RISK FACTORS FOR POOR TUBERCULOSIS TREATMENT OUTCOMES IN MAKASSAR, INDONESIA

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Abstract. Resistant tuberculosis is an important public health problem in South Sulawesi, Indonesia. We conducted a retrospective cohort study of 1,582 smear positive tuberculosis patients registered with the National Tuberculosis Program during 2007 in Makassar, Indonesia, to assess risk factors associated with poor tuberculosis treatment outcomes. Of the 1,582 patients, 265 had a poor treatment outcome. Of the 265 patients with a poor treatment outcome, 216 had defaulted on treatment, 7 failed treatment, 9 died and 33 transferred to another area. After adjusting for sex, age and BCG status, failure acid-fast bacilli (AFB) positive sputum to convert to AFB negative by 2-3 months was the only risk factor significantly associated with a poor treatment outcome (odds ratio 7.57; 95% CI: 1.22-47.1). We hypothesise this could represent resistant tuberculosis. Early identification of resistant tuberculosis is important and should be suspected in patients whose AFB positive sputum samples fail to convert to AFB negative by 2-3 months.

Keywords: tuberculosis, poor treatment outcome, defaulting, resistance, risk factors, Indonesia

INTRODUCTION

Indonesia has been listed as a high tuberculosis (TB) burden and high multi-drug resistant tuberculosis (MDR-TB) burden country by the WHO with an estimated TB prevalence of 281 cases per 100,000 population and an incidence of 187 cases per 100,000 population per year (WHO, 2011). In 2006 the case detection rate (CDR) in Indonesia exceeded 70% (DOTS target) for the first time, a level that remained stable over the next 5 years (WHO, 2011). However large differences are seen among provinces in Indonesia. The CDR varied between 31% and 85% in 2009 (NTBI, 2014a). In South Sulawesi the CDR in 2009 was estimated to be 38.7% (NTBI, 2004b) and the treatment success rate (TSR) in 2006 was 90.8% (DGDCEH, 2009).

Although the TSR exceeds international targets, patients with poor treatment

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outcomes are responsible for continuing transmission of TB and lack of improvement in the TSR. In addition, a poor treatment outcome is highly indicative of MDR-TB (Chang *et al*, 2004). Early detection and appropriate management of patients with indicators for a poor treatment outcome is essential for TB control programs.

All Indonesian health care institutions should be following international TB treatment recommendations of an initial phase lasting 2 months of receiving isoniazid, rifampicin, ethambutol and pyrazinamide, followed by a continuation phase lasting 4 months of receiving isoniazid and rifampicin (Collins and Jarrh, 2013). Fixed doses of two, three of four types of medications are recommended (Collins and Jarrh, 2013).

All acid-fast bacilli (AFB) sputum smear positive patients should be monitored for response to treatment with a follow-up sputum examination after two months, after five months and at the end of treatment (Collins and Jarrh, 2013). Monitoring AFB sputum smear negative cases is done clinically. When a patient fails to have an AFB sputum conversion from positive to negative by the third month of treatment, second line treatment should be started (Collins and Jarrh, 2013). Retreatment cases should start on second line treatment immediately upon diagnosis (TCTA, 2006).

However not all health care facilities have access to second line TB treatment drugs. No protocol exists for managing failure of sputum to convert to negative by 7 months treatment, since access to third line treatment regimens is even scarcer.

We determined to identify risk factors for poor treatment outcomes in Makassar, South Sulawesi, Indonesia among all AFB sputum positive patients registered at selected health facilities during 2007. Identifying these risk factors for poor treatment outcome could enable health workers to intervene early preventing further morbidity and potential spread to TB.

MATERIALS AND METHODS

Study design and population

A register-based retrospective cohort study was conducted in Makassar, the provincial capital of South Sulawesi, Indonesia. The register contains information about patients with TB in 14 districts of Makassar, and at 45 health centers, including hospitals and smaller health facilities working under the directly observed treatment-short cource (DOTS) program. The study evaluated 1,582 patients with a positive AFB sputum test, registered with the National TB Program (NTP) as pulmonary TB patient during 1 January-31 December 2007. Exclusion criteria were: unknown treatment outcome, age <15 years, living outside Makassar, having extra-pulmonary TB and having negative sputum sample for AFB at diagnosis. Ethical clearance for the study was obtained from the Hasanuddin University in Makassar.

Data collection

The TB program register was validated by cross-checking with individual TB treatment cards. The registers contained information about demographic characteristics, sputum status at diagnosis, type of patient (new or retreatment), type of treatment and sputum for AFB test results by 2-3 months and 5-7 months.

Treatment outcomes were reported following WHO classifications: cured and treatment completed (good treatment outcome), treatment failure, death, de-

Table 1
Baseline characteristics of 1,582 sputum positive TB patients included in the study.

Variable			All patients (%)	New patients (%) *N*=1,507	Retreatment patients (%) *N*=75
Sex		Male	968 (61.2)	916 (60.8)	52 (69.3)
		Female	614 (38.8)	591 (39.2)	23 (30.7)
Age		Median	36	36	39
		Inter Quartile Range	26-50	25-50	31-53
BCG vaccine		Yes	36 (37.5)	35 (37.2)	1 (50.0)
		No	60 (62.5)	59 (62.8)	1 (50.0)
		Unknown	1,486		
Sputum result	After 2-3 months	Positive	61 (4.3)	61 (4.5)	0 (0)
		Negative	1,355 (95.7)	1,295 (95.5)	60 (100)
		Unknown/missing	166	151	15
	After 5-7 months	Positive	6 (0.5)	6 (0.5)	0 (0)
		Negative	1,196 (99.5)	1,137 (99.5)	59 (100)
		Unknown/missing	380	364	26
Treatment outcome		Cured	1,190 (75.2)	1,131 (75.0)	59 (78.7)
		Treatment completed	54 (3.4)	53 (3.5)	1 (1.3)
		Died	9 (0.5)	7 (0.5)	2 (2.7)
		Failed treatment	4 (0.3)	4 (0.3)	0 (0)
		Defaulted	216 (13.7)	206 (13.7)	10 (13.3)
		Transferred out	33 (2.1)	31 (2.1)	2 (2.7)
		Unknown/missing	76 (4.8)	75 (5.0)	1 (1.3)
		Good outcome	1,244 (82.6)	1,184 (82.7)	60 (81.1)
		Poor outcome	262 (16.4)	248 (17.3)	14 (18.9)

faulted or transferred out (poor treatment outcomes) (Veen *et al*, 1998).

Data analysis

The data were analyzed using Microsoft Excel and Stata 9.2 (STATACorp LP, College Station, TX). For univariate analysis chi-square tests and Fisher's exact tests were used. For multivariate analysis, a backwards selection multivariate logistic regression model was used. All variables with a *p*-value <0.20 on univariate analysis (except for BCG status due to the large amount of missing data) were included from multivariate analysis. Patient characteristics included in the univariate and multivariate analyses are shown in Tables 1 and 2. Variables regarding AFB sputum conversion results by 2-3 months and 5-7 months were not modelled together, due to collinearity. Significance levels was set at $p<0.05$.

RESULTS

In 2007, 2,331 TB patients were registered with the NTP in Makassar, South Sulawesi, Indonesia. The baseline characteristics and treatment outcomes for 1,582 patients fulfilled inclusion criteria are shown in Table 1.

Table 2
Univariate and multivariate analyses of risk factors for poor treatment outcome among AFB smear positive TB patients.

	Variable	Good outcome	Poor outcome	OR	Adjusted OR	*p*-value
Sex	Male	812 (83.88)	156 (16.12)	1.12	1.76	0.49
	Female	505 (82.25)	109 (17.75)		(0.36-8.69)	
Age	<25	295 (86.51)	46 (13.49)	1.37	1.80	0.61
	>25	1,022 (82.35)	219 (17.65)		(0.18-17.46)	
BCG vaccine	Yes	27 (75.00)	9 (25.00)	0.75	1.24	0.82
	No	48 (80.00)	12 (20.00)		(0.19-8.10)	
Sputum results						
After 2-3 months	Positive	45 (73.77)	16 (26.23)	4.82	7.57	0.03
	Negative	1,262 (93.14)	93 (6.86)		(1.22-47.10)	
Type of patient	New	61 (81.33)	14 (18.67)	1.15	0.21	0.13
	Retreatment	1,256 (83.34)	251 (16.75)		(0.03-1.57)	

Risk factors for poor treatment outcomes

On multivariate analysis, two factors were found to be associated with poor treatment outcomes. Failure for AFB positive sputum to convert to AFB negative by 2-3 months [odds ratio (OR) 7.57; 95% CI: 1.22-47.1] was associated with a poor treatment outcome. The majority of patients with poor treatment outcomes were defaulters; therefore, failure for the sputum to convert from AFB positive to AFB negative by 2-3 months was significantly associated with defaulting on treatment (OR 2.47; 95%CI: 1.13-5.39). Patient age <25 years was also slightly more likely to be associated with a poor treatment outcome compared to older patients, but this association did not reach significance (OR 1.80; 95% CI: 0.18-17.46) (Table 2).

DISCUSSION

Drug resistant TB is a significant public health problem in Makassar. A study by Massi *et al* (2011) showed the proportion of TB cases resistant to at least one anti-tuberculosis drug was approximately 40% among both new and retreatment cases in the Makassar area. The percentage of MDR-TB was 4% among new cases and 19% among retreatment cases (Massi *et al*, 2011).

Another study (Muñoz-Sellart *et al*, 2010) found failure of ABF positive sputum to convert to AFB negative by 2-3 months was associated with a poor treatment outcome. This suggests drug resistance could be a reason for the need to retreat. In South Sulawesi, there are no available diagnostic tools to confirm drug resistance. However, based on the results of this study, one could hypothesize drug resistance and poor patient compliance with treatment play an important role in the problem of poor treatment outcomes in Makassar. Further studies are needed to confirm this.

The failure of AFB positive sputum to convert to AFB negative could suggest a suspected (M) DR-TB case. Yew *et al* (2000) found the mean time for AFB positive sputum convert to negative is about 2 months (standard deviation: 1 month) while failure to convert to negative by

4 months was rare. Waiting for the fifth month sputum examination result seems too late to change to second line treatment. Our study findings support testing at 2-3 months as recommended by the WHO (2010). Patients with AFB smear positive sputum by 2 months of treatment should be referred to a center that can test for MDR-TB. This would make testing the sputum at 5-7 months unnecessary and reduce the workload of the microscopy laboratories. Early testing and referral could also prevent the spread of resistant TB. Recently available, simple and affordable molecular assays to screen for MDR (Boehme *et al*, 2010) may be cost effective in these patients.

Second and third line TB treatment drugs need to be available throughout Indonesia to reduce the spread of MDR-TB.

This study had some limitations: due to register based data, no information could be obtained regarding the nutritional status of patients, or underlying diabetes. A body mass index (BMI) <18.5 (Leimane *et al*, 2005) and diabetes mellitus (Wang *et al*, 2009; Mi *et al*, 2013) have both been associated with adverse treatment outcomes and are risk factors for development of MDR-TB (Leimane *et al*, 2005; Chang *et al*, 2011).

The HIV status of the patients was unknown. Although treatment efficiency is similar between HIV positive and HIV negative patients, combination TB treatment and antiretroviral treatment (ART) may cause severe side effects, making it more for patients to be noncompliant with treatment (Onyebujoh *et al*, 2007). A study from Rwanda (Kayigamba *et al*, 2013) found adherence to TB treatment did not differ between HIV positive and HIV negative patients; however, those who were noncompliant with ART were more likely to be noncompliant with TB treatment. In our study some of the defaulting patients could have been HIV positive and noncompliant with their ART. The HIV prevalence in Indonesia is estimated to be 0.4% (UNAIDS, 2008). However, it is essential to test for HIV status when treating TB.

Registration, follow-up of treatment compliance and studying reasons for defaulting should give insight into reasons for TB noncompliance.

Early diagnosis and treatment of resistant TB, is important for appropriate treatment of TB and prevention of spread of resistant TB.

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