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RESEARCH ARTICLE

Treatment success and related factors of drug-susceptible and drug-resistant tuberculosis patients in Aceh referral hospital

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Abstract

Background: Tuberculosis (TB) remains one of the top ten causes of mortality worldwide. It is caused by a single infectious agent, *Mycobacterium tuberculosis*. Indonesia has the second highest cases globally and has a high burden of rifampicin-resistant (RR-TB). Xpert MTB/RIF has been used as a frontline test to detect RR-TB to improve treatment efficacy. **Objective:** This study aims to summarise the bacteriologic conversion rate as the patient's cured hallmark and related factors among adults confirmed to have pulmonary tuberculosis in a referral hospital in Aceh Province. **Method:** The authors assessed 1,244 bacteriologic test results of sputum samples from TB presumptive patients from January 1st to December 31st 2018, in the Clinical Microbiology Laboratory and evaluated bacteriologic conversion. **Result:** There were 361 bacteriologic-confirmed TB diagnoses, where 43 (11.9%) were RR-TB. Most TB patients (26.3%) were in close contact with active TB patients. **Conclusion:** The study showed TB patients' low follow-up rate and bacteriologic conversion. The high prevalence of TB among close contacts suggests a need for constant surveillance of this high-risk group to end the TB epidemic. Male, young adult, and Aceh Besar residents have observed factors in sputum conversion results.

Introduction

Tuberculosis (TB) is an ancient infectious disease caused by a single agent, *Mycobacterium tuberculosis*. It affects low- and middle-income countries more, as poor socioeconomic conditions are closely related to disease transmission in terms of morbidity, mortality, and cost of care (WHO, 2021; Marais, 2016).

Drug-resistant TB was one of the major concerned problems in managing TB. Resistance to isoniazid and rifampicin, as the most effective first-line drugs, is one of the most significant concerns because both rifampicin-resistant TB (RR-TB) and multi-drug resistance TB (MDR-TB) require treatment with a second-line regimen which shad longer treatment duration and risk of drug adverse effects (WHO, 2021; Khawbung, *et al.,* 2021; Zhang *et al.,* 2016). It leads to the low success rate of treating RR-TB in countries. (Khawbung *et al.,* 2021; Diacon, 2014).

Indonesia had the second highest number of TB cases globally, with a counted majority of 759/100,000, and is also considered a high-burden RR-TB country. Recently, 8,268 laboratory-confirmed MDR-TB cases were reported, and only 6,082 (61%) cases have started the treatment (Indonesia Health Ministry, 2022). The Indonesian National TB Programme (NTP) has used Xpert as a frontline test to detect RR-TB since 2012. However, only a limited number of healthcare facilities have access to Xpert, and many patients have limited access to second-line TB treatment (Wiwing *et al.,* 2015).

Aceh province has 14 referral hospitals and 87 satellite health service facilities for active drug-resistant TB patients, with around 47 Xpert machine facilities (Indonesia Health Ministry, 2022). Dr Zainoel Abidin Hospital was the hospital located in the capital city, which serves as a referral located in the capital city, serving referral cases from regions. The Xpert tests were initiated in mid-2014, and the result was reported to the health ministry database. However, the dynamics of TB cases, specifically rifampicin-resistant TB confirmed in the hospital, were not reported. This study evaluates the bacteriologic conversion of established TB patients and their distinguishing factors between January 1 and December 31, 2018, in Dr. Zainoel Abidin's hospital.

Methods

We assessed bacteriologic test results of sputum samples from TB presumptive patients from January 1st to December 31st 2018, in the Clinical Microbiology Laboratory of Dr. Zainoel Abidin Hospital. The subjects were either positive or negative sputum smear TB patients (Fig. 1). This study was approved by the Ethical Committee of Dr Zainoel Abidin Hospital and Faculty of Medicine, Aceh (088/EA/FK-RSUDZA/2022).

Diagnostic procedures were accomplished according to the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD) definitions. (WHO Geneval/IUTLD Paris, 1998)

The sputum smear-positive pulmonary TB patients are diagnosed by detecting acid-fast bacilli (AFB) in sputum smear examination or sputum culture. Drug sensitivity testing by Xpert of sputum samples was also done to characterise patients as rifampicin-sensitive or -resistant. Microscopic examinations were done in the clinical microbiology laboratory of Dr. Zainoel Abidin Hospital for those hospitalised or outpatients presumptive TB patients. The bacteriologic-confirmed TB patients' data were then assessed for the completion and cured status based on the results of their sputum re-examination during the study period. The bacteriologic monitoring was carried out after a two-month intensive phase and in the fifth month after completing the continuation phase.

According to the WHO/IUATLD guidelines, the treatment outcome was divided into six categories, as follows: cured (finished treatment with negative bacteriology results at the end of treatment), completed treatment (finished treatment without bacteriology result at the end of treatment), failure (remaining positive smear/culture at five months despite correct intake of medication), defaulted treatment (interrupted their treatment for two consecutive months or more after registration), death (died due to TB or other causes before or during treatment), and transfer out (treatment results are unknown due to emigration before or during treatment) ((WHO Geneva/IUTLD Paris, 1998).

Treatment success was defined as the sum of the cases that were cured and who completed treatment. The proportion of patients with a potentially bacteriologically unsuccessful outcome (failure) was also computed; however, the other products (default, death and transfer) were not noted in the laboratory data.

The recommended regimen for TB treatment (rifampicin-sensitive cases) in this study was isoniazid (INH), rifampicin, pyrazinamide, and ethambutol in the intensive phase (2 months). The continuation phase consisted of 4 months of INH and rifampicin. Treatment regimens and follow-ups of the patients could also be carried out in the patient origin region every two weeks.

Patients with rifampicin resistance temporarily will receive another regimen while having a Line Probe Assay (LPA) test for additional TB regimen sensitivity testing.

Statistical Analysis

Descriptive statistics were used to determine the number and percentage of all cases. Independent variables (sex, age group, and region) were entered into the univariate model.

Results

The flow chart of acid-fast bacilli (AFB) and Xpert MTB result test of pulmonary TB patients is depicted in Figure 1. Of the total tests done (1,244), 361 (29.3%) were smear positive, and 43 (11.8%) of them were patients with rifampicin-resistant.

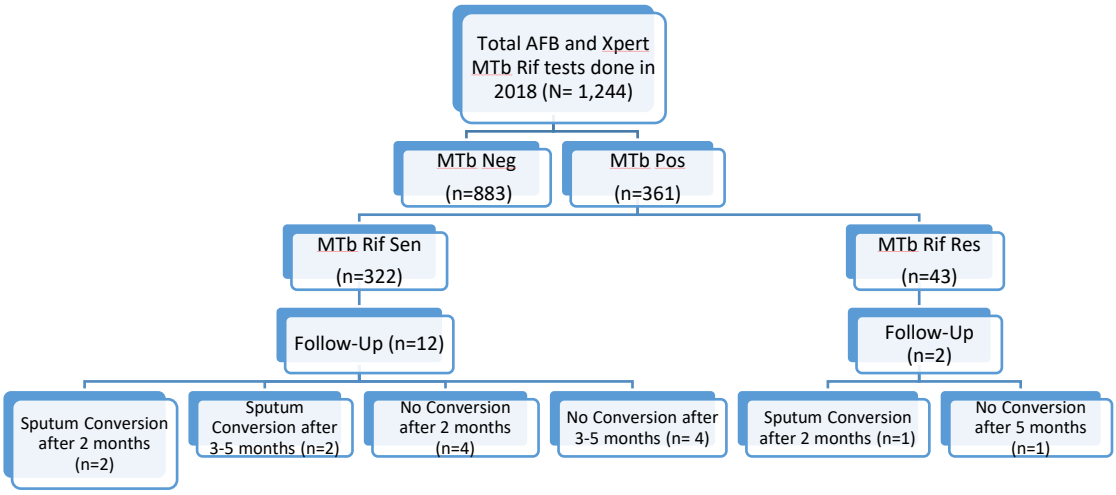

Figure 1: Flow chart of AFB and Xpert MTb result

The characteristics of pulmonary TB patients (rifampicin-sensitive and -resistant) are given in Table 1. Of the sputum smear-positive patients, 267 (73.9 %) were male, and of RR-TB patients, 35 (13,1%) were male. Of the total confirmed TB patients, 157 (43.5%) were from Banda Aceh and Aceh Besar region, where 7 (4.4%) were RR-TB patients. Most of RR-TB patients (83.7%) come from the region outside Banda Aceh and Aceh Besar. Ninety-five (26.3%) patients had close contact with MDR-TB patients, and 88 (92.6%) were drug-susceptible TB patients. Forty (11%) were new TB cases, and only one patient was confirmed as having TB with HIV patient.

Table I: Patient characteristic

Variable	MTb Rif Sen (n)	MTb Rif Res (n)	N (%)
Gender			
Male	232	35	267 (73.9)
Female	86	8	94 (26.1)
Age group (yo)			
18-24	16	1	17 (4.7)
25-34	28	5	33 (9.1)
35-44	28	7	35 (9.6)
45-54	41	7	48 (13.3)
55-64	35	7	42 (11.6)
≥65	22	3	25 (6.9)
Residence			
Banda Aceh and Aceh Besar	150	7	157 (43.5)
Outside Banda Aceh and Aceh Besar	168	36	204 (56.5)
Presumptive MDR-TB criteria			
1. Treatment failure of category 2 regimen	1	-	1 (0.2)
2- AFB (+) after the third month of category 2 regimens	2	1	3 (0.8)
3. Non-DOTS MDR patients (e.g. fluoroquinolone and kanamycin)	32	4	36 (9.9)
4. Treatment failure of category 1 regimens	12	2	14 (3.8)
5. AFB (+) after insert therapy and category 1 regimen	4	-	4 (1.1)
6. TB relapse	45	10	55 (15.3)
7. Treatment after default	21	8	29 (8)
8. Close contact with MDR-TB patients	88	7	95 (26.3)
9. TB with HIV	1		1 (0.2)
10- New cases	38	2	40 (11)

A total of 12 drug-susceptible TB patients had bacteriologic follow-up tests during the study period, and 4 (30%) had sputum smear conversion. However, only one RR-TB patient had a follow-up test, and none had conversion during the study period.

Discussion

Sputum smear conversion after a certain period of anti-TB drugs is an important marker to evaluate the response to anti-TB treatment (Horne *et al.,* 2010). Bacteriology conversion and drug concentration monitoring can be surrogate markers for defining the treatment outcome, along with clinical, radiological, and immunological features (Horne *et al.,* 2010; Perrin *et al.,* 2007). This retrospective cohort study explores the cure rate of a patient's sputum bacteriology status to predict TB treatment outcomes. Table I shows that most of the patients (52.2% and 83.7% with rifampicin-sensitive and -resistant TB, respectively) come from outside Banda Aceh and Aceh Besar, the nearest area to Dr. Zainoel Abidin hospital. It causes a small number of patients (14 of 361) to have bacteriology follow-up results because they may have the test in their origin region biweekly.

Four patients had negative AFB results after two months of treatment and after 3-5 months of TB treatment. Of two RR-TB patients, one patient had sputum conversion, and another five had no conversion in the second bacteriology test after five months of treatment. As sputum conversion result at the end of two months of treatment could be a valuable marker to predict patient treatment outcome (Calderwood *et al.,* 2021), patients with persistent positive AFB sputum may have worse prognoses than those with bacteriology conversions.

Most of the TB patients were male (73.9%) in the rifampicin-sensitive and –resistant group, and most RR-TB patients (48.8%) were 35 to 64 years of age. It was similar to other studies exploring the proximate risk factors for TB in the male group, such as smoking habit and alcohol use, specific immunological vulnerabilities in the male group, barriers faced by women in seeking care and presenting for diagnosis, and most recently, biological predispositions in male related to iron metabolism (Dodd, 2016; Nhamoyebonde *et al.,* 2014; Yates *et al.,* 2017).

This study noted a higher percentage of patients having close contact with MDR TB patients (26.3%) and the number of patients who experienced TB relapse (15.3%). The lower rate of HIV tests in TB patients is one of the other concerns, where only one patient was detected as HIV-positive. Having an HIV test for TB patients is critical, as most TB cases are co-infected with HIV, and it affects disease progressivity and treatment response (Gebremariam *et al.,* 2010).

Kinds of literature showed the different lengths of sputum and culture conversion times (Azarkar et al., 2016). This study revealed a mean conversion time of rif-sensitive of 67.5 and 81 days in RR-TB patients. This was longer compared to former research that reported a median time of 34 days of sputum conversion in TB, with an IQR of 28–54 (Tekalegn *et al.,* 2020). Poor RR-TB treatment outcomes were associated with former TB treatment, resistance to ofloxacin, and no culture conversion by the 3rd month of treatment (Cazabon *et al.,* 2017). The experimental factors that may be related to sputum conversion in this study were male, young adult (34-49 years old), and Aceh Besar residents (Table II).

Table II: Duration of bacteriologic conversion

Patient No.	Age	Gender	Residence	Follow-up test result	Duration (days)
1	57	M	BNA	**+**	61
2	71	M	Abes	**+**	73
3	45	F	Abes	**+**	69
4	34	M	BNA	**+**	63
5	87	M	Pidie	**+**	105
6	30	M	Abes	**+**	154
7	39	M	A.Jaya	**+**	217
8	46	M	Abes	**+**	308
9	34	F	A.Jaya	-	76
10	49	F	Abes	-	59
11	38	F	Abes	-	155
12	28	M	Abes	-	112
13	46	M	A.Timur	**+**	290 (Rif Res)
14	39	M	A.Timur	-	81 (Rif Res)

Conclusion

There was a low rate of bacteriologic conversion among TB-confirmed patients (rifampicin sensitive and –resistant TB), and patient characteristic factors such as male gender, young adult, and living in Aceh Besar tended to have bacteriologic conversion in Dr. Zainoel Abidin hospital.

Conflict of interest

The authors declare that there is no conflict of interest.

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