Original Article

Nutrition and clinical manifestations of pulmonary tuberculosis: A cross–sectional study in Shandong province, China

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Background and Objectives: The aim is to investigate the association between nutritional status and clinical picture of pulmonary tuberculosis (PTB). **Methods and Study Design:** A total of 613 pulmonary tuberculosis patients in Weifang city, Shandong province, China were included. Clinical and nutritional history, anthropometry, nutritionally relevant indicators including serum total protein and albumin, hemoglobin and lymphocyte count were measured. Adjustments were made for confounders in multivariable logistic models where tuberculosis activity (clinical symptoms and signs, sputum–smear tests or chest computerized tomography (CT)) was the dependent variable. **Results:** Hypoalbuminemia (OR=2.61; 95% CI, 1.69–4.03), anemia (OR=1.62; 95% CI, 1.04–2.51) and lymphocytopenia (OR=1.92; 95% CI, 1.21–3.05) were associated with a higher TB score (a clinical severity measure for pulmonary tuberculosis based on typical signs and symptoms); hypoalbuminemia (OR=1.75; 95% CI, 1.08–2.84) and anemia (OR=1.87; 95% CI, 1.14–3.08) were associated with a positive sputum smear; anemia (OR=3.58; 95% CI, 1.85–6.94) was associated with cavitation in CT. **Conclusions:** Hypoalbuminemia, anemia and lymphocytopenia were positively associated with the severity of clinical manifestation of PTB. Nutritional status may be a marker for the severity of the clinical manifestations of PTB.

Key Words: pulmonary tuberculosis, nutritional status, clinical manifestations, hypoalbuminemia, anemia

INTRODUCTION

Tuberculosis (TB) is a severe airborne contagious respiratory disease caused by *Mycobacterium tuberculosis* (*M. tuberculosis*)[1] and is also a chronic wasting disease. According to estimates from the WHO, approximately 10.0 million cases of TB were reported in 2020, causing approximately 1.4 million deaths; China has a considerably high TB burden, with 8.4% of global TB cases occurring in the country.[2]

Nutrition and its supplementation are important for a number of diseases.[3] Epidemiological studies have revealed that malnutrition plays a key role in the occurrence and development of TB.[4] Severely malnourished patients with PTB (body mass index [BMI] <16) are more likely to exhibit dyspnea, night sweats, hemoptysis, and cavitation.[5] Underweight status at baseline is independently associated with relapse risk among patients with TB.[6] Malnutrition may result in impaired immune function,[7] and increased susceptibility to M. tuberculosis.[8] Moreover, M. tuberculosis infection leads to an acute inflammatory host response,[9,10] accelerating protein loss[11] and inhibiting the production of serum albumin.[12] Hypoalbuminemia objectively reflects malnutrition, and the serum albumin concentration is a primary marker for nutritional status. Lymphocyte count, by contrast, is an objective indicator for the presence of inflammation.[13] Protein and energy deficits contribute to anemia, and patients with anemia are more frequently malnourished than are those without anemia.[14]

However, most studies have investigated the link between active PTB and malnutrition using BMI or underweight status as indicators of nutritional status. The associations between nutritional parameters such as serum total protein levels, the presence of hypoalbuminemia, anemia or lymphocytopenia, and typical clinical signs and symptoms such as the positive sputum smears or lung field lesions found in patients with PTB have received less attention. This study was conducted to examine the associations between the biochemical and hematological indicators that reflect nutritional status and the clinical manifestations present among patients with PTB before TB treatment.

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METHODS

Study design and population

This study was approved by the Medical Ethics Committee of Qingdao Municipal Center for Disease Control and Prevention and follows the Declaration of Helsinki. The study was registered in the Chinese Clinical Trial Registry (registration number ChiCTR–OCC–1900022294). We obtained informed consent from each individual participant, and all data have been maintained in strict confidence during the research process.

In this cross–sectional study, 613 patients with active PTB were selected from local TB clinics in Weifang, Shandong Province, from 2019 to 2021.

The adjusted eligibility criteria were as follows: (1) Patients were newly diagnosed as having PTB (according to China's National Tuberculosis Prevention and Control Guidelines;[15] if sputum smear results were positive, patients were diagnosed as having smear–positive PTB; if sputum specimens were negative and the results of computerized tomography (CT) scans of the chest and the presence of clinical symptoms were compatible with a diagnosis of active PTB, patients were diagnosed as having PTB after discussion with radiologists and clinicians.[15] (2) Participants were ≥18 years old, (3) were free of mental illness, and (4) agreed to sign the informed consent form.

The exclusion criteria were as follows: (1) patients with extrapulmonary tuberculosis, with multidrug–resistant tuberculosis (MDR–TB), or with other pulmonary diseases; (2) patients with severe organ dysfunction or complications such as those related to cardiovascular or lung disease, cancer, or HIV; (3) patients with impaired cognitive function or those with mental illnesses; (4) patients with liver or kidney dysfunction at baseline; or (5) patients who were pregnant or breast–feeding.

Procedures

A standard questionnaire to collect demographic characteristics (including age, gender, education level, area of residence, marital status, smoking and drinking) and clinical manifestations was administered by trained staff. The initial clinical manifestations of patients with PTB were assessed using a standard questionnaire to calculate a TB score. The TB score was calculated according to modified previous methods[16-18] and was used as a comprehensive index for the assessment of initial clinical symptoms. The TB score was based on the presence of typical manifestations of active PTB, including cough, sputum production, hemoptysis, chest pain, fever, night sweats, fatigue and loss of appetite. Patients who reported any of the eight listed symptoms, scored one point for each symptom. We calculated patient BMI through the following formula: BMI = weight (kg) / height (m)2. For a BMI of <16, 16–18, >18, two, one, and zero points were added to the TB score, respectively. In total, the TB scores ranged from 0 to 10. The patients were divided into two groups according to their TB score: patients with ≤3 points and patients with >3 points.

Sputum specimens were examined by microscopy to determine the presence and number of acid–fast bacilli (AFB). The AFB smears were examined through Ziehl–Nielsen acid–fast staining and the results were categorized as either positive or negative for the presence of AFB indicating active PTB. CT scans were conducted through the spiral technique, with the results of the CT scans categorized as exhibiting cavitation or not.

Peripheral venous blood was collected from each patient after an overnight 8–12–h fasting period. Blood was drawn from the antecubital vein using aseptic venipuncture from the cubital fossa and collected into labelled plain test tubes. The 5–mL blood sample was allowed to clot and subsequently centrifuged at 4000 rpm for 10 minutes. An automatic biochemical analyzer (Beckman AU5800) and an automatic hematology analyzer (XN1000) were employed to assay total protein (TP), albumin (ALB), hemoglobin (Hb) and lymphocyte count.

The reference value range for normal values was designated as TP: 60–80g/L.[19] Hypoalbuminemia was defined as an ALB value <35 g/L.[20] Anemia was determined according to Hb concentration (for men <120 g/L, for women <110 g/L).[21] Lymphocytopenia was defined as a lymphocyte count <1.0 (10^9/L).[22]

The investigators were trained by project members who checked the completed questionnaires. The data were entered independently by two project members and were verified twice.

Statistical analyses

The data analyses were conducted using SPSS 23.0. Quantitative data that conformed to a normal distribution are expressed as means and (standard deviations). Quantitative data that were not normally distributed are reported as medians and interquartile ranges. The distribution of categorical variables such as gender, education level, area of residence, marital status, smoking and drinking are presented as frequencies and percentages. The biochemical and hematological indicators related to nutritional status as independent variables were divided into two groups. A binary logistic regression analysis with forward stepwise strategy was performed to measure associations between nutritional parameters and the clinical manifestations of PTB. Normal biochemical and hematological indicators were used as a reference.

In the multivariate analysis, model 1 was adjusted for potential confounding factors that included age, gender, BMI, smoking, drinking, education level, area of residence, and marital status. Adjusted ORs with 95% CI are reported for the results of the logistic regression to indicate the strength and direction of the associations. All tests were two–sided, and $p<0.05$ or $p<0.01$ was considered statistically significant.

RESULTS

This cross–sectional study included 613 patients diagnosed as having PTB (Figure 1). The demographic characteristics are listed in Table 1. Sputum smear tests were conducted for 473 patients, with 208 (44.0%) being sputum-smear positive (Figure 1); moreover, 352 patients were evaluated by CT, with 142 (40.3%) patients exhibiting cavitation (Figure 1). Among the 613 participants, 67.5% were men. The majority of patients were between the ages of 18 and 44 years (58.2%), with the average age being 41.5±18.0 years. Most of the participants (63.6%) were married and were from rural areas (69.7%). The

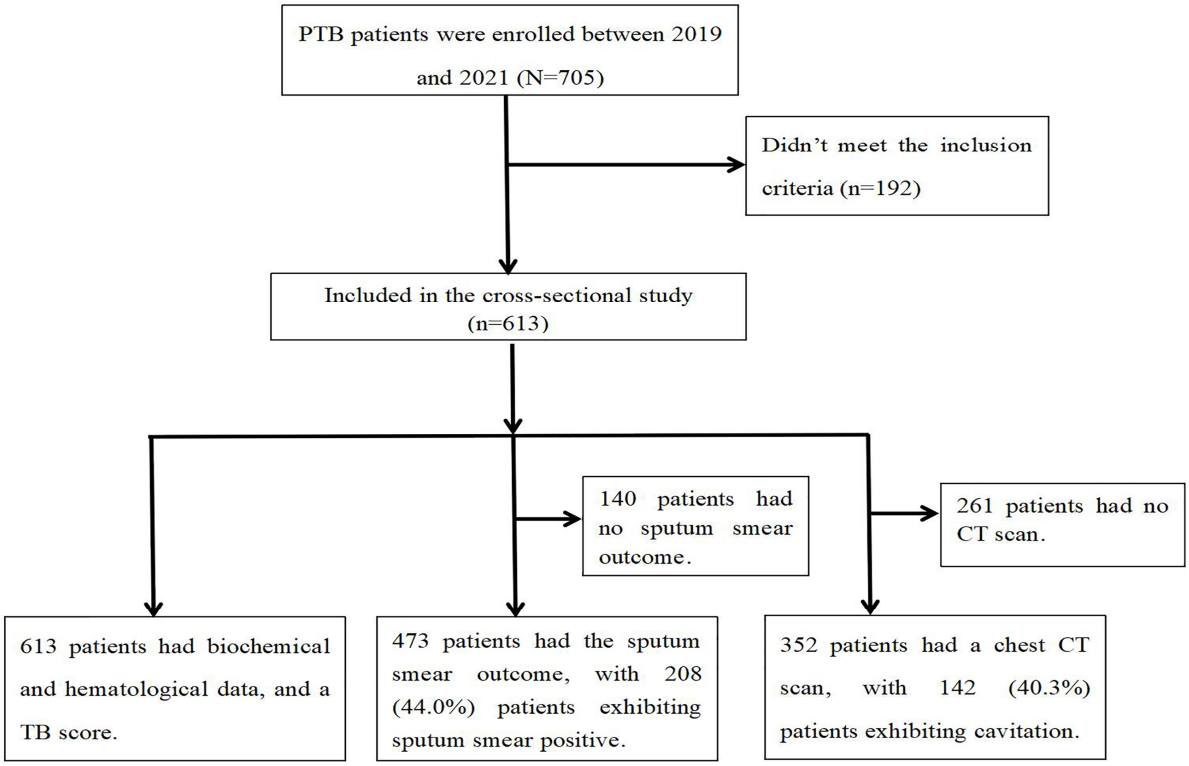

Figure 1. Study flow chart.

mean BMI of patients was 20.7, with 27.6%, 57.3%, and 15.2% of patients being underweight, normal weight, and overweight or obese, respectively. Moreover, 38.7% of the patients consumed alcohol, and 36.7% consumed tobacco.

The prevalence of each contributing parameter in the TB score is listed in Table 2. TB scores were conducted for 613 patients, with 213 (34.7%) exhibiting TB scores >3. The medians (interquartile ranges) of TB scores were 3.0 (2.0, 4.0). The most frequent clinical symptoms of tuberculosis patients were cough (75.0%) and sputum production (56.1%). Fatigue (30.0%) and fever (33.9%) were present in more than one-third of respondents. Hemoptysis (14.2%), chest pain (18.1), and night sweats (9.6%) were less common among patients with PTB.

The mean concentrations of serum TP, ALB, peripheral blood Hb, and lymphocyte counts among the study participants were 68.9±7.49 g/L, 38.7±5.74 g/L, 129.3±18.3g/L, and 1.52±0.64 (10^9/L), respectively. Among the 613 patients with PTB, 153 (25%), 130 (21.2%), and 111 (18.1%) patients exhibited hypoalbuminemia, anemia, and lymphocytopenia (Table 1), respectively.

After adjustments were made for multiple confounding factors, a higher TB score (TB score >3 points group) was positively associated with hypoalbuminemia (OR=2.61; 95% CI, 1.69–4.03), anemia (OR=1.62; 95% CI, 1.04–2.51) and lymphocytopenia (OR=1.92; 95% CI, 1.21–3.05) (Table 3). The associations between nutritional parameters of patients with PTB and typical clinical symptoms of PTB are presented in Table 4. In multivariate logistic regression, model 1 indicated that patients with PTB exhibited TP levels lower than the reference range, exhibited fever more frequently (OR=1.99; 95% CI, 1.12–3.54), and experienced greater loss of appetite (OR=2.21; 95% CI, 1.22–4.02); moreover, patients with PTB with hypoalbuminemia exhibited cough more frequently (OR=4.47; 95% CI, 2.31–8.66), exhibited greater sputum production (OR=1.78; 95% CI, 1.15–2.76) as well as fever (OR=3.98; 95% CI, 2.56–6.19), fatigue (OR=2.00; 95% CI, 1.30–3.09), loss of appetite (OR=1.92; 95% CI, 1.23–3.01) and weight loss (OR=1.81; 95% CI, 1.08–3.03). The presence of anemia among patients with PTB was associated with more frequent coughs (OR=1.99; 95% CI, 1.13–3.50), greater sputum production (OR=1.62; 95% CI, 1.03–2.54), presence of fever (OR=2.40; 95% CI, 1.56–3.68), fatigue (OR=1.81; 95% CI, 1.17–2.82), loss of appetite (OR=1.63; 95% CI, 1.03–2.56) and weight loss (OR=2.00, 95% CI, 1.20–3.33). Patients with PTB with lymphocytopenia experienced more frequent coughs (OR=3.10; 95% CI, 1.57–6.10), fever (OR=2.67, 95% CI, 1.71–4.17), fatigue (OR=1.67; 95% CI, 1.06–2.64), loss of appetite (OR=1.98; 95% CI, 1.23–3.19), and weight loss (OR=1.84; 95% CI, 1.08–3.14). Table 5 summarizes model 1, where multiple potential confounding factors were considered. Compared with the negative sputum–smear group, the results of the positive sputum smears were associated with hypoalbuminemia (OR=1.75; 95% CI, 1.08–2.84) and anemia (OR=1.87; 95% CI, 1.14–3.08). Compared with the non–cavitation group, the presence of cavitation was strongly associated with anemia (OR=3.58; 95% CI, 1.85–6.94; Table 6). Moreover, as is indicated in Table 3, Table 5 and Table 6, the proportions of TB scores >3 points, positive sputum smear test results, and the presence of cavitation in patients combined with TPs below the reference value were 53.2%, 49.0% and 52.0%, respectively. For patients with hypoalbuminemia, the values were 58.8%, 62.3% and 56.5%, respectively, and for patients with anemia, the values were 52.3%, 62.2% and 60.9%, respectively. For patients with lym-

Table 1. Baseline characteristics for the included pulmonary tuberculosis patients

Characteristics	N	%
Age-group		
18-44	357	58.2
45-65	180	29.4
≥66	76	12.4
Gender		
Women	199	32.5
Men	414	67.5
Residence		
Urban	186	30.3
Rural	427	69.7
Marital status		
Single	195	31.8
Married	390	63.6
Widowed	15	2.4
Divorced	13	2.1
Education		
Unknown	17	2.8
illiteracy	24	3.9
Primary and junior high school	246	40.1
Senior and technical secondary school	244	39.8
Diploma or higher	82	13.4
Alcohol consumption		
Yes	237	38.7
No	376	61.3
Smoking status		
Smoker	225	36.7
Non-smoker	388	63.3
BMI (kg/m^2)		
<18.5	169	27.6
18.5-23.9	351	57.3
≥ 24.0	93	15.2
Hypoalbuminemia		
Yes	153	25.0
No	460	75.0
Anemia		
Yes	130	21.2
No	483	78.8
Lymphocytopenia		
Yes	111	18.1
No	502	81.9

BMI: body mass index.
Categorical variables are presented as N and %

Table 2. Clinical symptoms and TB score for the included pulmonary tuberculosis patients†

Parameters	Points assigned	N (%)
Cough	1	460 (75.0)
Sputum production	1	344 (56.1)
Hemoptysis	1	87 (14.2)
Chest pain	1	111 (18.1)
Fatigue	1	184 (30)
Night Sweats	1	59 (9.6)
Fever	1	208 (33.9)
Loss of appetite	1	163 (26.6)
BMI<16	2	35 (5.7)
16≤BMI≤18	1	97 (15.8)
BMI>18	0	481 (78.5)

BMI: body mass index.
†Categorical variables are presented as N and %

phocytopenia, the values for those with TB scores >3 points, positive sputum smear tests, and cavitation were 54.1%, 55.8% and 57.6% respectively.

DISCUSSION

In the present study, we observed that hypoalbuminemia, anemia, and lymphocytopenia were positively associated with the severity of initial symptoms (as indicated by the increased TB scores), with positive sputum smears, and with the presence of cavitation before anti–tuberculosis treatment in patients with PTB. Additionally, abnormal values for biochemical and hematological indicators were strongly related to the typical clinical signs and symptoms of PTB. Therefore, our data suggest that the poor nutritional status may affect the severity of the initial clinical manifestations of PTB.

Malnourished patients with TB have lower serum albumin concentrations.[12] One possible reason is that protein–calorie malnutrition reduces the effectiveness of host defense mechanisms and cell–mediated immunity[23] and also lowers visceral protein levels[24,25] in patients with TB. Our study revealed that hypoalbuminemia was positively associated with the severity of clinical signs and symptoms and positive sputum smear results. Poor nutritional status has been reported as significantly associated with a higher number of symptoms (fever and weight loss), and a higher proportion of cases that were sputum–smear positive.[26] Hypoalbuminemia has been highlighted as a predictive risk factor for in–hospital mortality in patients with TB.[27] By contrast, weight loss and malnutrition in patients with PTB may be caused by a reduction in food intake or other TB–related factors such as metabolic abnormalities, poor nutrient absorption, fever, and anorexia.[4] This may lead to the "anabolic block" that occurs in patients with TB, whereby ingested amino acids are utilized for oxidation rather than for protein synthesis.[28]

Anemia is common among patients with TB and is associated with the inhibition of erythropoietin production caused by the increased presence of cytokines and changes in iron metabolism.[29] In our study, we found that being anemic was significantly associated with more severe clinical presentation as evidenced by a higher TB score among patients with PTB. Moreover, patients who were anemic were more likely to exhibit positive sputum smear results. This finding is similar to that of a survey conducted in Tanzania that determined that anemia was associated with delayed sputum smear conversion.[30] Our study revealed that patients with PTB and anemia also exhibited cavitation on chest CT. Studies have indicated that patients with TB presenting with increased numbers and greater diversity of lung lesions exhibited lower concentrations of hemoglobin, suggesting anemia,[31] and the affected lungs and cavitation were significantly associated with hemoglobin levels.[32] Population studies have reported that malnutrition leads to the downregulation of type 1 cytokines such as interleukin (IL)–2 and interferon-gamma (INF-γ), and to the upregulation of type 2 cytokines such as IL–4 and IL–10.[33] These cytokines can change pathogenesis of TB under the impact of malnutrition on bacterial clearance, and lead to the formation of cavitation.[34] One study demonstrated that larger cavity volume, especially that in closer proximity to the airways, was associated with higher cough frequency, higher bacillary burden, and delayed culture conversion.[35]

Table 3. Logistic regression analysis for the association between nutritional status and TB score at baseline (N=613)

	TB score >3 n (%)	OR (95% CI)	
		Crude model†	Model 1‡
TP below the reference			
No	180 (32.7)	Reference	Reference
Yes	33 (53.2)	2.35 (1.38, 3.98)*	1.68 (0.920, 3.07)
Hypoalbuminemia			
No	123 (26.7)	Reference	Reference
Yes	90 (58.8)	3.91 (2.67, 5.74)**	2.61 (1.69, 4.03)**
Anemia			
No	145 (30.0)	Reference	Reference
Yes	68 (52.3)	2.56 (1.72, 3.77)**	1.62 (1.04, 2.51)*
lymphocytopenia			
No	153 (30.5)	Reference	Reference
Yes	60 (54.1)	2.68 (1.77, 4.08)**	1.92 (1.21, 3.05)**

TP: total protein; N: the total number of patients in TB score>3 group
†Crude model was not adjusted.
‡Model 1 was adjusted for age, gender, smoking, drinking, BMI, education completed, marital status, residence.
*p<0.05, **p<0.01

Table 4. Logistic regression analysis for the association between nutritional status and clinical symptoms of pulmonary tuberculosis

	OR (95% CI) †					
	Cough	Sputum production	Fever	Fatigue	Loss of appetite	Weight loss
TP lower than reference	1.34 (0.631, 2.84)	1.24 (0.677, 2.27)	1.99 (1.12, 3.54)*	1.60 (0.898, 2.86)	2.21 (1.22, 4.02)**	1.52 (0.775, 2.96)
Hypoalbuminemia	4.47 (2.31, 8.66)**	1.78 (1.15, 2.76)*	3.98 (2.56, 6.19)**	2.00 (1.30, 3.09)**	1.92 (1.23, 3.01)**	1.81 (1.08, 3.03) *
Anemia	1.99 (1.13, 3.50)*	1.62 (1.03, 2.54)*	2.40 (1.56, 3.68)**	1.81 (1.17, 2.82)**	1.63 (1.03, 2.56)*	2.00 (1.20, 3.33)**
lymphocytopenia	3.10 (1.57, 6.10)**	1.48 (0.930, 2.36)	2.67 (1.71, 4.17)**	1.67 (1.06, 2.64)*	1.98 (1.23, 3.19)**	1.84 (1.08, 3.14)*

TP: total protein.
†OR (95%CI): odds ratio (95% confidence interval) adjusted for age, gender, smoking, drinking, BMI, education completed, marital status, residence.
*p<0.05, **p<0.01.

Table 5. Logistic regression analysis for the association between nutritional status and sputum smear results (N=473)

	AFB (+), n (%)	OR (95% CI)	
		Crude model†	Model 1‡
TP below the reference			
No	189 (43.4)	Reference	Reference
Yes	25 (49.0)	1.26 (0.702, 2.25)	0.807 (0.428, 1.52)
Hypoalbuminemia			
No	137 (38.2)	Reference	Reference
Yes	71 (62.3)	2.68 (1.73, 4.13)**	1.75 (1.08, 2.84)*
Anemia			
No	147 (39.2)	Reference	Reference
Yes	61 (62.2)	2.56 (1.62, 4.04)**	1.87 (1.14, 3.08)*
lymphocytopenia			
No	160 (41.3)	Reference	Reference
Yes	48 (55.8)	1.79 (1.12, 2.87)*	1.31 (0.786, 2.19)

AFB (+): acid-fast bacilli smear positivity; TP: total protein.
†Crude model was not adjusted.
‡Model 1 was adjusted for age, gender, smoking, drinking, BMI, education completed, marital status, residence.
*p<0.05, **p<0.01.

Our study found a significant association among lymphocytopenia and cough, fever, fatigue, loss of appetite, weight loss, and higher TB scores in patients with PTB. Studies have reported that CD4 lymphocytopenia was associated with positive sputum smear results and signs of cough and wasting.[36] Patients with TB with extended disease frequently exhibit malnourishment and lymphopenia.[37] Previous animal experiments have indicated that nutritional deficiencies resulted in reduced lymphocyte counts, inability to endure the increased production of

Table 6. Logistic regression analysis for the association between nutritional status and lung cavitation (N=352)

	Cavitation, n (%)	OR (95% CI)	
		Crude model†	Model 1‡
TP below the reference			
No	129 (39.4)	Reference	Reference
Yes	13 (52.0)	1.66 (0.736, 3.76)	0.985 (0.395, 2.46)
Hypoalbuminemia			
No	94 (35.2)	Reference	Reference
Yes	48 (56.5)	2.39 (1.45, 3.92)**	1.59 (0.873, 2.88)
Anemia			
No	100 (35.3)	Reference	Reference
Yes	42 (60.9)	2.85 (1.66, 4.89)**	3.58 (1.85, 6.94)**
lymphocytopenia			
No	108 (36.9)	Reference	Reference
Yes	34 (57.6)	2.33 (1.32, 4.11)**	1.73 (0.899, 3.33)

TP: total protein.
†Crude model was not adjusted.
‡Model 1 was adjusted for age, gender, smoking, drinking, BMI, education completed, marital status, residence.
*p<0.05, **p<0.01.

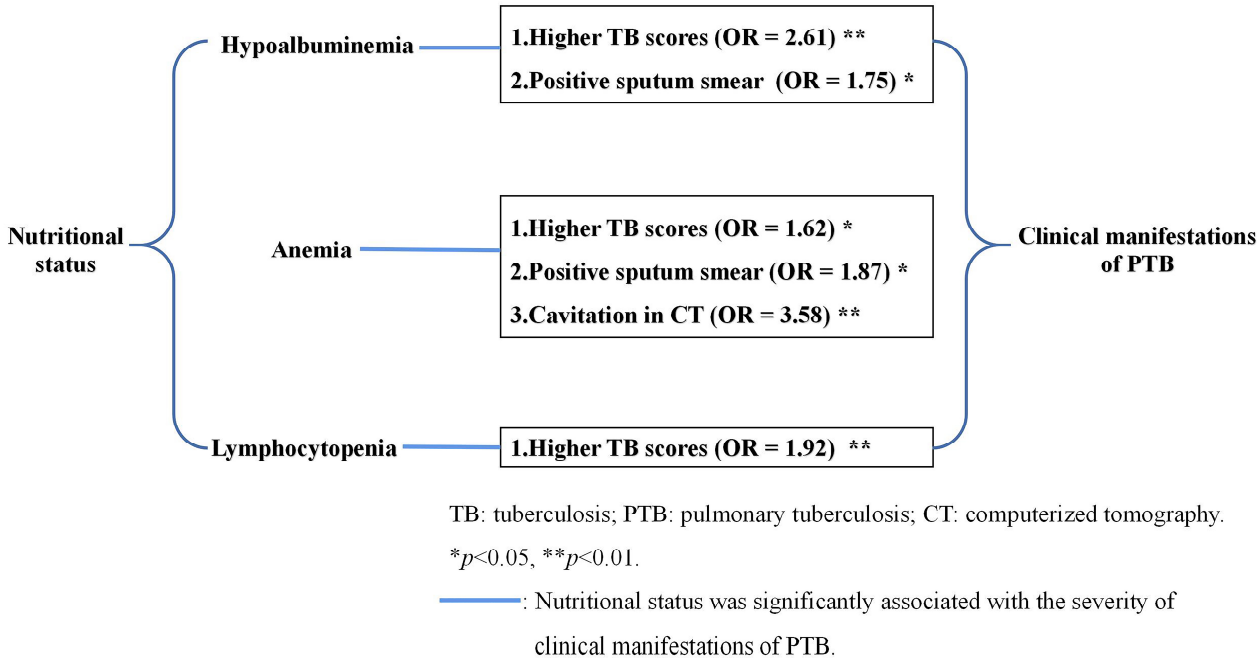

Figure 2. Graphical abstract.

INF–γ[38] and decreased the expressions of nitric oxide synthase (NOS)-2,[39] which plays a crucial role in generating mycobactericidal nitrogen oxide.

The present study has several limitations. First, this was a cross–sectional study that employed a single timepoint assessment, and only included hospitalized patients. Prospective studies are required to confirm our results. Second, the associations between nutritional parameters and the initial clinical manifestations of PTB do not indicate a cause–and–effect relationship at the time of diagnosis. Third, the population of this study did not include any patients with MDR–TB. MDR–TB is known to strongly affect the nutritional status of patients with TB. The present results, therefore, should not be applied to areas where MDR–TB is prevalent.

Despite these limitations, this study has some strengths and merits. First, the TB score is a comprehensive index used to indicate the severity of initial tuberculosis symptoms. Second, hematological and biochemical measurement is a low–cost procedure that is simple to perform and available to tuberculosis patients upon hospital admission. Moreover, some markers can be used to determine patient nutritional status.

Conclusion

The results of this study reveal that poor improvements in nutritional status during the initial phases of PTB treatment are associated with a risk of more severe clinical signs and symptoms, positive sputum smear results, and the presence of cavitation. These results suggest that greater attention should be given to the crucial role that malnutrition plays in patient disease management. Alleviating the severity of PTB may require the synergistic effects of nutritional recovery and TB therapy.

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AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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