Poor Tuberculosis Treatment Outcomes Associated with Older Age, Previous Treatment, HIV and Drug Resistance at Seven Hospitals in Indonesia

Dampak Buruk Pengobatan Tuberkulosis Berhubungan dengan Usia Lanjut, Pengobatan Sebelumnya, HIV dan Resistensi Obat di Tujuh Rumah Sakit di Indonesia

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Abstract

Indonesia is a high burden country for tuberculosis (TB), multidrug-resistant (MDR) TB, and TB-HIV. We aimed to determine factors associated with poor TB treatment outcomes. A hospital-based TB Registry at seven referral hospitals in Java and Bali included data from patients aged ≥ 15 years who were diagnosed with TB from 1 January 2014 - 31 December 2015. The factors were assessed by logistic regression. From 2,051 TB patients, 1,180 (57.5%) were male and median age was 38 years (IQR 27-50 years), 452 (22%) had previous TB treatment history, 1,447 (70.6%) had pulmonary TB, 216 (10.5%) TB-HIV, 296 (14.4%) TB-DM and 248 (12.1%) were resistant to ≥ 1 anti-TB drug. Treatment outcome was unknown for 135 (6.6%) subjects and 1,137 (55.4%) who were still on treatment. Among the 779 with available outcome, 358 (46%) were treatment success, 248 (31.8%) transferred out, 112 (14.4%) defaulted, 46 (5.9%) died and 15 (1.9%) failed. After controlling other factors, poor TB treatment was associated with age ≥ 38 years ($p=0.003$; aOR 1.58; 95% CI 1.2-2.1), previous history of TB treatment ($p<0.001$; aOR 2.55; 95% CI 1.5-4.2) and resistance to ≥ 1 anti-TB drug ($p<0.001$; aOR 11.66; 95% CI 3.8-36.1). Mortality was associated with previous history of TB treatment ($p=0.003$; aOR 3.87; 95% CI 1.7-9.6), TB-HIV ($p=0.001$; aOR 10.43; 95% CI 4.2-26.1), and resistance to ≥ 1 anti-TB drug ($p=0.001$; aOR 9.48; 95% CI 2.6-34.0). Treatment in TB patients with older age, history of previous TB treatment, HIV, and drug resistance should be closely monitored.

Keywords: Indonesia, tuberculosis, treatment outcome

Abstrak

Indonesia adalah negara dengan beban tinggi untuk tuberkulosis (TB), TB resisten obat (MDR) dan TB-HIV. Analisis ini bertujuan untuk menentukan faktor yang terkait dengan luaran pengobatan TB yang buruk. Registri TB berbasis rumah sakit di tujuh rumah sakit rujukan di Jawa dan Bali mencakup data dari pasien berusia ≥ 15 tahun yang didiagnosis TB dari 1 Januari 2014 - 31 Desember 2015. Faktor-faktor tersebut dinilai dengan regresi logistik. Dari 2.051 pasien TB, 1.180 (57,5%) laki-laki dan median usia 38 tahun (IQR 27-50 tahun), 452 (22%) memiliki riwayat pengobatan TB sebelumnya, 1.447 (70,6%) memiliki TB paru, 216 (10,5%) TB-HIV, 296 (14,4%) TB-DM dan 248 (12,1%) resisten terhadap ≥ 1 obat anti-TB. Luarannya pengobatan TB tidak diketahui untuk 135 (6,6%) subjek dan 1.137 (55,4%) yang masih dalam pengobatan. Di antara 779 dengan luaran pengobatan diketahui, 358 (46%) pengobatan berhasil, 248 (31,8%) pindah, 112 (14,4%) putus pengobatan, 46 (5,9%) meninggal dan 15 (1,9%) gagal. Setelah dikontrol terhadap faktor lain, luaran pengobatan TB yang buruk dikaitkan dengan usia ≥ 38 tahun ($p = 0,003$; aOR 1,58; 95% CI 1,2-2,1), riwayat pengobatan TB sebelumnya ($p < 0,001$; aOR 2,55; 95% CI 1,5-4,2) dan resistansi terhadap ≥ 1 obat anti-TB (p

$<0,001$; aOR 11,66; 95% CI 3,8-36,1). Kematian dikaitkan dengan riwayat pengobatan TB sebelumnya ($p = 0,003$; aOR 3,87; 95% CI 1,7-9,6), TB-HIV ($p = 0,001$; aOR 10,43; 95% CI 4,2-26,1), dan resistansi terhadap ≥ 1 anti-TB obat ($p = 0,001$; aOR 9,48; 95% CI 2,6-34,0). Pengobatan pada pasien TB dengan usia yang lebih tua, riwayat pengobatan TB sebelumnya, HIV dan resistansi obat harus dipantau secara ketat.

Kata kunci: Indonesia, tuberkulosis, luaran pengobatan

Introduction

Despite the declining trend in tuberculosis (TB) incidence rate between 2000 and 2018, Indonesia is considered a high-burden country for TB, multidrug resistant (MDR) TB and TB/HIV.¹ Indonesia has the second highest number of TB cases globally, with an estimated TB prevalence of 647/100,000. Indonesia is also among the 27 high-burden MDR-TB countries that accounted for more than 50% of estimated MDR-TB cases occurring worldwide in 2013. The prevalence of HIV among incident TB cases in Indonesia is 3.2%, which is slightly under India and Cambodia.²

The percentage of patients treated successfully is a key indicator for monitoring and evaluating the effectiveness of the TB Directly Observed Therapy (DOT) program. Globally, an 85% treatment success rate is reported for the new and relapse TB cases who are treated in 2017 and the same rate is reported for Indonesia.¹ The initial treatment for active TB disease requires the combination of at least three drugs for a minimum duration of six months. Incomplete treatment increases the risk of TB transmission, resistance, morbidity and mortality.

Studies have included older age, alcohol use, HIV, low body mass index, anemia and treatment delay as some of the factors associated with poor TB treatment outcomes.³⁻⁶ Monitoring the TB treatment outcome is needed to evaluate the effectiveness of TB management and to identify potential barriers for TB control. However, this has not been well studied in Indonesia. Therefore, this analysis aimed to determine factors associated with poor treatment outcomes among TB patients at seven hospitals in Indonesia.

Methods

A hospital-based TB registry was established in 2014 at seven referral hospitals in Java and Bali. Patients aged 15 years and older who attended the hospitals as outpatients and were diagnosed with

TB (ICD-10 code A15-A19) between 1 January 2014 and 31 December 2015 were included in the registry. Data on socio demographics, clinical characteristics, treatment, and treatment outcome were abstracted from the patients' medical records. Ethical approval No. LB.02.01/5.2/KE423/2014 was obtained from the Health Research Ethics Committee of the National Institute of Health Research and Development, Ministry of Health of Indonesia.

In this analysis, we included participants whose data were collected until 12 January 2016. The baseline characteristics were grouped based on reported TB treatment history, i.e. treatment naïve (had never received TB treatment) and previously treated. Previously treated TB composed of patients who experienced relapse after receiving successful treatment, those who returned after default, and those who started receiving a re-treatment regimen after having treatment failure, as well as other patients (i.e., those who do not fit to any of the aforementioned categories, such as those who received unknown or unstandardized treatment regimens). Resistance to at least one anti-TB drug was based on Xpert MTB-Rif or drug susceptibility test results. HIV and diabetes mellitus (DM) status were based on physician's diagnosis as stated in the patients' medical records. The poor TB treatment outcome of interest was a composite of failed, lost to follow up, transferred out and mortality (all-cause). Logistics regression was used to assess the determinants of the poor TB treatment outcomes. Significant factors with p -value <0.20 were included in a multivariate model. We reported the unadjusted and adjusted odds ratio (aOR) with 95% confidence intervals (CI). All the analysis was conducted with SPSS ver. 22.

Results

A total of 2,051 participants were included in this analysis (**Table 1**). The dominant participants were male and range of age was 25-44 years old.

Pulmonary TB was the predominant type of TB and previously treated TB was documented in 22% of the participants. Cases of TB-HIV and TB-DM were both below 20%. Acid fast bacilli (AFB) smear positive TB and resistance to at least one anti-TB drug were higher in the previously treated than in treatment-naïve participants.

Treatment outcome was unknown for 135 subjects (6.6%) and 1,137 subjects (55.4%) were still on treatment (**Figure 1**). Among the 779 participants with available data on treatment outcome, TB treatment success was lower in the previously treated than in treatment naïve TB

(24.8% vs 50.2%) (**Figure 2**).

After controlling other factors, poor TB treatment was associated with age 38 years and older, history of previous TB treatment and resistance to at least one anti-TB drug (**Table 2**). After controlling other factors, mortality was associated with history of previous TB treatment, positive HIV), and resistance to at least one anti-TB drug (**Table 3**).

Discussions

Our results showed that only 46% of the TB registry participants had successful TB treatment. Older age, history of previous TB treatment, HIV

Table 1. Baseline Characteristics of the TB Registry Participants

Characteristics		Total		TB treatment naïve		Previously treated TB	
		N	%	n	%	n	%
Age (years)	<25	398	19,4	348	21,8	50	11,1
	25-44	913	44,5	705	44,1	208	46,0
	45-64	636	31,0	469	29,3	167	36,9
	65+	104	5,1	77	4,8	27	6,0
	Median (IQR)	38	(27-50)	36	(26-50)	42	(30-52)
Sex	Male	1180	57,5	904	56,5	276	61,1
	Female	871	42,5	695	43,5	176	38,9
AFB smear	Positive	981	47,8	632	39,5	349	77,2
	Negative	632	30,8	559	35,0	73	16,2
	Not available	438	21,4	408	25,5	30	6,6
Type of TB	Pulmonary TB	1447	70,6	1025	64,1	422	93,4
	Extra pulmonary TB	580	28,3	551	34,5	29	6,4
	Mixed	24	1,2	23	1,4	1	0,2
HIV status	TB-HIV	216	10,5	183	11,4	33	7,3
	TB-non-HIV	1182	57,6	868	54,3	314	69,5
	Not available	653	31,8	548	34,3	105	23,2
DM status	TB-DM	296	14,4	181	11,3	115	25,4
	TB-non-DM	1679	81,9	1348	84,3	331	73,2
	Not available	76	3,7	70	4,4	6	1,3
Resistance to at least 1 anti-TB drug	Resistant*	248	12,1	23	1,4	225	49,8
	Sensitive	391	19,1	289	18,1	102	22,6
	Not available	1412	68,8	1287	80,5	125	27,7
Total (n, %)		2051	100	1599	78,0	452	22,0

AFB: acid fast bacilli; DM: diabetes mellitus; IQR: interquartile range

*based on either Xpert MTB-Rif or drug susceptibility test

Figure 1. Overall Distribution of Treatment Course and Outcomes in the TB Registry

Figure 2. Distribution of Available Treatment Outcome by TB Treatment History

positive, and resistance to at least one anti-TB drug were significantly associated with poor TB treatment outcomes. The rate of TB treatment success in this study was much lower than the 85% success rate reported globally.¹ And this result still lower than a study in India that reported TB treatment success rate was 72.5%, while in China was 95%, where both are countries with high burden of TB.^{7,8}

Older age (≥ 38 years) was significantly associated with poor TB treatment in this study and was consistent with recent studies.⁹⁻¹¹ Previously

treated TB in this study (22%) was higher than the 11% reported in India, a country with the highest TB burden in the world.¹² Older aged patients, especially those with previously treated TB, are often clinically more complicated. They are more difficult to manage and may stay infectious for a longer time. They also bear individual risks of experiencing drug resistance and poor treatment outcomes, thus became an important group for TB control and should not be neglected.^{13,14}

This study showed a 10.5% proportion of

TB-HIV and the odds for all-cause mortality was at least ten times higher among TB/HIV when compared to TB patients who were HIV negative. The proportion of TB/HIV among TB patients in this study was higher than that reported in India (3.1%) and Denmark (4.6%).^{15, 16} To address the dual burden of TB and HIV, the WHO have advocated

and emphasized the need for integrated TB and HIV services, and provided guideline on collaborative TB-HIV activities for national programs and other stakeholders. In Indonesia, the TB-HIV collaborative activities have been initiated, and enhancement of these activities is among the strategies outlined in the national strategic plan for TB control.

Table 2. Risk Factors for Poor TB Treatment

Variable		Total		Not Success		Success		p	OR (95% CI)	aOR (95% CI)
		n	%	n	%	n	%			
Age (years)	≥38	392	50,3	233	55,3	159	44,4	0,003	1,55 (1,2-2,1)	1,58 (1,2-2,1)
	<38	387	49,7	188	44,7	199	55,6		Ref.	Ref.
Sex	Male	444	57,0	242	57,5	202	56,4	0,624	1,04 (0,8-1,4)	-
	Female	335	43,0	179	42,5	156	43,6		Ref.	
Type of TB	Extra pulmo- nary	235	30,2	132	31,4	103	28,8	0,759	1,12 (0,8-1,6)	-
	Mixed	8	1,0	5	1,2	3	,8	0,672	1,48 (0,3-6,2)	
	Pulmonary	536	68,8	284	67,5	252	70,4		Ref.	
TB treatment history	Previously treated	129	16,6	97	23,0	32	8,9	<0,001	3,05 (1,9-4,7)	2,55 (1,5-4,2)
	Naive	650	83,4	324	77,0	326	91,1		Ref.	Ref.
HIV status	Positive	57	7,3	29	6,9	28	7,8	0,875	1,03 (0,6-1,8)	-
	Not available	285	36,6	173	41,1	112	31,3	0,118	1,54 (1,1-2,1)	
	Negative	437	56,1	219	52,0	218	60,9		Ref.	
DM status	Positive	66	8,5	43	10,2	23	6,4	0,295	1,66 (0,9-2,8)	-
	Not available	17	2,2	9	2,1	8	2,2	0,293	0,99 (0,4-2,6)	
	Negative	696	89,3	369	87,6	327	91,3		Ref.	
Resistance to at least 1 anti- TB drug	Resistant	48	6,2	44	10,5	4	1,1	<0,001	22,43 (7,6-65,8)	11,66 (3,8-36,1)
	Not done	576	73,9	326	77,4	250	69,8	<0,001	2,65 (1,8-3,7)	3,68 (2,4-5,7)
	Sensitive	155	19,9	51	12,1	104	29,1		Ref.	Ref.

aOR: adjusted odds ratio

Drug resistance TB is a significant barrier to effective TB care and prevention which often resulted from unsupervised and inappropriate treatment, and could be seen as programmatic problem. The treatment of drug-resistant TB is complicated and inappropriate management can have life-threatening results. This study showed resistance to at least one anti-TB drug was associated with eleven times higher odds for poor treatment outcome when compared to those without resistance, with only four out of the 44 resistant participants had successful treatment. The proportion of poor TB treatment outcomes among those with resistance to at least one TB drug in this

study (92%) was much higher than that reported in India (55%).¹⁷ This results must be responded with appropriate care to address drug resistance among TB patients and to limit further spread.

The major strength of our study is the data from major TB referral hospitals in Java and Bali. In this study, we showed which factors were associated with treatment outcome. This study results could help clinician and TB national program in managing TB patients.

Due to the timing of data extraction, more than half of TB patients were still on treatment. However, we still have a large number

Table 2. Risk Factors for Mortality among TB Patients

Variable		Total		Not Success		Success		p	OR (95% CI)	aOR (95% CI)
		n	%	n	%	n	%			
Age (years)	≥38	392	50,3	26	56,5	366	49,9	0,386	1,30 (0,7-2,4)	-
	<38	387	49,7	20	43,5	367	50,1		Ref.	
Sex	Male	444	57,0	31	67,4	413	56,3	0,142	1,60 (0,8-3,0)	1,26 (0,6-2,6)
	Female	335	43,0	15	32,6	320	43,7		Ref.	Ref.
Type of TB	Extra pulmo- nary	235	30,2	8	17,4	227	31,0	0,052	0,46 (0,2-1,0)	0,67 (0,2-2,5)
	Mixed	8	1,0	0	0	8	1,1	0,999	0	0
	Pulmonary	536	68,8	38	82,6	498	67,9		Ref.	Ref.
TB treatment history	Previously treated	129	16,6	23	50,0	106	14,5	0,003	5,91 (3,2-10,9)	3,87 (1,7-9,6)
	Naïve	650	83,4	23	50,0	627	85,5		Ref.	Ref.
HIV status	Positive	57	7,3	14	30,4	43	5,9	<0,001	5,86 (2,8-12,2)	10,43 (4,2-26,1)
	Not available	285	36,6	9	19,6	276	37,7	0,651	0,59 (0,3-1,3)	-
	Negative	437	56,1	23	50,0	414	56,5		Ref.	Ref.
DM status	Positive	66	8,5	10	21,7	56	7,6	0,847	3,59 (1,7-7,7)	-
	Not available	17	2,2	3	6,5	14	1,9	0,254	4,3 (1,2-15,7)	
	Negative	696	89,3	33	71,7	663	90,5		Ref.	
Resistance to at least 1 anti- TB drug	Resistant	48	6,2	17	37,0	31	4,2	0,001	22,43 (7,6-65,8)	9,48 (2,6-34,0)
	Not done	576	73,9	25	54,3	551	75,2	0,060	2,66 (1,8-3,7)	2,99 (0,9-9,4)
		155	19,9	4	8,7	151	20,6		Ref.	Ref.

aOR: adjusted odds ratio

of TB patients for the analysis. Despite the lack of treatment adherence, which is an important factor associated with treatment outcome¹⁸, we believe with the effect size reported in our study. Adding other potential confounders will not make the results changed drastically into not significant or changed the direction of the effect (risk factor into protective factors or vice versa).

This study has some important implications. First, there is a need for more focused attention on the more vulnerable older population, which presents with worse treatment outcomes than other age groups. A reasonable step would be to systematically screen for potential comorbidities among TB patients, such as DM, which are more common in aging populations. Second, there is a need for an earlier community HIV testing and treatment among TB patients to prevent late presentation of HIV with severe disease. Third, there is also a need for earlier testing for drug resistance among TB

patients, including among newly diagnosed TB to identify transmitted resistance.

Conclusion

To avoid poor treatment among TB patients in Indonesia, special attention should be given to patients with older age, history of previous TB treatment, HIV and drug resistance. Close monitoring should be given specifically to these patients to ensure they stay on treatment. More effort should be made to identify drug resistance and HIV among TB patients.

Author Contributions

DA wrote first draft of the paper and prepared the references. DA and RMI processed and analyzed the data. AY, ADH, AKS retrieved and managed the data. MK supervised data management and analysis. All authors read and approved the final manuscript.

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