Hypoalbuminemia and Lymphocytopenia are Predictive Risk Factors for In-hospital Mortality in Patients with Tuberculosis

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Abstract

Objective The aim of this study was to clarify the association between nutritional state on admission and in-hospital death in tuberculosis (TB) patients, including a high proportion of elderly patients.

Methods A retrospective cohort study of 246 TB patients was conducted. The serum albumin concentrations and peripheral blood lymphocyte counts were measured on admission, and the primary outcome of interest was in-hospital death. Patient mortality was categorized into two groups: TB death and non-TB death. A multivariate analysis was performed to evaluate the relationship between nutritional state on admission and in-hospital mortality in TB patients.

Results The median [interquartile range] patient age was 79 [69-83] years, and the in-hospital death rate was 20.73% (TB death: 26 patients; non-TB death: 25 patients). The multivariate analysis revealed that the serum albumin concentrations (OR: 0.21, 95% CI: 0.10-0.41; $p < 0.0001$) and peripheral blood total lymphocyte counts (Category 2 [627.2 - $1,106.7/\text{mm}^3$] vs. 1 [$<627.2/\text{mm}^3$]. OR: 0.28, 95% CI: 0.11-0.73; $p = 0.009$, Category 3 [$>1,106.7/\text{mm}^3$] vs. 1. OR: 0.24, 95% CI: 0.08-0.76, $p = 0.015$) on admission were significantly associated with all in-hospital deaths in the TB patients. The serum albumin concentrations and peripheral blood total lymphocyte counts were also found to be associated with in-hospital deaths directly caused by TB.

Conclusion Hypoalbuminemia and lymphocytopenia on admission are predictive risk factors for in-hospital mortality in TB patients. Nutritional defects should thus receive special attention in order to reduce TB patient mortality, particularly among elderly patients.

Key words: tuberculosis, prognosis, malnutrition

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Introduction

New drugs and intensive treatments have improved the prognoses of patients with tuberculosis (TB) (1). In addition, new methods such as polymerase chain reaction (PCR) and QuantiFERON-TB enable early diagnosis of TB disease and TB infection (2, 3). Nevertheless, TB remains a life-threatening disease that claims the lives of many hospital

patients worldwide (4, 5). In 2010, there were an estimated 8.8 million incident cases of TB, 1.1 million deaths among HIV-negative patients with TB and an additional 0.35 million deaths among HIV-positive patients throughout the world (4). In Japan, there were 22,681 incident cases of TB in 2011, 53.8% of which involved patients over 70 years of age (6).

TB and malnutrition tend to correlate strongly with each other (7). Nutritional depletion is often seen in patients diag-

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Table 1. Types of TB Patients Included in the Study

Type of TB	Number of patients n=246
Pulmonary TB	223
Pulmonary only	213
Combined with extrapulmonary TB	10
Extrapulmonary TB only	10
Miliary TB	13
Type of extrapulmonary TB	Number of patients n=20
Pleurisy	11
Lymphadenitis	3
Nephrotuberculosis	3
Others	3

TB: tuberculosis

nosed with TB (8-10), and malnutrition appears to increase the risk of developing TB in animal models (11). We previously reported a relationship between computed tomography findings and malnutrition in pulmonary TB patients (12). Malnourished TB patients have also been found to exhibit delayed recovery and higher mortality rates than well-nourished patients (7). Among various parameters reported to be possible risk factors for TB patient mortality, malnutrition is believed to contribute the greatest risk (13-18).

The serum albumin levels are an important marker of a patient's nutritional state (13) and are widely used in many countries. However, only a few published studies have evaluated the association between hypoalbuminemia and in-hospital death among relatively young TB patients (13-15, 18). The average age of Japanese TB patients is significantly higher than these patients. Lymphocytopenia is also an important marker of severe malnutrition (19); however, the relationship between lymphocytopenia and in-hospital death in TB patients is not well known. The objective of this study was to evaluate the association between the nutritional state (as measured by the serum albumin concentration and the peripheral blood total lymphocyte count) on admission and in-hospital mortality in TB patients, including elderly patients. In-hospital deaths were also categorized in order to analyze the association between nutritional state and all deaths, as well as TB-specific deaths.

Materials and Methods

Study population

A retrospective study was conducted using 246 consecutive patients admitted to the TB ward of the National Hospital Organization Omuta National Hospital between January 2004 and January 2008. A detailed summary of all TB patient types is displayed in Table 1. The study included 223 pulmonary TB patients, 20 extrapulmonary TB patients and 13 miliary TB patients. The extrapulmonary TB cases included pleurisy (n=11), lymphadenitis (n=3) and nephrotuberculosis (n=3). Two hundred and thirty patients (93.5%) had positive sputum smears and required isolation in our hospital. Sixteen patients required hospitalization in order to receive anti-TB chemotherapy regardless of negative sputum

smears due to their poor general condition.

Two hundred and thirty-eight patients exhibited positive cultures and/or PCR results for *Mycobacterium tuberculosis*, while six patients showed histopathology patterns characteristic of TB, i.e., chronic granulomatous inflammation with caseation necrosis. Two patients were diagnosed with tuberculosis pleurisy following pleural effusion examinations (lymphocyte-rich effusion, adenosine deaminase: ADA ≥ 70 IU/L) (20). All patients who received anti-tuberculosis chemotherapy were treated with a combination of rifampicin, isoniazid, ethambutol (or streptomycin) and pyrazinamide.

Study design

Nutritional parameters (the serum albumin concentration and the peripheral blood total lymphocyte count) were recorded upon hospital admission. The comorbidity factors included malignancy, diabetes mellitus (DM), steroid therapy, renal failure, heart disease, other pulmonary diseases and cerebrovascular disorders. We assessed TB severity according to the radiographic extent of the lesions and the mean duration of TB symptoms prior to treatment. The radiographic extent of TB lesions was examined by dividing each lung on plain chest radiograph into upper, middle and lower zones. Each zone encompassed one third of the craniocaudal distance of the lung on frontal radiograph, and the number of zones with lesions was counted (14). Other characteristics of interest included the age and sex of the patients.

The primary outcome of interest was in-hospital death, and its association with two nutritional markers, namely the serum albumin concentration and the peripheral blood lymphocyte count, were examined.

In-hospital deaths were categorized into two groups: TB death and non-TB death. TB deaths included deaths directly caused by TB such as those due to respiratory failure or TB weakness (patients who became severely symptomatic and died as a result of TB).

The causes of non-TB death included malignancy, pneumonia and other underlying diseases noted during inpatient TB treatment.

This study was approved by the Ethics Board of the National Hospital Organization Omuta National Hospital.

Statistical analysis

Data for continuous variables are presented as the mean $\pm$ standard deviation (SD) for variables that followed a normal distribution and as the median (interquartile range [IQR]) for variables that did not follow a normal distribution. Moreover, we tested nonlinear relationships between continuous variables and the logarithm of odds using piecewise linear spline. We categorized variables that showed significant nonlinear relationships into tertiles based on their distribution and then reanalyzed the data.

Age, sex, malignancy, DM, steroid therapy, renal failure, heart disease, other pulmonary diseases, cerebrovascular disorders, radiographic extent and duration of symptoms before treatment were potential confounders. A logistic regression

Table 2. Patient Characteristics (n=246)

Variables	
Age (years)	79 (69-83)
Sex (male/female)	144 / 102
Comorbidities*	
Malignancy	38 (15.45)
Diabetes mellitus	36 (14.63)
Steroid therapy	7 (2.85)
Renal failure	14 (5.69)
Heart disease	29 (11.79)
Other pulmonary diseases	39 (15.85)
Cerebrovascular disorders	18 (7.32)
Laboratory data	
Serum albumin (g/dL)	3.41 ± 0.72
Total lymphocyte count (/mm ³)	877.8 (512.0-1240.2)
Radiographic extent (zones)	3 (2-4)
Duration of symptoms (weeks)	4 (2-9)

Values are presented as the mean ± standard deviation, the median (interquartile range) or number of patients (%) unless otherwise indicated.

* Some patients had multiple comorbidities.

Table 3. Univariate Analysis for In-hospital Death (TB and Non-TB Causes of Death)

	Univariate OR (95% CI)	p value
Serum albumin (g/dL)	0.15 (0.09-0.28)	<0.0001*
Total lymphocyte count †		
Category 1	1 (referent)	
Category 2	0.18 (0.08-0.40)	<0.0001*
Category 3	0.09 (0.03-0.23)	<0.0001*
Age (year)	1.07 (1.03-1.10)	0.0002*
Sex (male)	1.39 (0.73-2.63)	0.316
Malignancy	2.00 (0.93-4.31)	0.077
Diabetes mellitus	0.09 (0.01-0.68)	0.020*
Steroid therapy	10.49 (1.97-55.78)	0.006*
Renal failure	5.86 (1.93-17.76)	0.002*
Heart disease	1.88 (0.80-4.41)	0.150
Other pulmonary diseases	1.64 (0.75-3.57)	0.213
Cerebrovascular disorders	2.03 (0.72-5.71)	0.178
Radiographic extent (zone)	1.47 (1.22-1.78)	<0.0001*
Duration of symptoms (week)	0.99 (0.97-1.02)	0.566

TB: tuberculosis, OR: odds ratio, CI: confidence interval

*Statistically significant.

†Total lymphocyte count was categorized into tertiles based on the distribution (Category 1: < 627.2/mm³, Category 2: 627.2-1,106.7/mm³, Category 3: >1,106.7/mm³).

analysis was used to assess the association between nutritional state on admission and in-hospital death. Univariate odds ratios (ORs) were estimated for each nutritional parameter and potential confounder. Candidate confounding variables were selected using results from the univariate analyses. Multivariate-adjusted odds ratios were estimated from the multivariate logistic regression model with variables selected from the candidates using a backward selection procedure. All analyses were performed using statistical software (SAS ver.9.2, SAS Institute Inc., Cary, NC, USA). A p value of <0.05 was considered statistically significant.

Results

The patient characteristics are displayed in Table 2. A total of 246 patients with TB were examined (median age: 79 [IQR: 69-83] years; 144 men and 102 women). There were no patients with multidrug-resistant (MDR) TB. Ten patients had previously undergone treatment for TB. The mean ± SD or median (IQR) nutritional parameters for the serum albumin levels and the total lymphocyte counts were 3.41±0.72 g/dL and 877.8 (IQR: 512.0-1,240.2)/mm³, respectively. The median radiographic extent was three (IQR: 2-4) zones, and the median duration of symptoms before treatment was four (IQR: 2-9) weeks.

Of the 246 patients, 51 (20.73%) died while hospitalized (TB death: 26 patients; non-TB death: 25 patients). Of the non-TB deaths, malignancy was the most frequent cause (n=7), followed by aspiration pneumonia (n=3) and renal failure (n=2). The average length of stay (from admission to the hospital to death) in the 51 patients with in-hospital death was 61.5 days (26 patients with TB death: 33.5 days [range: 1-113 days], 25 patients with non-TB death: 90.7 days [range: 4-453 days]). Twenty-three patients were unable to be discharged from the hospital even after their sputum smears became negative because their general condition remained poor, and they died in the hospital.

The average time from admission to the hospital to the start of anti-TB chemotherapy was 3.4±6.52 days in the patients with in-hospital death. Three patients died immediately after admission due to their poor general condition and did not receive anti-TB chemotherapy.

The mean albumin concentration and lymphocyte count in the TB patients who died in the hospital were lower than in those who survived. The average serum albumin levels for the in-hospital death and survivor groups were 2.76 g/dL and 3.58 g/dL, respectively, while the median total lymphocyte counts were 476.2 (IQR: 194.0-648.0)/mm³ and 945.0 (IQR: 632.5-1,323.0)/mm³, respectively.

As a significant nonlinear relationship was detected for the total lymphocyte counts, we categorized these values into tertiles based on their distribution and reported the results of the categorized data (Category 1: <627.2/mm³, Category 2: 627.2-1,106.7/mm³, Category 3: >1,106.7/mm³).

A univariate analysis (Table 3) revealed that the serum albumin concentration on admission (OR: 0.15, 95% confidence interval [CI]: 0.09-0.28; p<0.0001) and the peripheral blood total lymphocyte count on admission (Category 2 vs. 1. OR: 0.18, 95% CI: 0.08-0.40; p<0.0001, Category 3 vs. 1. OR: 0.09, 95% CI: 0.03-0.23, p<0.0001) were each significantly associated with all in-hospital deaths (including TB and non-TB deaths) in the TB patients.

A multivariate analysis (Table 4) revealed that the serum albumin concentration on admission (OR: 0.21, 95% CI: 0.10-0.41; p<0.0001) and the peripheral blood total lymphocyte count on admission (Category 2 vs. 1. OR: 0.28, 95% CI: 0.11-0.73; p=0.009, Category 3 vs. 1. OR: 0.24, 95% CI: 0.08-0.76, p=0.015) remained associated with all in-hospital deaths in the TB patients.

A univariate analysis (Table 5) revealed that the serum albumin concentration on admission (OR: 0.12, 95% CI: 0.05-0.27; p<0.0001) and the peripheral blood total lymphocyte

Table 4. Multivariate Analysis for In-hospital Death (TB and Non-TB Causes of Death)

	Adjusted OR† (95% CI)	p value
Serum albumin (g/dL)	0.21 (0.10-0.41)	<0.0001*
Total lymphocyte count††		
Category 1	1 (referent)	
Category 2	0.28 (0.11-0.73)	0.009*
Category 3	0.24 (0.08-0.76)	0.015*
Age (year)	1.05 (1.00-1.10)	0.038*
Diabetes mellitus	0.07 (0.01-0.71)	0.024*
Steroid therapy	17.4 (2.42-124.5)	0.005*

TB: tuberculosis, CI: confidence interval

* Statistically significant.

† Adjusted odds ratios (ORs) estimated from a logistic regression model. We selected candidates of confounding variables using results of the univariate analyses. Then we analyzed data in multivariate analysis with variables selected from the candidates using a backward selection procedure.

†† Total lymphocyte count was categorized into tertiles based on the distribution (Category 1: <627.2/mm³, Category 2: 627.2-1,106.7/mm³, Category 3: >1,106.7/mm³).**Table 5. Univariate Analysis for In-hospital Death (TB Causes of Death Only)**

	Univariate OR (95% CI)	p value
Serum albumin (g/dL)	0.12 (0.05-0.27)	<0.0001*
Total lymphocyte count †		
Category 1	1 (referent)	
Category 2	0.10 (0.03-0.36)	0.0004*
Category 3	0.13 (0.04-0.39)	0.0004*
Age (year)	1.06 (1.02-1.11)	0.006*
Sex (male)	0.65 (0.29-1.48)	0.302
Malignancy	0.85 (0.24-3.03)	0.799
Diabetes mellitus	0.18 (0.02-1.40)	0.101
Steroid therapy	12.59 (2.00-79.30)	0.007*
Renal failure	7.50 (2.11-26.70)	0.002*
Heart disease	2.08 (0.71-6.13)	0.183
Other pulmonary diseases	1.79 (0.66-4.85)	0.252
Cerebrovascular disorders	2.77 (0.82-9.35)	0.100
Radiographic extent (zone)	1.61 (1.25-2.07)	0.0002*
Duration of symptoms (week)	0.99 (0.96-1.03)	0.672

TB: tuberculosis, OR: odds ratio, CI: confidence interval

* Statistically significant.

† Total lymphocyte count was categorized into tertiles based on the distribution (Category 1: <627.2/mm³, Category 2: 627.2-1,106.7/mm³, Category 3: >1,106.7/mm³).

count on admission (Category 2. vs. 1. OR: 0.10, 95% CI: 0.03-0.36; p=0.0004, Category 3 vs. 1. OR: 0.13, 95% CI: 0.04-0.39, p=0.0004) were each significantly associated with in-hospital deaths directly related to TB.

A multivariate analysis (Table 6) revealed that the serum albumin concentration on admission (OR: 0.15, 95% CI: 0.06-0.37; p<0.0001) remained significantly associated with in-hospital deaths directly related to TB. Regarding the lymphocyte count on admission, the OR for Category 2 vs. Category 1 was statistically significant (OR: 0.13, 95% CI: 0.03-0.61; p=0.010), although the OR for Category 3 vs. Category 1 was not significant (OR: 0.46, 95% CI: 0.13-1.67; p=0.235). Because the number of TB deaths was too small (26 patients) to apply a multivariate analysis using several factors, we reported the results of a multivariate logistic model that included the albumin level and total lymphocyte count only.

Table 6. Multivariate Analysis for In-hospital Death (TB Causes of Death Only)

	Adjusted OR † (95% CI)	p value
Serum albumin (g/dL)	0.15 (0.06-0.37)	<0.0001*
Total lymphocyte count††		
Category 1	1 (referent)	
Category 2	0.13 (0.03-0.61)	0.010*
Category 3	0.46 (0.13-1.67)	0.235

TB: tuberculosis, CI: confidence interval

* Statistically significant.

† Adjusted odds ratios (ORs) estimated from a logistic regression model.

†† Total lymphocyte count was categorized into tertiles based on the distribution (Category 1: < 627.2 /mm³, Category 2: 627.2-1,106.7 /mm³, Category 3: >1,106.7 /mm³).

phocyte count only.

Thirty-five of the total 51 in-hospital deaths were early in-hospital deaths (death occurring within 90 days after admission). The serum albumin concentration on admission (OR: 0.20, 95% CI: 0.09-0.43; p<0.001) was also found to be significantly associated with early death; however, the lymphocyte count on admission was not found to be significantly associated with early death in the multivariate analysis.

Discussion

TB and malnutrition tend to correlate strongly with each other, as nutritional depletion is often seen in patients initially diagnosed with TB (8-10). Malnutrition is a risk factor for TB incidence. Nutrition and demographic changes have stronger adverse effects on TB in a high-incidence country (India) than in a low-incidence country (Korea) (21). Our study examined the association between the serum albumin levels and the blood lymphocyte counts and in-hospital death in a group of TB patients, including a high proportion of elderly patients. The results of this study demonstrate an association between hypoalbuminemia and lymphocytopenia, important markers of severe malnutrition (13, 19), and in-hospital death from any cause in TB patients. These findings suggest that hypoalbuminemia and lymphocytopenia on admission are predictive risk factors for mortality in hospitalized patients with TB, many of whom are elderly. To reduce the incidence and mortality of TB, managing nutrition and providing appropriate anti-chemotherapy are very important.

Several methods can be used to assess the nutritional state of pulmonary TB patients. Onwubalili et al. used triceps skinfold thickness, arm muscle circumference, the serum albumin level, the iron level, body mass index (BMI) and total iron binding capacity as nutritional indicators (8); however, measuring triceps skinfold thickness or arm muscle circumference is uncommon in TB patients. In this study, BMI was also excluded from the analysis because the heights and body weights of some patients could not be measured due to poor health on admission. We instead focused on the serum albumin levels and total lymphocyte counts. The serum al-

bumin levels are very easy to measure and are widely used to evaluate nutritional status. Total lymphocyte counts are also easy to assess, and malnutrition causes lymphocytopenia (19).

The serum albumin concentration is an important marker of nutritional status; however, few published studies have examined hypoalbuminemia as a predictor of TB patient mortality (13-15, 18). Matos et al. reported that a low serum albumin level on admission is an independent predictor of in-hospital death in TB patients (13). That study was conducted in Brazil, with a major difference in the average age of the TB patients (41.1 ± 15.2 years) compared to our study (79 [IQR: 69-83] years). In a study of Korean patients that found an association between nutritional deficits and TB death, the average age was also younger (53.2 ± 20.4 years) than that observed in our patients (14). The high patient mortality rate observed in the present study may be due to the greater proportion of elderly patients included in this study, likely a result of the advanced age of TB patients in Japan. Latent TB can be reactivated when patients become older and malnourished or immunocompromised. The adjusted OR data obtained in this study revealed that malnutrition in TB patients on admission is the most important predictive risk factor of in-hospital mortality, even among elderly patients. The present study also found an association between low serum albumin levels and both in-hospital deaths directly caused by TB and in-hospital deaths from all causes.

There is presently no established cut-off value for the serum albumin level that represents nutritional deficits in TB patients. Matos et al. divided the serum albumin levels into ≤ 2.7 g/dL and > 2.7 g/dL (13). Kim et al. defined hypoalbuminemia as < 3.0 g/dL (14). We did not categorize the serum albumin levels in this study, although we did record the average serum albumin levels for patients who suffered in-hospital deaths and in-hospital survivors to be 2.76 g/dL and 3.58 g/dL, respectively.

A significant association was also found between the peripheral blood total lymphocyte count on admission and in-hospital death in TB patients. Our results demonstrate that lymphocytopenia is an independent risk factor for in-hospital mortality in patients with TB according to a multivariate analysis. Malnutrition causes lymphocytopenia as well as hypoalbuminemia (19), and our study suggests that lymphocytopenia is another important predictor of TB outcomes.

There is a possibility that the association between malnutrition and high in-hospital mortality merely reflects the fact that patients with malnutrition represent severely ill TB patients. Even with these factors, the multivariate analysis still showed that hypoalbuminemia and lymphocytopenia are significantly associated with in-hospital deaths. To elucidate the relationship between hypoalbuminemia or lymphocytopenia and the prognoses of TB patients in more detail, longitudinal assessments of these biomarkers of nutritional status should be performed.

The present study is associated with several limitations. First, HIV serology was not routinely examined in all patients. Although this study was performed in a rural area with a low prevalence of AIDS, this limitation should be noted when applying the results of our study to TB patients. Second, the study population did not include any MDR-TB patients. MDR-TB is believed to significantly affect the prognoses of TB patients, and the results of the present study cannot be applied to areas where MDR-TB is prevalent. Third, because the number of TB deaths was too small (26 patients) to apply a multivariate analysis using several factors, we reported the results of a multivariate logistic model that included the albumin level and the total lymphocyte count only.

Conclusion

Our study showed that diagnoses of hypoalbuminemia and lymphocytopenia on admission are independent predictors of in-hospital mortality in TB patients, including a high proportion of elderly patients. Better management of patients with TB should involve greater attention to malnutrition, and reducing the mortality of such patients may require nutritional recovery as well as anti-TB chemotherapy.

The authors state that they have no Conflict of Interest (COI).

Each author's role in the study: Dr. Okamura was the primary author and also contributed to the planning of the study and data analysis. Dr. Nagata contributed to the writing of the manuscript, planning of the study and data analysis. Dr. Nakanishi contributed to the planning of the study and data analysis. Drs. Wakamatsu, Ikegame, Kajiki and Takayama contributed to the data analysis. Koji Yonemoto contributed to the statistical analyses.

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