Clinical Profiles and Prediction of Treatment Failure in Patients with Tuberculosis

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Abstract

Background To improve the treatment outcomes for tuberculosis (TB) efforts to reduce treatment failure are necessary. The aim of our study was to describe the characteristics of subjects who had failed treatment of tuberculosis and identify the risk factors for treatment failure and poor compliance using national data.

Methods A multicenter cross-sectional study was performed for tuberculosis subjects whose final outcome was reported as treatment failure during 2015–2017. The same number of subjects with treatment success during the same study period were randomly selected for comparison. Demographics, microbiological, radiographic, and clinical data were collected based on in-depth interviews by TB nurse specialists at all Public Private Mix (PPM) participating hospitals in South Korea.

Results A total of 52 tuberculosis patients with treatment failure were enrolled. In a multivariable analysis, the presence of diabetes, previous history of tuberculosis, and cavity were identified as risk factors for treatment failure; and Medicaid support was a favorable factor for treatment success (area under the curve (AUC): 0.76). Age, diabetes, pre-existing lung disease, positive sputum acid-fast bacilli (AFB) smear result, and presence of multi-drug-resistant tuberculosis (MDR-TB) were significantly associated with presence of cavity. Younger age, and lower body mass index (BMI) were associated with poor compliance during treatment (AUC: 0.74).

Conclusion To reduce treatment failure, careful evaluation for the presence of diabetes, underlying lung disease, cavity, results of sputum AFB smears, and socioeconomic status is needed. To enhance treatment compliance, more attention should be paid to younger patients with lower BMIs during follow-up.

Background

Tuberculosis (TB) remains an unsolved public health problem despite the strenuous efforts exerted from numerous countries (1). In spite of the high economic status and medical services system, South Korea is included as an intermediate TB burden country and is in first place for TB development among the countries that are members of Organization for Economic Co-operation and Development (2). To overcome this situation, the Public Private Mix (PPM) collaboration model that supports diagnosis and treatment of TB has been implemented as a national TB control strategy; and as a consequence, the rate of TB has been decreasing. However, a considerable rate of treatment failure still exists, complicated by the development of drug resistance, and disease-related morbidities and mortalities that prevent the curing of TB. To triumph in battling tuberculosis, further efforts to decrease poor outcome such as treatment failure and increase treatment compliance are needed. Clinical characteristics of those who had failed treatment are limited because of difficulties in collecting appropriate subjects. In previous studies, human immunodeficiency virus (HIV) co-infection, previous history of TB, sputum smear positive after two months of treatment, male gender, young or advanced age, drug resistance, and residence in a

solitary area have been proposed as risk factors for poor outcome (3–9). However, such studies were performed on a small number of patients in high TB burden countries with limited medical resources. Because South Korea has a different socioeconomic environment, a low rate of HIV infection and high access to medical services (10, 11), a different strategy to control TB is required in South Korea.

The aim of our study was to describe the subjects' characteristics and to identify the risk factors of treatment failure and poor compliance for the purpose of predicting risk group to improve treatment outcomes. Collecting enough treatment failure cases from individual institutions was difficult, therefore, we collected national data of treatment failure cases from all the PPM participating hospitals.

Materials And Methods

In South Korea, physicians must notify diagnosis and treatment of TB when they initially diagnose or suspect TB and multi-drug-resistant tuberculosis (MDR-TB). Under the PPM project, all the patients are followed during treatment until the report of final treatment outcomes by TB nurse specialists dispatched to private PPM hospitals. TB nurse specialists record information about medications, side effects, compliance into Korean National TB Surveillance System of PPM hospitals (12). More than 210 TB nurse specialists at 127 PPM hospitals and 236 public health officials at 254 public health centers across the country work under the PPM projects. Approximately 69% of new TB patients were treated at PPM hospitals in 2017. From January 2015 to December 2017, data of subjects who failed TB treatment were collected from all the PPM participating hospitals and TB nurse specialists at each hospital completed treatment failure case report forms. Treatment failure was defined as remaining culture positive after four months of treatment or at the end of treatment (13). Baseline characteristics such as age, sex, body mass index (BMI), respiratory symptoms, previous history of TB, co-existing comorbidities, and smoking and alcohol history were recorded. Furthermore, results of radiographic, microbiological, and clinical data including sputum smear, drug susceptibility test, treatment regimen, and treatment compliance were retrospectively collected by TB nurse specialists. After collecting information about treatment failure cases, same number of subjects with treatment success during same study period were randomly selected and the characteristics of these two groups were compared. Additionally, the characteristics of treatment compliance and non-compliance groups were also compared. Based on the results, prediction model for treatment failure was constructed.

Statistical analysis

Subjects' characteristics were presented as the mean and standard deviation for continuous variables and as relative frequencies for categorical variables. Statistical analysis was performed using R (version 3.6.0). Means were compared using a t-test or analysis of variance (ANOVA) and categorical variables were compared using a chi-squared test. For multivariable analysis, logistic regression with the backward elimination method was performed based on Akaike information criterion (AIC). To compare the predictive power in each model, the area under curve (AUC) of the receiver operating characteristic curve (ROC) was calculated using the ROCR package.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki. The Korea Centers for Disease Control and Prevention has the authority to hold and analyze surveillance data for public health and research purposes.

Results

Baseline characteristics

A total of 52 subjects who failed treatment and 50 who had treatment success during the study period were enrolled. Demographic and clinical characteristics of these participants were summarized in Table 1. Mean age was 44.5 years, and 38 (73.1%) were males. Among them, 29 (55.8%) were newly diagnosed cases, 12 (23.1%) were recurred cases, 7 (13.5%) were re-treatment cases after failure, and 3 (5.8%) were re-treatment cases after treatment cessation. Twenty-seven (51.9%) were sputum acid-fast bacilli (AFB) smear positive. The initial treatment regimen was as follows: HREZ was administered to 40 (76.9%) patients, HRE was administered to 1 (1.9%) patient, and 11 (21.2%) patients were administered others.

The demographic and clinical characteristics of the randomly selected subjects who succeeded in treatment, during the same study period, are also summarized in Table 1. Age, sex, BMI, and smoking and alcohol history were not significantly different between the two groups. However, presence of diabetes mellitus, previous history of TB, and sputum AFB smear positivity were increased in the treatment failure group. In addition, cavity was found more frequently on chest radiography in the treatment failure group. Compared to subjects without cavity, those with cavity presented with more underlying lung disease, diabetes, and positive sputum AFB smear results. Detailed characteristics comparing these groups are summarized in Supplemental Table S1. Nineteen (36.5%) subjects in the treatment failure group had MDR-TB. The characteristics of the treatment failure group without evidence of MDR-TB are summarized in Table 1. Fifty (28.8%) subjects presented non-compliance during treatment. A comparison of the characteristics between the treatment compliant and the non-compliant groups are summarized in Supplemental Table S2. Non-compliant subjects were younger ($P = 0.02$) and less obese ($P = 0.02$) than compliant subjects. Previous history of TB was less frequent in the non-compliant group. There was no association between age and BMI in both sexes ($P = 0.12$, Supplemental Figure S1). Relative distribution of overlaps among subjects who failed treatment, presented with MDR-TB, and were non-compliant are summarized in Supplemental Figure S2.

Prediction of treatment failure and non-compliance

In multivariable analysis, presence of diabetes mellitus, previous history of TB, presence of cavity, and absence of Medicaid support were independent risk factors for treatment failure in all study subjects (Table 2). The AUC of the ROC of this model was 0.760 (Figure 1A). Younger age, presence of diabetes, presence of pre-existing lung disease, positivity of sputum AFB smear, and presence of MDR-TB were significantly associated with presence of cavity (Table 2). In subjects without MDR-TB, presence of

diabetes (odds ratio (OR) = 3.72, 95% confidence interval (CI): 0.99-13.99), presence of cavity (OR = 3.04, 95% CI: 1.00-9.31), and absence of Medicaid support (OR = 0.15, 95% CI: 0.01-1.61) were selected for predicting treatment failure, and the AUC of the ROC curve for this model was 0.70 (Supplemental Figure S3). For the compliance during treatment, younger age and lower BMI were associated with poor drug compliance, and the AUC of the ROC curve for this model was 0.74 (Figure 1B).

Table 1
Clinical characteristics comparing treatment success group and treatment failure group

	Treatment success (N = 50)	Treatment failure (N = 52)	Non-MDR failure (N = 33)	P-value	
				Tx success vs. failure	Tx success vs. failure (only non-MDR)
Age	44.0(31.5–65)	44.5(29.5–67)	42.0(28.0–60.0)	0.84	0.50
Male sex	28(56.0%)	38(73.1%)	23(69.7%)	0.11	0.19
BMI	21.1 ± 2.88	20.9 ± 3.07	20.58 ± 2.83	0.72	0.45
Smoking				0.62	0.64
Current	10(20.0%)	13(25.0%)	7(21.9%)		
Ex-	10(20.0%)	7(13.5%)	4(12.1%)		
Never	30(60.0%)	32(61.5%)	22(66.7%)		
Drinking				0.20	0.34
Heavy	3(6.0%)	3(5.8%)	1(3.0%)		
Social	19(38.0%)	19(36.5%)	13(39.4%)		
None	24(48.0%)	30(57.7%)	19(57.6%)		
Underlying disease					
Diabetes	5(10.0%)	4(26.9%)	9(27.3%)	0.04	0.06
Lung ds	3(6.0%)	4(7.7%)	1(3.0%)	0.98	0.97
Heart ds	1(2.0%)	3(5.8%)	1(3.0%)	0.34	0.41
Liver ds	2(4.0%)	1(1.9%)	0(0%)	> 0.99	0.70
Kidney ds	1(2.0%)	3(5.8%)	2(6.6%)	0.58	0.21
Prev TB Hx	8(16.0%)	19(36.5%)	10(30.3%)	0.01	0.01
Symptom					
Cough/sputum	20(40.0%)	29(55.8%)	18(54.5%)	0.16	0.18
Dyspnea	10(20.0%)	7(13.5%)	4(12.1%)	0.53	0.79

BMI, body mass index; ds, disease; Hx, history; R, resistance; INH, isoniazid; RFP, rifampin; MDR, multi-drug resistance

	Treatment success (N = 50)	Treatment failure (N = 52)	Non-MDR failure (N = 33)	P-value	
				Tx success vs. failure	Tx success vs. failure (only non- MDR)
Chest pain	7(14.0%)	3(5.8%)	2(6.1%)	0.29	0.44
Hemoptysis	1(2.0%)	3(5.8%)	3(9.1%)	0.64	0.34
Fever	5(10.0%)	3(5.8%)	2(6.1%)	0.67	0.82
Weakness	0(0%)	1(1.9%)	1(3.0%)	> 0.99	0.83
Weight loss	6(12.0%)	4(7.7%)	2(6.1%)	0.69	0.60
Asymptomatic	17(34.0%)	15(28.8%)	9(27.3%)	0.73	0.69
Enrollment				0.01	0.04
Newly diagnosed	42(84.0%)	29(55.8%)	23(69.7%)		
Recurred	8(16.0%)	12(23.1%)	5(15.2%)		
Retreatment	0(0%)	7(13.5%)	3(9.1%)		
Default	0(0%)	3(5.8%)	2(6.1%)		
Social Hx					
Occupation	18(36.0%)	23(44.2%)	17(51.5%)	0.62	0.47
Marriage	28(56.0%)	33(63.5%)	20(60.6%)	0.13	0.35
Family	31(62.0%)	45(86.5%)	28(84.8%)	0.01	0.07
Medicaid	6(12.0%)	1(1.9%)	1(3.0%)	0.10	0.30
CPA					
Normal	4(8.0%)	2(3.8%)	1(3.1%)	0.17	0.22
Cavity (+)	8(17.0%)	26(50.0%)	12(36.4%)	0.001	0.07
Unilateral	26(52%)	23(44.2%)	17(51.5%)	0.30	0.29
Bilateral	17(34%)	27(51.9%)	14(42.4%)		
AFB smear				< 0.001	0.20

BMI, body mass index; ds, disease; Hx, history; R, resistance; INH, isoniazid; RFP, rifampin; MDR, multi-drug resistance

	Treatment success (N = 50)	Treatment failure (N = 52)	Non-MDR failure (N = 33)	P-value	
				Tx success vs. failure	Tx success vs. failure (only non-MDR)
Positive	11(23.4%)	27(51.9%)	13(39.4%)		
DST				<0.001	0.002
All sensitive	46(92.0%)	21(40.4%)	21(63.6%)		
R to INH	2(4.0%)	5(9.6%)	5(15.2%)		
R to RFP	1(2.0%)	5(9.6%)	2(15.2%)		
Any other R	1(2.0%)	2(3.8%)	2(6.1%)		
Treatment regimen				< 0.001	0.003
HREZ	38(76.0%)	40(76.9%)	28(84.8%)		
HRE	11(22.0%)	1(1.9%)	1(3.0%)		
Others	1(2.0%)	11(21.2%)	4(12.1%)		
Drug compliance				< 0.001	< 0.001
Good compliance	50(100%)	37(71.2%)	24(72.7%)		
Poor compliance	0(0%)	15(28.8%)	9(2.7%)		
BMI, body mass index; ds, disease; Hx, history; R, resistance; INH, isoniazid; RFP, rifampin; MDR, multi-drug resistance					

Table 2
Multivariable analysis for treatment failure, presence of cavity, and treatment compliance

	Risk factors	Odds ratio	95% CI
Treatment failure	Diabetes mellitus	3.25	0.89–11.91
	Previous history of TB	2.32	0.72–7.41
	Medicaid	0.11	0.01–1.29
	Presence of Cavity	4.78	1.72–13.23
Cavity	Age	0.954	0.92–0.99
	Diabetes mellitus	4.328	1.08–17.31
	Pre-existing lung disease	12.547	1.13–139.63
	Sputum smear positive	6.834	2.14–21.81
	MDR-TB	9.133	1.93–43.28
Poor compliance	Age	0.965	0.93–0.99
	Body mass index	0.749	0.58–0.96
TB, tuberculosis; MDR, multi-drug resistance			

Discussion

In our study, we compared the characteristics of subjects of treatment failure with those of treatment success and built a prediction model for treatment failure with high predictive power. The presence of diabetes, previous history of TB, and cavity were independent risk factors for treatment failure; and Medicaid support was a favorable one for treatment success. For the presence of cavity, younger age, diabetes, pre-existing lung disease, positive sputum AFB smear, and MDR-TB were independent risk factors. Since treatment compliance is an essential component of treatment success, younger age and lower BMI were unfavorable predictors for compliance; and these predictors were connected to each other acting as complicated effect modifiers.

The first model for predicting treatment failure by Kalhori et al. (14) used clinical data including old age, male sex, body weight, nationality, prisoner status, and previous history of TB and achieved an AUC of 0.70. Recently, Sauer et al. (15) tried to predict treatment failure by machine learning using demographic and laboratory data and reported a best AUC of 0.74. However, this model lacked information about comorbidities; our model included such variables and yielded considerably high prediction power, an AUC of 0.76. Furthermore, our model was constructed based on routinely collected data we recruited retrospectively that were easily gathered in clinical practice.

The remarkable traits to review carefully are presence of diabetes and age. Diabetes is known to be associated with development of TB, possibly mediated by several mechanisms of proinflammatory cytokine (16-20), especially if diabetes related complications co-exist (21). In our study, we identified that diabetes was not only related to development of TB, but also related to treatment failure and presence of cavity. Older age is a well-known risk factor for the development of TB and higher TB-related death rate (22, 23). However, younger age was related to presence of cavity, and poor compliance to treatment. Furthermore, there had been reports that BMI is inversely associated with the risk of TB (24). Obesity presented a protective effect while lower BMI was associated with development of TB (25) and higher TB-related mortality (26). However, BMI is also associated with metabolic syndrome such as diabetes mellitus (27), so these opposite effects of BMI could confuse their role on TB (25). In our study population, BMI in subjects with diabetes had a non-significant difference with those without diabetes (20.75 vs. 22.30; $P = 0.13$), and instead, BMI was related to poor compliance to treatment. Medicaid support was associated with more treatment success and ensures the importance of national efforts such as the PPM program in defeating tuberculosis.

Although our study revealed the complex associations of several risk factors, there are limitations that should be noted when interpreting our results. This study is a retrospective case control study and data were recruited after results of the sputum culture reports came out, so there could be some missing information for each variable. The problem of recall bias from patients, families, and TB nurse specialists may exist. Additionally, these cases were recruited from PPM participating hospitals, and although approximately 70% of TB patients are treated under the PPM program, this could limit making generalizations from our study.

Conclusions

In conclusion, in order to reduce treatment failure the presence of diabetes, previous history of TB, underlying lung disease, sputum AFB smear results and socioeconomic status should be carefully evaluated; and more attention has to be given to younger patients with lower BMIs during follow-up to improve treatment compliance. Further, larger studies are needed in order to confirm our findings.

List Of Abbreviations

AFB, acid-fast bacilli; BMI, body mass index; CI, confidence interval; MDR-TB, multi-drug-resistant tuberculosis; OR, odds ratio; PPM, Public Private Mix; ROC, receiver operating characteristic curve; TB, tuberculosis; AUC, under the curve

Declarations

Ethics approval and consent to participate

The Korea Centers for Disease Control and Prevention has the authority to hold and analyze surveillance data for public health and research purposes.

Consent for publication

Not applicable

Availability of data and materials

The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Competing interests

None

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Authors' contributions

KJS, KHK, MJ, KHW, LJ, PJS, and LSS conceived of the analysis. HKK performed all analysis. LSS, KJS, and PJS supervised the research project. HKK and LSS drafted the manuscript. JM, HWK, JL, KJS, and PJS provided substantive review and edited to the manuscripts. All authors read and approved the final manuscript.

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Figures

Figure 1

Receiver operating curve for predicting treatment failure (A) and non-compliance to treatment (B)

Supplementary Files

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