatment failure	95	16.7
5. TB patients whose sputum remains smear-positive after two months of category I treatment	32	5.6
6. Relapse	298	52.3*
7. Return after default	80	14.0
8. Presumptive TB close contacts of a known DR-TB patient	8	1.4
9. TB-HIV co-infection who did not respond to TB treatment	2	0.3

Note. * the most common presumptive DR-TB criteria

Table 2 Xpert MTB/RIF Ct Values on Presumptive DR-TB Criteria³

Presumptive DR-TB Criteria	Xpert MTB/RIF Ct values			
	VL-L		M-H	
	n	%	n	%
1. Category II treatment failure	4	19.1	17	80.9
2. TB patients whose sputum remains smear-positive after 3 months of category II treatment	6	37.4	10	62.6
3. TB patients who have a history of non-standard treatment and use quinolones or 2nd line drug injections for at least one month	8	44.4	10	55.6
4. Category I treatment failure	25	26.4	70	73.6
5. TB patients whose sputum remains smear-positive after two months of category I treatment	8	25.0	24	75.0
6. Relapse	83	27.8	215	72.2
7. Return after default	27	33.7	53	66.3
8. Presumptive TB close contacts of a known DR-TB patient	5	62.5	3	37.5
9. TB-HIV co-infection who did not respond to TB treatment	1	50.0	1	50.0

Note: H=high (Ct≤16), M=Medium (16<Ct≤22), L=low (22<Ct≤28), and VL=very low (28<Ct≤38)

**Figure 1 Distribution of Presumptive DR-TB Criteria based on Xpert MTB/RIF Ct Values**

Note: 1=Category II treatment failure, 2=TB patients whose sputum remains smear-positive after three months of category II treatment, 3=TB patients who have a history of non-standard treatment and use quinolones or 2nd line drug injection for at least one month, 4=Category I treatment failure, 5= TB patients whose sputum remains smear-positive after two months of category I treatment, 6= Relapse, 7=Return after default, 8=Presumptive TB close contacts of a known DR-TB patient, 9= TB-HIV who is not responding to TB treatment, H=high (Ct≤16), M=Medium (16<Ct≤22), L=low (22<Ct≤28), and VL=very low (28<Ct≤38).

Discussion

This study found that relapse cases were the most common criteria for presumptive DR-TB among 570 DR-TB patients at Dr. Hasan Sadikin General Hospital during 2016–2019. Interestingly, of 5,541 TB patients with presumptive DR-TB criteria, 3,303 patients (59.6%) were categorized as relapse cases.² Relapse cases (52.3%) being the most common presumptive DR-TB criteria in TB-RR patients are understandable. Another study conducted at three clinics offering Programmatic Management of Drug-Resistant Tuberculosis (PMDT) services in West Java, Central Java, and East Java in 2011–2013 had the same results.⁶ Additionally, a study in Cambodia showed similar results even though it did not use the same nine criteria as in Indonesia.⁷ Relapse case was the most common presumptive DR-TB criteria among Cambodia's DR-TB patients. On the other hand, a study in India with five presumptive DR-TB criteria showed that the most common presumptive DR-TB criteria among DR-TB patients were treatment failure cases.⁸

A relapse case is a patient whose recent treatment outcome is cured or completed but returned with TB symptoms.³ Relapse cases can be due to the recurrent original infection or reinfection with new *M. tuberculosis*.³ Moreover, Indonesia still has a high burden of DR-TB and a high transmission rate of drug-resistant *M. tuberculosis*, which can contribute to the high number of relapse cases caused by reinfection.^{1,9} In addition, the leading cause of a high proportion of MDR/RR-TB among relapse cases was a failure to diagnose MDR/RR-TB at the first presentation.¹⁰ Recurrent cases also contribute to the high number of relapse cases in Indonesia. Recurrent cases can be due to inadequate treatment, poor compliance during drug-susceptible tuberculosis (DS-TB) treatment, and individual vulnerability such as low nutrition, diabetes mellitus, HIV infection, old age, and residual lung damage from previous TB disease.¹¹

In addition to relapse cases, the results of this study also showed that most of the contributors to the high number of DR-TB patients were the presumptive DR-TB criteria related to DS-TB treatment. A study in China found that recurrent infections are more common than reinfection.¹² There has been no study that distinguishes recurrent tuberculosis and reinfection in Indonesia.

Xpert MTB/RIF has been used to detect DR-TB rapidly in Indonesia since 2012. Xpert

MTB/RIF detects *M. tuberculosis* resistance to rifampicin and Ct values to estimate the bacterial load. The Xpert MTB/RIF Ct values are comparable to smear microscopy as a measure of *M. tuberculosis* burden.¹³ However, the Xpert MTB/RIF Ct values cannot replace culture as a measurement of *M. tuberculosis* burden because of the low correlation between Xpert MTB/RIF Ct value and culture positivity.¹³ Ct values in the medium and high categories, especially Ct<21 are more likely to give positive smear results than the low and very low categories.

Xpert MTB/RIF was used to examine patients with one or more presumptive DR-TB criteria. This study found that relapse cases were high for both the medium-high and very low-low categories. This was understandable because more than 50% of RR-TB patients came from relapse cases as the presumptive DR-TB criteria. On the other hand, another result study showed that the percentage of each presumptive criteria tended to give high-medium Ct values. This study also showed that among the nine presumptive DR-TB criteria, the highest percentage of Ct values in the medium-high category was category II treatment failure (80.9%). Category II is designed to overcome isoniazid resistance and reduce the risk of rifampicin resistance. The category II regimen comprised of eight months of rifampicin, ethambutol, and isoniazid supplemented with streptomycin for the initial two months and pyrazinamide for three months.¹⁴ The wide use of rifampicin throughout the whole treatment course from category I and II regimens increases the prevalence of rifampicin resistance among previously treated TB patients.¹⁵ The World Health Organization (WHO) recommends that category II regimens should no longer be prescribed to patients requiring TB retreatment and that drug-susceptibility testing (DST) should be performed for treatment options.¹⁴ The most available DST is Xpert MTB/RIF, but it can only detect rifampicin resistance.¹⁶ Category II regimen is still prescribed for patients requiring retreatment and who are sensitive to rifampicin.¹⁴

According to the study result, the most common presumptive DR-TB criteria in DR-TB patients were relapse cases. However, the criteria that had the highest percentage of medium-high Ct values were category II treatment failure. The Ct values estimate the bacterial load in patients.⁴ In category II treatment failure, the DST can be delayed because the test follows the treatment's

timeline. Meanwhile, a relapse case will be tested as soon as the patient has suspected TB symptoms.³ However, relapse case patients are more likely to have diagnostic delays because of the lack of distribution of Xpert MTB/RIF testing in Indonesia.¹⁷ Patients from outside rural areas have longer diagnostic delays than patients from the city.¹⁸ Interestingly, most patients administered at MDR-TB Clinic Dr. Hasan Sadikin General Hospital have poor knowledge of DR-TB.¹⁹ They are mostly unaware of the etiology and risk factors of DR-TB, transmission and the name of the drug they received during treatment. The level of knowledge will affect their effort in looking for treatment and compliance towards DR-TB treatment. Delay in diagnosis and initiation of DR-TB treatment can contribute to the high bacterial burden, estimated with high Ct values.²⁰ The amount of bacterial burden can affect treatment success, one of the factors that independently increase treatment success in DR-TB is AFB smear $\leq +1$, which means it has a low bacterial burden.²¹ Relapse case still has a high percentage of Ct values in the medium-high category (72.2%).

The limitation of this study is that from the many RR-TB patients at Dr. Hasan Sadikin Bandung General Hospital, not all have information on the Ct values on Xpert MTB/RIF results.

To conclude, relapse cases are the most common presumptive DR-TB criteria among DR-TB patients, and category II treatment failure has a high percentage of having a high bacterial burden based on Xpert MTB/RIF Ct values. These presumptive DR-TB criteria should receive more attention from clinicians in managing the TB therapy.

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