Effect of persistent malnutrition on pulmonary tuberculosis treatment: A cross-sectional study in Weifang, China

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ABSTRACT

Background and Objectives: Malnutrition is associated with pulmonary tuberculosis (PTB). The aim of this study is to investigate the association between persistent malnutrition and the effect of PTB treatment. **Methods and Study Design:** A total of 915 PTB patients were included. Baseline demographic information, anthropometry, and nutritional indicators were measured. The treatment effect was assessed by combinations of clinical manifestations, sputum smear, chest computerized tomography, gastrointestinal symptoms, and the indexes of liver function. Persistent malnutrition was considered when one or more indicators of malnutrition were lower than the reference standards in two tests on admission and after one month of treatment. Clinical symptom score (TB score) was used to assess the clinical manifestations. The generalized estimating equation (GEE) was used to assess the associations. **Results:** In GEE analyses, patients with underweight had a higher incidence of TB score >3 (OR=2.95; 95% CI, 2.28-3.82) and lung cavitation (OR=1.36; 95% CI, 1.05-1.07). Hypoproteinemia was associated with a higher risk of TB score >3 (OR=2.73; 95% CI, 2.08-3.59) and sputum positive (OR=2.69; 95% CI, 2.08-3.49). Anemia was associated with a higher risk of TB score >3 (OR=1.73; 95% CI, 1.33-2.26), lung cavitation (OR=1.39; 95% CI, 1.19-1.63), and sputum positive (OR=2.69; 95% CI, 2.08-3.49). Lymphocytopenia was associated with a higher risk of gastrointestinal adverse reactions (OR=1.12; 95% CI, 1.16-1.93). **Conclusions:** Persistent malnutrition within one month of treatment can adversely affect anti-tuberculosis treatment. Nutritional status during anti-tuberculosis treatment should be continuously monitored.

Key Words: pulmonary tuberculosis, persistent malnutrition, generalized estimating equation, hypoproteinemia, TB score

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by the *Mycobacterium tuberculosis* (*M.tb*) and typically affects the lungs.[1] The World Health Organization estimated 10.6 million people fell ill with TB in 2021. China has a high TB burden, which had 0.78 million TB incidences in 2021.[2] TB prevention and treatment are still major public health concerns.[3]

Malnutrition is one of the determinants of the infection and development of TB, underweight, decreased body protein levels, and decreased lymphocyte count are the main manifestations of malnutrition,[4] which can increase the risk of drug toxicity, disease

recurrence, and death during TB treatment.[5,6] Studies have reported that pulmonary tuberculosis (PTB) patients with underweight are more prone to dyspnea, diarrhea, night sweats, hemoptysis, and cavitation.[7] Hypoproteinemia and lymphopenia are risk factors for death in hospitalized TB patients.[8] In an Indonesian study, the presence of pulmonary lesions and cavitary lesions in patients with sputum smear-positive TB was significantly associated with BMI and hemoglobin levels at diagnosis.[9]

An extensive literature search showed that the studies on the relationship between malnutrition and anti-TB treatment effects stayed at the nutritional level of patients before treatment, however, persistent malnutrition have been neglected. Studies have shown that the incidence of malnutrition varies during hospitalization, and the prevalence of malnutrition increases significantly.[10,11] TB can induce or worsen pre-existing malnutrition by decreasing appetite and increasing catabolism.[12,13] A majority of patients had malnutrition at diagnosis, which persisted during the treatment in a significant proportion of them,[5] we should explore the impact of malnutrition during treatment on clinical treatment outcomes. Therefore, this study investigated the occurrence of persistent malnutrition in PTB patients within one month of treatment and analyzed the effect of persistent malnutrition within one month on TB treatment.

MATERIALS AND METHODS

Ethics

The Qingdao Center for Disease Control and Prevention's Ethic Committee of Medicine gave its approval to the study. The Declaration of Helsinki was followed when conducting the study. Written informed consent was provided by each participant. At the Chinese Clinical Trial Registry, the trial was documented (registration number Chi CTR–OCC–1900022294).

Study design and population

The study was conducted between 2019 and 2021, participants with active PTB were recruited from the TB clinics, which were located in Weifang, Shandong Province. The eligibility criteria include: (1) newly diagnosed PTB patients, the diagnostic criteria were in line with the Chinese National Tuberculosis Prevention and Control Guideline (2008);[14] (2) patients were 18 to 80 years old; (3) received standard anti-TB treatment for patients; (4) voluntarily sign the informed consent form and cooperate with the relevant questionnaire. The exclusion criteria include: (1) extrapulmonary tuberculosis; (2) patients infected with non-

tuberculous mycobacteria; (3) patients with serious complications such as malignant tumors, gastrointestinal, cardiovascular, and respiratory diseases; (4) patients with severe mental illness and cognitive dysfunction; (5) patients during lactation or pregnancy; (6) patients with missing baseline data.

Procedure

A standard questionnaire regarding the participants' demographic details, such as age, gender, marital status, diabetes, and habits (such as smoking and drinking), was given to them when they entered the hospital. The follow-up periods ended after one month of treatment. The clinical manifestations of the TB patients, including cough, sputum production, hemoptysis, chest pain, fatigue, night sweats, fever, and appetite loss, were evaluated using a standard questionnaire. The severity of symptoms and signs of patients was evaluated by clinical symptom score (TB score).[15] TB score was given one point if any of the eight clinical symptoms above appeared, and zero points if they did not. The body mass index (BMI) was calculated by the following formula: BMI = weight (kg) / height $(m)^2$, two points for a BMI less than 16; One point for a BMI of 16-18; and a BMI more than 18 was given zero points. In total, the range of TB scores was 0-10. According to patients with a TB score $\leq$3 points and patients with a TB score >3 points were separated into two groups.

During the follow-up periods, all participants received the same standard TB treatment, which used isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB).[16] Each patient's peripheral venous blood was drawn following an overnight fast (8 hours). Total protein (TP), albumin (ALB), hemoglobin (Hb), lymphocyte count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (GGT) were measured using an automatic biochemical analyzer (Beckman AU5800) and an automatic hematological analyzer (XN1000). Sputum samples were collected from the patients, microscopy was used to check for the presence and count of acid-fast bacilli (AFB) in sputum samples, and the outcomes for the presence of AFB were classed as either positive or negative. A baseline and first-month computed tomography (CT) scan of the chest was collected from the patients. Patients were considered to have gastrointestinal adverse reactions when they had any of the following symptoms: nausea, vomiting, abdominal distension, diarrhea, loss of appetite, or constipation.[17] Abnormal liver function was defined as higher than the upper limit of normal (ULN). The ULN for AST, ALT and GGT was 40 U/L, 40 U/L, 40U/L.[18,19] Underweight was defined as a BMI less than18.5

kg/m^2;[20] hypoalbuminemia was defined as an ALB value <35 g/L or TP value <60 g/L;[21] anemia was defined in terms of Hb concentration (for men <120 g/L, for women <110 g/L);[22] lymphocytopenia was defined as a lymphocyte count <1.0 (109/L).[23] When one or more indicators of malnutrition (BMI, TP, ALB, Hb, TLC) were lower than the reference standards in two tests on admission and after one month of treatment, the patient was determined persistent malnutrition within one month of treatment.[24]

The members of the project team conducted training sessions for the participating personnel who checked the completed questionnaires from the TB clinics. At least one other project member reviewed the completed survey. Two project participants recorded the data, and their work was double-checked with each other.

Statistical analysis

SPSS version 23.0 statistical software was used to sort out and analyze the data. The qualitative data were expressed as frequencies and percentages. The patients were divided into two groups based on nutrition-related indicators. The intergroup difference was tested by a χ^2 test or Fisher's exact test. The clinical manifestations, sputum test results, lung lesions, gastrointestinal symptoms, and liver function of patients with PTB were measured on admission and after one month of treatment. Correlation of measurements and missing data are unavoidable due to the measurement of data from the same person at multiple time periods, the generalized estimating equation (GEE) was used for the analysis. And normal nutritional status was used as a reference standard. Both univariate and multivariate analyses were used, the model of the multivariate analysis was adjusted for potential confounding factors, including age, gender, smoking, drinking, marital status, diabetes, BMI, TP, ALB, and HB. Adjusted OR and 95 % CI were reported to indicate the strength and direction of associations. And $p<0.05$ was considered statistically significant.

RESULTS

A total of 1027 PTB patients were recruited from a hospital in Weifang City, Shandong Province, China (Figure 1). Among them, 9 patients were less than 18 years old, 74 patients did not have complete baseline information, 16 patients declined to participate in this study, and 13 patients had serious complications. 915 patients completed the follow-up periods. In addition, 897 cases of sputum smear outcome and 862 cases of chest CT scan were collected

before treatment, 733 cases of sputum smear outcome and 792 cases of chest CT scan were collected after one month of treatment.

According to the basic survey data of the participants, 365 patients overall (39.9%) experienced persistent malnutrition (at least one of underweight, hypoproteinemia, anemia, and lymphopenia) during one month of anti-TB treatment. Gender, drinking, and diabetes were similar between the well-nourished group and the malnourished group. However, there were substantial differences in the distribution of age (p<0.001), smoking (p=0.046), and marital status (p=0.003) among patients (Table 1).

The treatment effect were compared between the patients with and without malnutrition after one month of anti-TB treatment (Figure 2). Compared with the patients in the well-nourished group, the patients in the malnourished group had a higher incidence of TB score >3, sputum positive, lung cavitation and gastrointestinal adverse reactions. The incidence of abnormal liver function was similar between the well-nourished group and the malnourished group. Nutritional status was shown in Figure 3, the incidence of malnutrition, underweight, hypoproteinemia, anemia, and lymphocytopenia was 39.9%, 24.6%, 12.7%, 15.0%, and 8.63%.

After adjusting for multiple confounding factors, GEE analysis showed that patients with underweight within one month had a significantly higher incidence of TB score >3 (OR=2.95; 95% CI, 2.28-3.82) and lung cavitation (OR=1.36; 95% CI, 1.05-1.07) than patients without underweight after one month of treatment. In model 1, no significant effect of underweight on sputum positive (OR=1.03; 95% CI, 0.78-1.35), gastrointestinal adverse reactions (OR=1.17; 95% CI, 0.91-1.49), and abnormal liver function (OR=0.87; 95% CI, 0.68-1.11) was observed after one month of treatment (Table 2).

The association between hypoproteinemia and the outcome of one-month anti-TB treatment in GEE analysis was shown in Table 3. Compared to the patients without hypoproteinemia, hypoproteinemia was positively associated with the risk of TB score >3 (OR=2.73; 95% CI, 2.08-3.59), sputum positive (OR=2.69; 95% CI, 2.08-3.49), gastrointestinal adverse reactions (OR=2.13; 95% CI, 1.65-2.75) and abnormal liver function (OR=1.37; 95% CI, 1.05-1.79) in model 1.

A similar analysis was conducted to explore the association between anemia and the outcome of one-month anti-TB treatment (Table 4). Compared to the patients without anemia, anemia was associated with a higher risk of TB score >3 and gastrointestinal adverse reactions during treatment, the OR of the TB score >3 was 1.73 (95% CI: 1.33-2.26) and the

OR of the gastrointestinal adverse reactions was 1.50 (95% CI: 1.16-1.93). In addition, patients with anemia had a higher chance of developing lung cavitation (OR=1.39; 95% CI, 1.19-1.63) and sputum positive (OR=2.69; 95% CI, 2.08-3.49) than patients without anemia.

The OR of lymphocytopenia and the outcome of one-month anti-TB treatment were shown in Table 5. After adjusting age, gender, smoking, drinking, marital status, diabetes, and BMI, the OR of lymphocytopenia and gastrointestinal adverse reactions was 1.12 (95% CI: 1.16-1.93). In contrast, lymphocytopenia did not significantly influence the TB score >3, sputum positive, lung cavitation, and abnormal liver function.

DISCUSSION

This study investigated the relationship between persistent malnutrition within one month and anti-TB treatment outcomes in patients with PTB. After one month of treatment, underweight was significantly associated with the incidence of clinical manifestations and lung cavitation. Hypoproteinemia was strongly related to the incidence of clinical manifestations, sputum positive, and adverse drug reactions. The incidence of clinical manifestations, lung cavitation, adverse drug reactions, and sputum positivity were all positively correlated with anemia. We also found that lymphopenia may increase the incidence of adverse drug reactions. The current results indicated that the severity of clinical manifestations and the incidence of adverse drug reactions were greatly affected by the persistence of malnutrition within one month.

This study found that patients with underweight within one month of treatment had higher TB scores and a higher risk of lung cavitation. This finding was similar to a study in Latvian, which showed patients with underweight (BMI< 18.5 kg/m^2) were associated with more severe clinical symptoms and signs, a higher proportion of sputum positive cases, and more prominent cavity lesions on chest X-rays.[25] The reason for this phenomenon may be that patients with lower BMI may inhibit cell-mediated immune responses,[13,26] change T lymphocyte subsets,[27] and lead to impaired expression of T cell-mediated cytokines at the gene and protein levels. Specifically, the expression of type 1 cytokines such as interleukin (IL)-2 and interferon-gamma (INF-γ) is down-regulated, and the expression of type 2 cytokines such as IL-4 and IL-10 is up-regulated.[28,29] Abnormal expression of these cytokines may reduce the body's ability to clear pathogens, and even lead to more severe lung lesions.[30] A study has shown that higher cough frequency, higher bacillary burden, and delayed culture

conversion were all linked to bigger cavity volumes, especially those located near the airways.[31]

Our research found that patients with hypoproteinemia within one month of treatment had higher TB scores and a higher risk of developing sputum positive. Serum protein levels are lower in malnourished TB patients,[32] low protein nutritional status affects cellular immunity mediated by T cells and macrophages, which play an important role in resisting mycobacterium tuberculosis and removing bacteria from the body.[26] This study found that the risk of gastrointestinal adverse reactions and abnormal liver function in patients with hypoproteinemia was higher than non-hypoproteinemia, which was similar to previous studies.[33] The possible reasons are that anti-TB drugs mainly combine with plasma albumin to exert drug effects, patients with hypoproteinemia decreased drug binding to protein, increased free drug concentration and drug accumulation, and eventually increased the burden on the liver.[34,35] Bile acids and immunoglobulin antibodies secreted by the liver reach the intestine through the "gut-liver" axis,[36] causing intestinal flora disorder and damaging gastrointestinal mucosal cells.[37] Therefore, patients with PTB are prone to gastrointestinal adverse reactions and abnormal liver function.[38]

Anemia is common in TB patients, and the occurrence of anemia is related to the inhibition of erythropoietin caused by abnormal expression of cytokines and changes in iron metabolism.[39] Our study found that patients with anemia within one month of treatment had higher TB scores and a higher risk of developing sputum positive. A similar study in Tanzania showed that anemia in patients with PTB before anti-TB treatment was significantly associated with a positive sputum smear after two months of treatment.[40] The reason may be that iron metabolism disorder in anemia patients affects the utilization of iron by macrophages in the body, which affects the host's innate immune response to pathogen infection,[41] and provides favorable conditions for the development of TB.[42] We also found that anemia was significantly associated with the incidence of lung cavitation, and other studies have shown that anemia was associated with an increase in the type and number of lung lesions in patients.[9,43] This may be due to excessive inflammatory response during the development of TB, which mediates the formation of granuloma in the body and causes lung tissue damage.[44]

In addition, this study found that patients with lymphopenia within one month of treatment had a higher risk of gastrointestinal adverse reactions. The possible reasons for this phenomenon were as follows: low TLC nutritional status reduces food intake by affecting

leptin levels,[45] which reduces nutrient absorption rate and increases the risk of gastrointestinal symptoms such as loss of appetite in patients.

Our study has several strengths. First, this study focused on the persistent malnutrition of PTB patients at the initial stage of treatment, emphasizing the impact of persistent malnutrition within one month of treatment on the clinical therapeutic effect. Second, the TB score is a comprehensive index that indicates the severity of TB symptoms for each participant, hematology and biochemical measurements are a low-cost procedure that is simple to perform and collect. Third, statistical methods used GEE to analyze longitudinal data from repeated measurements, and overcome the problems with correlation of repeated measurement data and missing data.

There are some limitations in this study. First, the population in this study did not include any multidrug-resistant tuberculosis (MDR-TB) patients. MDR-TB is known to strongly influence the nutritional status of TB patients. Second, TB patients under 18 years old were not included in this study, and there were significant differences in efficacy and side effects between children and adults after medication.[46] Future work can be further discussed for the occurrence and development of TB in special populations. Thirdly, this study evaluated the occurrence of persistent malnutrition during the first month of treatment, and only included hospitalized patients; a longer follow-up study is needed to confirm our results.

Conclusion

In conclusion, persistent malnutrition within one month of treatment can adversely affect anti-TB treatment. we need to pay attention to the nutritional status during anti-TB treatment, and continuous monitoring and improvement of malnutrition would bring greater welfare and feedback for better effect of anti-TB therapy.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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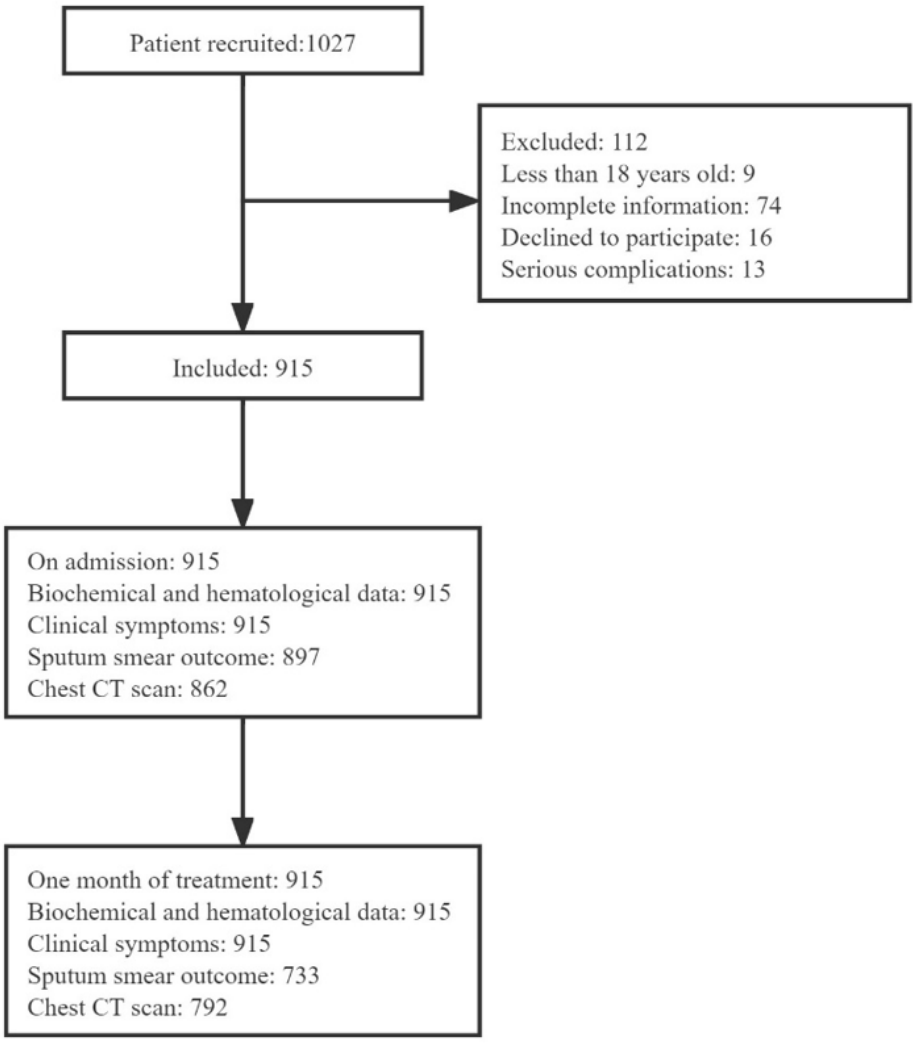


Figure 1. Flow chart of the study population

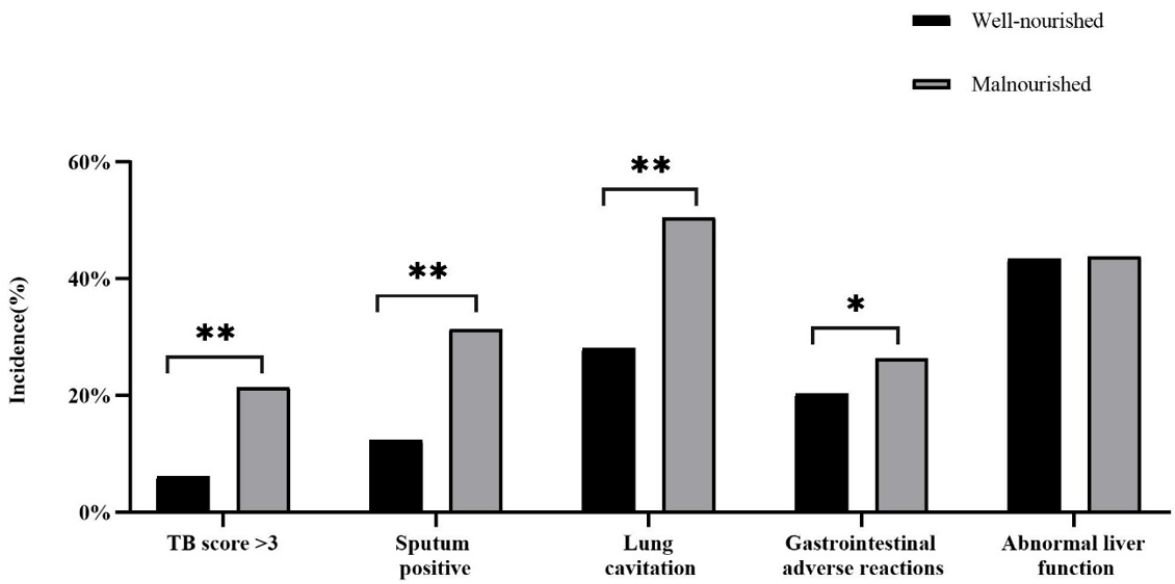


Figure 2. The treatment effect of pulmonary tuberculosis patients *p<0.05, **p<0.01

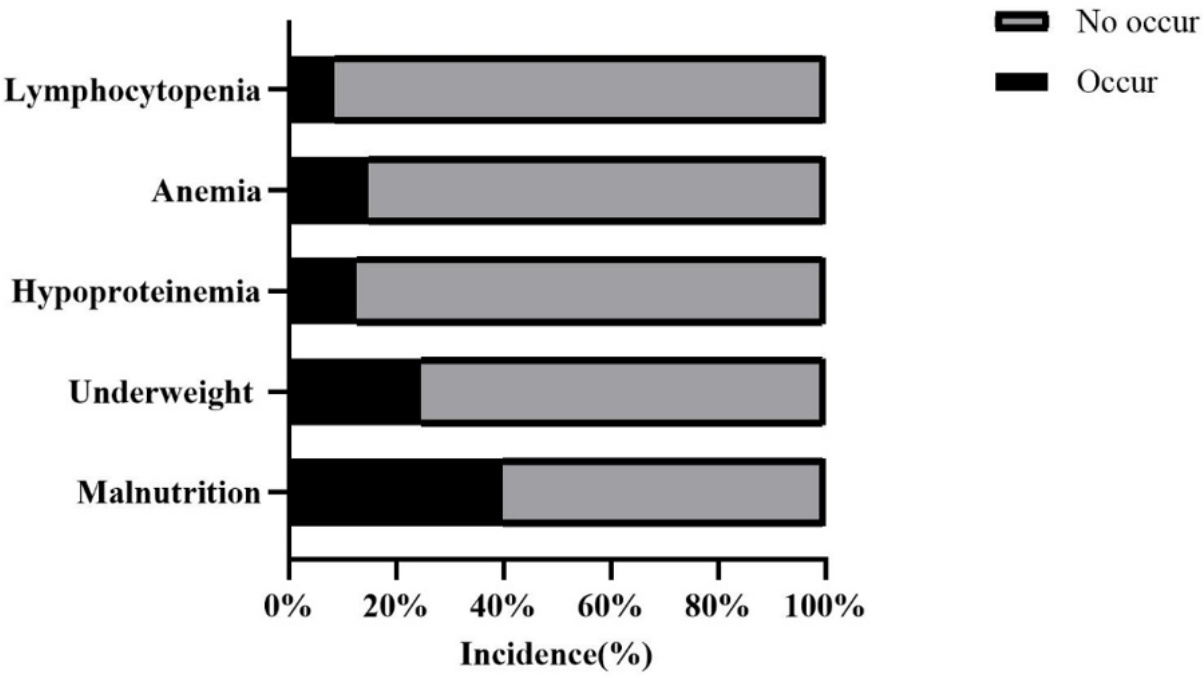


Figure 3. Nutritional status of pulmonary tuberculosis patients

Table 1. Baseline characteristics of study subjects (n=915)

Characteristic	All (n = 915)	Well-nourished (n = 550)	Malnourished (n = 365)	*p*
Age (years)				< 0.001
18 ~ 44	499 (54.5)	333 (60.5)	166 (45.5)	
45 ~ 64	270 (29.5)	167 (30.4)	103 (28.2)	
≥ 65	146 (16.0)	50 (9.1)	96 (26.3)	
Gender				0.477
Men	602 (65.8)	367 (66.7)	235 (64.4)	
Women	313 (34.2)	183 (33.3)	130 (35.6)	
Marital status				0.003
Married	607 (66.3)	369 (67.1)	238 (65.2)	
Single	269 (29.4)	168 (30.5)	101 (27.7)	
Widowed/Divorced	39 (4.3)	13 (2.4)	26 (7.1)	
Smoking				0.046
No	551 (60.2)	346 (62.9)	205 (56.2)	
Yes	364 (39.8)	204 (37.1)	160 (43.8)	
Drinking				0.362
No	581 (63.5)	356 (64.7)	225 (61.6)	
Yes	334 (36.5)	194 (35.3)	140 (38.4)	
Diabetes				0.827
No	818 (89.4)	493 (89.6)	325 (89.0)	
Yes	97 (10.6)	57 (10.4)	40 (11.0)	

BMI: body mass index.
Data are presented as n (%).

Table 2. The association between underweight and the outcome of one-month anti-TB treatment

Group	Crude model †		Model 1 ‡	
	OR (95%CI)	*p* §	OR (95%CI)	*p* §
TB score >3				
Non-underweight	Reference	<0.001	Reference	<0.001
Underweight	3.85 (3.03,4.88)		2.95 (2.28,3.82)	
Sputum positive				
Non-underweight	Reference	0.001	Reference	0.850
Underweight	1.49 (1.17,1.89)		1.03 (0.78,1.35)	
Lung cavitation				
Non-underweight	Reference	0.001	Reference	0.020
Underweight	1.46 (1.17,1.83)		1.36 (1.05,1.76)	
Gastrointestinal adverse reactions				
Non-underweight	Reference	0.002	Reference	0.225
Underweight	1.45 (1.15,1.82)		1.17 (0.91,1.49)	
Abnormal liver function				
Non-underweight	Reference	0.443	Reference	0.252
Underweight	0.91 (0.73,1.15)		0.87 (0.68,1.11)	

OR: odds ratio; CI: confidence interval.
†Crude model unadjusted.
‡Model 1 adjusted for age, gender, smoking, drinking, marital status, diabetes, total protein, albumin, and hemoglobin.
§Generalized estimation equation.

Table 3. The association between hypoproteinemia and the outcome of one-month anti-tuberculosis treatment

Group	Crude model †		Model 1‡	
	OR (95%CI)	*p*§	OR (95%CI)	*p*§
TB score >3				
Non-hypoproteinemia	Reference	<0.001	Reference	<0.001
Hypoproteinemia	4.14 (3.25,5.27)		2.73 (2.08,3.59)	
Sputum positive				
Non-hypoproteinemia	Reference	<0.001	Reference	<0.001
Hypoproteinemia	3.52 (2.77,4.48)		2.69 (2.08,3.49)	
Lung cavitation				
Non-hypoproteinemia	Reference	<0.001	Reference	0.436
Hypoproteinemia	1.23 (1.10,1.39)		1.05 (0.92,1.21)	
Gastrointestinal adverse reactions				
Non-hypoproteinemia	Reference	<0.001	Reference	<0.001
Hypoproteinemia	2.62 (2.07,3.30)		2.13 (1.65,2.75)	
Abnormal liver function				
Non-hypoproteinemia	Reference	0.016	Reference	0.020
Hypoproteinemia	1.34 (1.06,1.69)		1.37 (1.05,1.79)	

OR: odds ratio; CI: confidence interval.
†Crude model unadjusted.
‡Model 1 adjusted for age, gender, smoking, drinking, marital status, diabetes and BMI.
§Generalized estimation equation.

Table 4. The association between anemia and the outcome of one-month anti-tuberculosis treatment

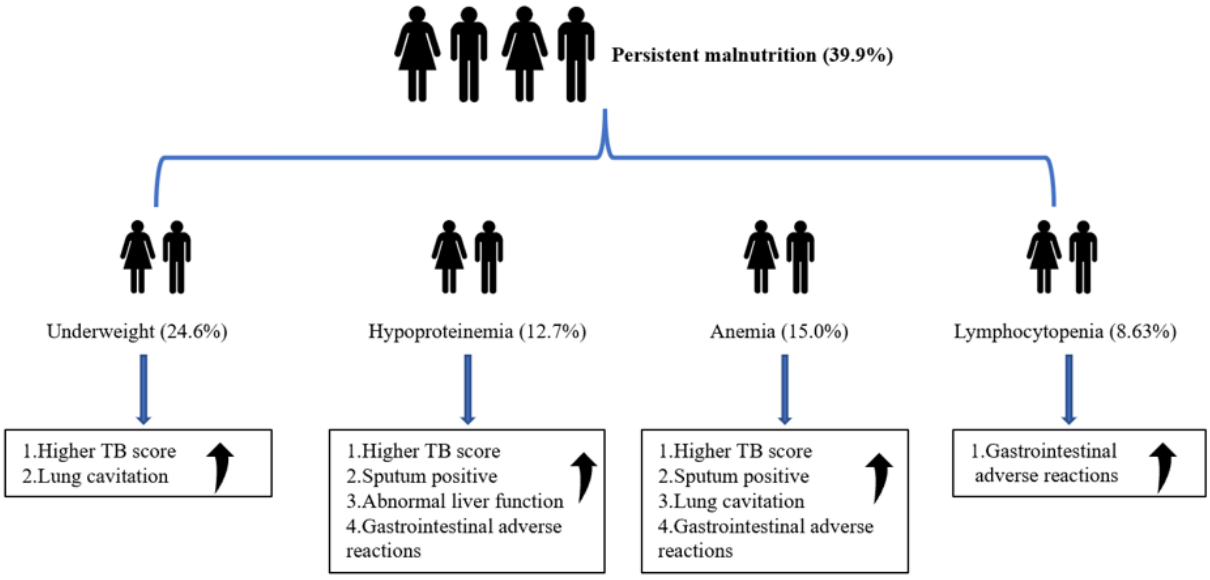
Group	Crude model †		Model 1‡	
	OR (95%CI)	*p*§	OR (95%CI)	*p*§
TB score >3				
Non-anemia	Reference	<0.001	Reference	<0.001
Anemia	2.59 (2.02,3.32)		1.73 (1.33,2.26)	
Sputum positive				
Non-anemia	Reference	<0.001	Reference	<0.001
Anemia	2.69 (2.12,3.43)		2.23 (1.72,2.88)	
Lung cavitation				
Non-anemia	Reference	<0.001	Reference	<0.001
Anemia	1.49 (1.30,1.71)		1.39 (1.19,1.63)	
Gastrointestinal adverse reactions				
Non-anemia	Reference	<0.001	Reference	0.002
Anemia	1.88 (1.49,2.40)		1.50 (1.16,1.93)	
Abnormal liver function				
Non-anemia	Reference	0.959	Reference	0.516
Anemia	1.01 (0.79,1.29)		1.09 (0.84,1.42)	

OR: odds ratio; CI: confidence interval.
†Crude model unadjusted.
‡Model 1 adjusted for age, gender, smoking, drinking, marital status, diabetes and BMI.
§Generalized estimation equation.

Table 5. The association between lymphocytopenia and the outcome of one-month anti-tuberculosis treatment

Group	Crude model †		Model 1‡	
	OR (95%CI)	*p*§	OR (95%CI)	*p*§
TB score >3				
Non-lymphocytopenia	Reference	0.006	Reference	0.179
Lymphocytopenia	1.40 (1.10,1.77)		1.18 (0.93,1.51)	
Sputum positive				
Non-lymphocytopenia	Reference	0.031	Reference	0.524
Lymphocytopenia	1.28 (1.02,1.60)		1.08 (0.85,1.36)	
Lung cavitation				
Non-lymphocytopenia	Reference	0.021	Reference	0.172
Lymphocytopenia	1.18 (1.03,1.36)		1.12 (0.95,1.30)	
Gastrointestinal adverse reactions				
Non-lymphocytopenia	Reference	<0.001	Reference	0.001
Lymphocytopenia	1.59 (1.27,1.98)		1.47 (1.17,1.83)	
Abnormal liver function				
Non-lymphocytopenia	Reference	0.939	Reference	0.738
Lymphocytopenia	0.99 (0.80,1.23)		0.96 (0.77,1.20)	

OR: odds ratio; CI: confidence interval.
†Crude model unadjusted.
‡Model 1 adjusted for age, gender, smoking, drinking, marital status, diabetes and BMI.
§Generalized estimation equation.



Graphical abstract