

Association between Body Mass Index and Sputum Culture Conversion among South Korean Patients with Multidrug Resistant Tuberculosis in a Tuberculosis Referral Hospital

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Background: Multidrug-resistant tuberculosis (MDR-TB) is an important global health problem. Furthermore, the time to identify a positive sputum culture is an important risk factor for the spread of tuberculosis, and several factors can predict a prolonged time to culture conversion. Moreover, the relationship between poor nutritional status and infectious disease is clearly established. Therefore, the present study aimed to investigate the association between body mass index (BMI) and sputum culture conversion within 3 months among patients with MDR-TB.

Materials and Methods: We retrospectively evaluated 218 patients with MDR-TB who were treated at a large tuberculosis referral hospital in South Korea between January 2005 and December 2010. The outcome of interest was defined as sputum culture conversion within 3 months, and we analyzed the association between BMI and this outcome.

Results: Among the 218 patients, 53 patients (24.3%) had a low BMI (<18.5 kg/m²). In the multivariate Cox proportional-hazards regression analysis, failure to achieve sputum culture conversion within 3 months was independently associated with having a low BMI (hazard ratio [HR]: 1.741, 95% confidence interval [CI]: 1.006–3.013; *P* = 0.047) and a positive sputum smear at the initiation of therapy (HR: 8.440, 95% CI: 1.146–62.138, *P* = 0.036).

Conclusion: Low BMI (<18.5 kg/m²) was an independent risk factor for failure to achieve sputum culture conversion within 3 months among patients with MDR-TB.

Key Words: Tuberculosis; Multidrug-resistant; Nutritional status; Risk factors; Sputum

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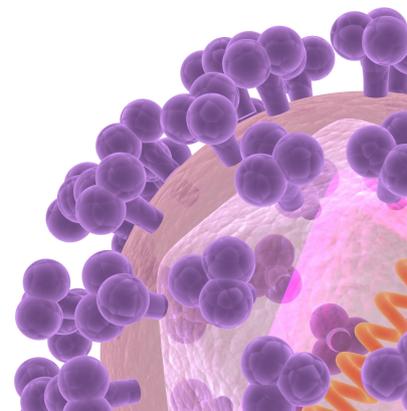
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Introduction

There were an estimated 9.7 million cases of tuberculosis (TB) in 2014 [1], and multi-drug resistant tuberculosis (MDR-TB) is a major global health problem, despite global control efforts. Furthermore, the increasing incidence of MDR-TB can create challenges regarding TB control in many countries. In this context, MDR-TB is defined as resistance to at least rifampicin and isoniazid, which are the two most effective first-line anti-TB drugs. In 2014, there were an estimated 300,000 MDR-TB cases (range: 220,000-370,000), and approximately 54% of these cases occurred in India, China, and the Russian Federation [2]. Moreover, in 2014, 53% of the MDR-TB cases were among new cases and 47% of the MDR-TB cases were previously treated TB cases [2].

TB is the important infectious disease in South Korea, and nation-wide reporting identified 787 patients with MDR-TB in 2015, which represented an 8.1% decrease from the previous year [3]. However, among the Organization for Economic Co-operation and Development countries, South Korea still maintains the highest ranking in terms of the incidence, prevalence, and mortality of MDR-TB [1]. Although most patients with drug-susceptible TB can be cured using a 6-month course of treatment, most MDR-TB cases are treated for ≥ 20 months using the daily administration of drugs that are more toxic, more expensive, and less effective, compared to the drugs that are used to treat drug-susceptible TB [4, 5]. Furthermore, treatment is only successful in approximately one-half of patients with MDR-TB, which is related to the high rates of loss to follow-up (28%) and death (15%) [5].

Positive sputum culture results from patients with pulmonary TB are the most important factor in controlling the spread of MDR-TB, as these patients expel droplets that can carry infectious bacilli through coughing or sneezing [6]. There are also several factors that can predict a prolonged time to culture conversion: cavitory lesions on radiographic images, uncontrolled diabetes mellitus, old age, and the total number of administered anti-TB drugs [7]. Furthermore, the relationship between poor nutritional status and infectious disease is clearly established [8], some reports have demonstrated that malnutrition could be a risk factor for TB mortality [9], and other reports have suggested that malnutrition is related to treatment failure [10]. Therefore, the present study aimed to evaluate the association between body mass index (BMI; as a measure of nutritional status) and sputum culture conversion within 3 months among a population of South Korean patients with MDR-TB.

Materials and Methods

1. Study population and ethical considerations

This retrospective study's design was approved by the ethics committee of the National Masan Tuberculosis Hospital (Korean National Institute of Health). We identified all patients who were treated for MDR-TB between January 2005 and December 2010 at a tertiary TB referral hospital in South Korea (the National Masan Hospital). Suspected cases of MDR-TB are generally identified by various units at the National Masan Tuberculosis Hospital or other healthcare facilities, and are referred to the MDR-TB clinic at the National Masan Tuberculosis Hospital. The patients' medical records were reviewed to collect data regarding their demographic characteristics, TB treatment history, chest radiographs, comorbidities, drug susceptibility testing (DST) results, and clinical outcomes. Patients were excluded from the present study if their records did not contain information regarding their height and weight. All patients had been followed-up every month until they completed their treatment regimen.

2. Sputum cultures and DST

The diagnosis of MDR-TB was established using sputum cultures and DST results. Sputum specimens were processed using sodium hydroxide and N-acetyl-L-cysteine to screen for acid-fast bacilli, based on the Ziehl-Neelsen method. All cultures were performed using the MB/BacT liquid culture system (bioMérieux, Durham, NC, USA) and Ogawa agar slants (egg-based medium). DST was performed using Lowenstein-Jensen agar slants and the following drugs: isoniazid (0.2 mg/mL), rifampicin (40 mg/mL), ethambutol (2.0 mg/mL), streptomycin (10 mg/mL), kanamycin (40 mg/mL), ofloxacin (2.0 mg/mL), ethionamide (40 mg/mL), cycloserine (30 mg/mL), and para-aminosalicylic acid (1 mg/mL). Drug resistance for all drugs was defined as growth of $>1\%$ (vs. the control) in Lowenstein-Jensen media [11]. Sputum culture conversion was defined as two consecutive negative sputum cultures at least 30 days apart. We defined time to conversion as the time from the initiation of therapy to the first of the two negative sputum cultures.

3. Treatment

The Korean guidelines for TB treatment were used to treat patients based on their DST results and treatment history. Treatment for each patient was only started or modified after discussion between a group of TB specialists. The typical treatment regimen consisted of at least four targeted oral drugs and one injectable drug. Where possible, the four oral

drugs were administered for the full term of treatment and the injectable drug was administered for 8 months. The injectable drug was administered 6 times per week for the first 2 months, and then 3 times per week thereafter. Renal function, hepatic function, smears, and cultures were assessed monthly until the end of treatment. Some patients were followed-up after their discharge from the hospital, and the typical duration of treatment was 12–36 months, based on the culture results, changes in the chest radiographs, and history of TB treatment.

4. Definition

Pre-treatment BMI was measured for each patient, and was calculated as body mass divided by height squared (kg/m^2). The BMI value attempts to quantify an individual's tissue mass, and individuals are categorized as underweight, normal weight, overweight, or obese, based on their BMI value. The commonly accepted BMI ranges are $<18.5 \text{ kg}/\text{m}^2$ for underweight and $18.5\text{--}25 \text{ kg}/\text{m}^2$ for normal weight. The patients in the present study were categorized as having a low BMI ($<18.5 \text{ kg}/\text{m}^2$) or assigned to the control group (BMI of $\geq 18.5 \text{ kg}/\text{m}^2$). The outcome of interest was defined as sputum culture conversion within 3 months, and we analyzed the association between BMI and this outcome.

5. Data analysis

Descriptive analyses were performed using Pearson's chi-square test (for categorical variables) and the t-test (for con-

tinuous variables). The characteristics of the low BMI and control groups were compared, and differences with a P-value of <0.05 were considered statistically significant. Cox proportional-hazards regression analysis was used to investigate the association between BMI or other factors and sputum culture conversion within 3 months. All analyses were performed using SPSS software (version 18.0, IBM Corp., Armonk, NY, USA), and missing data were not replaced or imputed.

Results

Between January 2005 and December 2010, 218 patients were treated for MDR-TB at our hospital. A total of 164 patients (75.2%) were men, and the overall mean patient age was 41.7 ± 14.2 years (men: 41.2 ± 13.2 years, women: 43.4 ± 16.7 years). Ninety-two patients (42.2%) were resistant to one or more injectable drugs, and 48 patients (22.0%) were resistant to one or more fluoroquinolone. Lung cavitation was confirmed on the chest radiographs for 120 patients (55.0%), and 136 patients (62.4%) had been treated for TB. Positive sputum cultures at the start of treatment were observed for 84.4% of the patients. The mean time to culture conversion was 3 months, and approximately 70% of the patients achieved sputum culture conversion within 3 months. The mean overall BMI was $20.0 \pm 3.3 \text{ kg}/\text{m}^2$, and 53 patients (24.3%) had a BMI of $<18.5 \text{ kg}/\text{m}^2$ (Table 1). The patients received different em-

Table 1. Patient characteristics according to body mass index

	All patients No. (%) (n = 218)	BMI of $\geq 18.5 \text{ kg}/\text{m}^2$ No. (%) (n = 165)	BMI of $<18.5 \text{ kg}/\text{m}^2$ No. (%) (n = 53)	P-value
BMI (kg/m^2)	20.0 ± 3.3	21.4 ± 2.5	15.8 ± 1.5	
Mean age (years)	41.7 ± 14.2	41.4 ± 14.6	42.8 ± 12.8	0.543
Male sex	164 (75.2)	119 (72.1)	45 (51.1)	0.069
Previously treated for tuberculosis ^a	136 (62.4)	103 (62.4)	33 (62.3)	1.000
With cavitation (n = 198) ^b	120 (55)	88 (53.3)	32 (60.4)	0.238
Smear positive at the start of treatment	184 (84.4)	137 (83)	47 (88.7)	0.39
Side effects ^c	82 (37.6)	62 (37.6)	20 (37.7)	1.000
Fluoroquinolone resistance ^d	48 (22)	38 (23)	10 (18.9)	0.574
Injectable drug resistance ^e	92 (42.2)	73 (44.2)	19 (35.8)	0.338

Data are reported as mean \pm standard deviation or number (%). Differences were evaluated using the independent samples t-test or Pearson's chi-square test, as appropriate.

^aPatients who denied receiving any anti-tuberculosis treatment or having a >30 -day history of anti-tuberculosis treatment.

^bChest radiography or computed tomography was performed for all 198 patients.

^cSide effects: drug eruption, nausea, vomiting, abdominal discomfort, peripheral neuropathy, nephrotoxicity, hepatic toxicity, ototoxicity, and hypothyroidism.

^dIncluded levofloxacin, moxifloxacin, or ofloxacin

^eIncluded kanamycin, streptomycin, or amikacin.

BMI, body mass index.

Table 2. Anti-tuberculosis drugs used for 218 patients with multidrug-resistant tuberculosis

	BMI of ≥ 18.5 kg/m ²	BMI of < 18.5 kg/m ²	<i>P</i> -value
	No. (%) (n = 165)	No. (%) (n = 53)	
Ethambutol	19 (11.5)	9 (17)	0.346
Pyrazinamide	72 (43.6)	28 (52.8)	0.269
Streptomycin	81 (49.1)	31 (58.5)	0.27
Kanamycin	85 (51.5)	22 (41.5)	0.212
Amikacin	2 (1.2)	2 (3.8)	0.249
Prothionamide	161 (97.6)	53 (100)	0.574
Para-aminosalicylic acid	132 (80)	44 (83)	0.693
Cycloserine	161 (97.6)	49 (92.5)	0.1
Levofloxacin	86 (52.1)	26 (49.1)	0.753
Ofloxacin	37 (22.4)	9 (17)	0.445
Moxifloxacin	62 (37.6)	21 (39.6)	0.871

BMI, body mass index.

Table 3. Cox proportional hazards regression analysis of risk factors for sputum culture conversion within 3 months among 218 patients with multidrug-resistant tuberculosis

Risk factors	Total	Conversion ^a n (%)	Univariate		Multivariate	
			HR (95% CI)	<i>P</i> -value ^b	HR (95% CI)	<i>P</i> -value ^b
BMI of < 18.5 kg/m ²	53	30 (56.6)	1.974 (1.191–3.272)	0.008	1.741 (1.006–3.013)	0.047
Age of ≥ 40 years	110	74 (67.3)	1.286 (0.795–2.081)	0.305	1.304 (0.767–2.218)	0.327
Male sex	164	110 (67.1)	1.548 (0.843–2.842)	0.158	1.724 (0.878–3.385)	0.113
Cavitation	120	88 (66.7)	1.269 (0.737–2.183)	0.5	0.85 (0.481–1.503)	0.577
Smear positive ^c	184	118 (64.1)	11.276 (1.564–81.298)	0.016	8.44 (1.146–62.138)	0.036
Side effects	82	57 (69.5)	0.899 (0.547–1.478)	0.675	1.115 (0.642–1.935)	0.7
FQ resistance	48	30 (62.5)	1.523 (0.885–2.621)	0.129	1.64 (0.890–3.021)	0.113
ID resistance	92	60 (65.2)	1.190 (0.736–1.924)	0.477	1.029 (0.612–1.731)	0.914

^aWithin 3 months after the initiation of therapy.

^bBoldface indicates a significant difference compared to the baseline characteristics.

^cThe sputum smear was positive at the initiation of therapy.

HR, hazard ratio; CI, confidence interval; BMI, body mass index; FQ, fluoroquinolone; ID, injectable drug.

pirical initial treatments, and the most commonly used drugs were prothionamide, cycloserine, para-aminosalicylic acid, levofloxacin, pyrazinamide, moxifloxacin, ofloxacin, and ethambutol; streptomycin or kanamycin were commonly used as injectable drugs (Table 2). We did not detect any significant differences in the drugs that were used for the low BMI and control groups.

The univariate Cox proportional-hazard regression analyses revealed that failure to achieve sputum culture conversion within 3 months was significantly associated with a positive sputum smear at the initiation of treatment (hazard ratio [HR]: 11.276, 95% confidence interval [CI]: 1.564–81.298; $P = 0.016$)

and a BMI of < 18.5 kg/m² (HR: 1.974, 95% CI: 1.191–3.272; $P = 0.008$). Age, sex, cavitation, side effects during treatment, resistance to fluoroquinolone, and resistance to injectable drugs were not significantly associated with failure to achieve sputum culture conversion. The multivariate Cox proportional-hazard regression analysis confirmed that failure to achieve sputum culture conversion was independently associated with a BMI of < 18.5 kg/m² (HR: 1.741, 95% CI: 1.006–3.013; $p = 0.047$) and a positive sputum smear at the initiation of treatment (HR: 8.440, 95% CI: 1.146–62.138; $P = 0.036$) (Table 3, Fig. 1). A total of 200 patients (91.7%) achieved sputum culture conversion during their treatment. Among the 53 patients

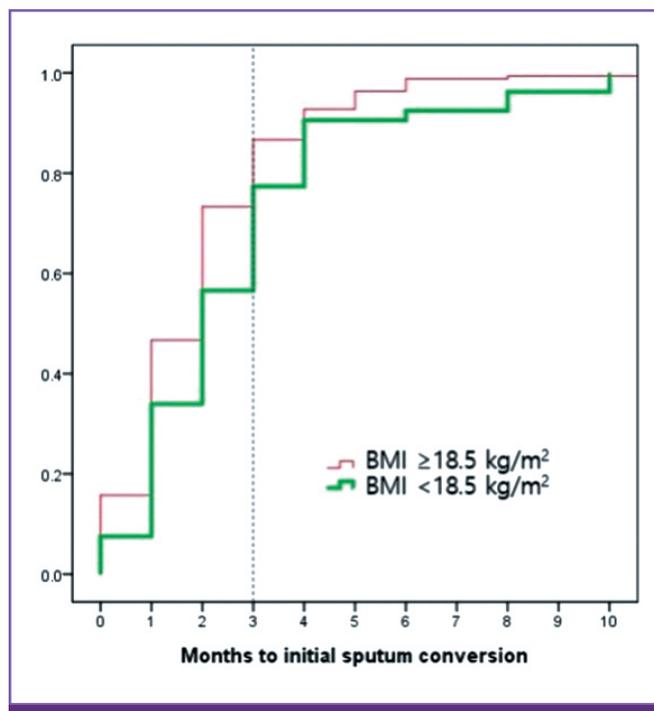


Figure 1. Time to initial sputum culture conversion according to body mass index. The time to conversion among patients with a body mass index of $<18.5 \text{ kg/m}^2$ was significantly longer, compared to the group with a normal body mass index.

BMI, body mass index.

Table 4. The sputum culture conversion results

	BMI of $\geq 18.5 \text{ kg/m}^2$ No. (%)	BMI of $< 18.5 \text{ kg/m}^2$ No. (%)
Achieved SCC	153 (92.7)	47 (88.7)
Defaulted before achieving SCC	2 (1.2)	0 (0)
Failed SCC	9 (5.5)	4 (7.5)
Died before achieving SCC	1 (0.6)	2 (3.8)
Total	165	53

BMI, body mass index; SCC, sputum culture conversion.

with a BMI of $<18.5 \text{ kg/m}^2$, 47 patients (88.7%) achieved sputum culture conversion (Table 4).

Discussion

It is important to control MDR-TB, and positive sputum culture results from patients with pulmonary TB can be used to help control the spread of MDR-TB. In this context, transmission occurs when a person inhales droplets that contain *Mycobacterium tuberculosis*, which subsequently enters the al-

veoli of the lungs. Thus, prolonged periods of infectiousness may increase the likelihood of spreading MDR-TB [6]. However, few studies have evaluated predictors of initial sputum conversion among patients with MDR-TB. In Latvia, the significant predictors of initial sputum culture conversion were previous treatment for MDR-TB using second-line drugs, a high initial sputum colony count ($\geq 3+$), bilateral cavitation, and a higher number of resistant drugs at the initial treatment [12]. In the present study, we found that a low BMI ($<18.5 \text{ kg/m}^2$) and a positive sputum smear at the initiation of treatment were independently associated with failed sputum culture conversion within 3 months. However, our overall sputum conversion rate (91.7%) was higher than the rates from previous studies [13, 14], which indicates that the underlying management protocol functioned reasonably well. Nevertheless, patients with a positive smear culture at the initiation of treatment exhibited a high risk of failed sputum culture conversion (HR: 8.440, 95% CI: 1.146–62.138; $P = 0.036$), which may be related to these patients having a high initial high bacillary burden. For example, Holtz et al. have reported that a high initial sputum colony count ($\geq 3+$) was significantly associated with delayed sputum conversion (odds ratio: 10.8, 95% CI: 1.3–91.1) [12].

Malnutrition has well-established effects on immune function [15], and the accompanying decrease in immunity may increase susceptibility to many infectious diseases [16, 17]. For example, Scrimshaw et al. have suggested that malnutrition reduced the concentrations of immunoglobulins, interleukin-2 receptors, and T-cell subsets (helper, suppressor-cytotoxic, and natural killer cells) among patients with TB [18]. The most useful measure of malnutrition in adults is BMI, and low BMI ($<18.5 \text{ kg/m}^2$) is associated with increased TB-related morbidity and mortality [19, 20]. Furthermore, several study have demonstrated that low BMI is a risk factor of mortality among patients with TB who are co-infected with HIV [10], and underweight status (BMI of $<18.5 \text{ kg/m}^2$) was significantly associated with severe clinical symptoms and a higher proportional of positive sputum cultures. Moreover, in South Africa, underweight status was a significant predictor of more advanced TB disease (odds ratio: 14.2, 95% CI: 4.4–46.2) [1]. Our findings regarding the risk of being underweight are also similar to the findings of Kurbatova et al., who reported that underweight patients had a low sputum conversion rate (HR: 0.82, 95% CI: 0.72–0.93; $P = 0.002$), compared to patients with MDR-TB who had a BMI of $\geq 18.5 \text{ kg/m}^2$ [20].

The present study has several limitations. First, we only evaluated patients from a single TB referral hospital, which may

have introduced selection bias and limits the extrapolation of our findings to the entire population of South Korean patients with MDR-TB. Second, our study only evaluated a relatively small sample of MDR-TB cases, and larger studies are needed to validate our findings regarding the predictors of outcomes in cases of MDR-TB. Third, we were unable to perform long-term follow-up, which limits any conclusions regarding the long-term trends for this disease.

In the present study, underweight status and a positive initial sputum smear were associated with failing to achieve sputum culture conversion within 3 months among a single-center population of patients with MDR-TB. Our findings suggest that underweight status and a positive initial sputum smear might be risk factors for community transmission from patients with MDR-TB.

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Conflicts of Interest

No conflicts of interest.

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