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CD8 T Cell Count was not Associated with the Severity of Pulmonary Tuberculosis

Min Qi#, Xi Xiang#, Quan-Xian Liu, Dao-Yan Tang, Jian-Qing He*

#Both authors contributed equally to this work

Department of Pulmonary and Critical Care Medicine, West China Hospital, Sichuan University, Chengdu, 610041, People's Republic of China

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***For Correspondence:**
Jian-Qing He, Department of Pulmonary and Critical Care Medicine, West China Hospital, Sichuan University, No. 37 Guoxue Alley, Chengdu, 610041, People's Republic of China
E-mail: jianqing_he@scu.edu.cn

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ABSTRACT

Purposes: Tuberculosis is still a global health threat, among those, severe pulmonary tuberculosis causes significant mortality. CD8 T cell plays an important role in the pathogenesis of tuberculosis. However, the association between CD8 T cell count and the severity of Pulmonary TB (PTB) has not been evaluated.

Methods: Patients admitted to a tertiary hospital from January 2013 to December 2017 and diagnosed as PTB with T cell subtypes tested were screened for recruitment. We compared the demographics and clinical manifestations between severe PTB patients and non-severe PTB patients, then analyzed the independent risk factors related to severe PTB after adjusting covariates.

Results: There were 279 patients enrolled for analysis, 180 patients were severe PTB (64.5%) and 99 patients were non-severe PTB (35.5%). Through univariate and multivariate analysis, lung cavity (aOR 4.631, 95% CI [1.798-12.853], P=0.002) and albumin (aOR 0.952, 95% CI [0.905-1.000], P=0.05) were associated severe PTB. While CD4 T cell count (aOR 1.00, 95% CI [0.999-1.001], P=0.794), CD8 T cell count (aOR 1.00, 95% CI [0.999-1.001], P=0.973), and lymphocyte (aOR 0.82, 95% CI [0.389-1.774], P=0.603) were not associated with severe PTB.

Conclusion: Lung cavity and lower albumin level were related with an increased risk of severe PTB, while CD4, CD8 T cells count and lymphocytes were not with the severity of PTB. May be not the count, but the function of T cells plays a crucial role in the pathogenesis of tuberculosis.

Keywords: Pulmonary tuberculosis; Severe tuberculosis; CD8 T cell; CD4 T cell; Lymphocyte; Pathogenesis

INTRODUCTION

Tuberculosis (TB) is an old infectious disease that is still one of the leading causes of death from a single infectious agent globally during the COVID-19 pandemic, killing over 1 million people around the world each year [1]. The pathogenic bacteria of TB is *Bacillus Mycobacterium tuberculosis* (M.tb), which is spread between people through inhaling aerosols expelled by coughing from the sick, especially for those who cough lasting for 2 weeks. It is reported that nearly a quarter of the world's population is infected with M.tb while staying in a clinically silent state with no elimination of the infection but no clinical signs of diseases and no contagiousness [2], namely, the Latent TB Infection (LTBI). All people with LTBI are at risk of progressing to active TB during their lifetime, but only 5%-10% of LTBI will develop into an active disease eventually. The clear mechanism of the complicated host-pathogen interaction is still unknown.

During the infection process, innate immunity and adaptive immunity play distinct roles in the defense and elimination of M.tb [3]. While adaptive immunity, mediated by T lymphocytes, is the determined factor of the outcome and TB severity [4]. CD4 T cells and CD8 T cells are the two major components of T lymphocytes, there is sufficient evidence supporting that CD4 T cells release cytokines, such as interferon-γ (IFN-γ) in response to M.tb specific antigens to enhance the phagocytosis of macrophage [5-7] to control TB, mice, and macaques with depleted CD4 T cells or humans with deficient CD4 T cells, particularly those with HIV, are dramatically susceptible to reinfection of TB or progress into active TB from LTBI [8]. While CD8 T cells were initially thought not as necessary as CD4 T cells in response to TB infection, now it has been recognized that they also play a critical and complex role [9]. CD8 T cells have the potential to kill the M.tb infected macrophages depending on the production of perforin, expression of granzymes, and granulysins [9], moreover, CD8 T cells could release varieties of cytokines, including IFN- γ, TNF, IL-17, IL-6, IL-10, TGF- β [10] in active TB diseases [6], the IFN- γ produced by CD8 T cells is considered as an important cytokine in the defense of TB. However, the roles of other cytokines produced by CD8 T cells are still not exactly known [9]. In the study of CD4 T cells, Mthembu et al., found that CD4 count was independently associated with the production of IFN- γ no matter the HIV status [11], and in HIV patients were more likely presented with disseminated diseases and miliary infiltrates [12]. While in the study of CD8 T cells, the study in rhesus macaques showed that the depletion of CD8 T cells led to a decreased vaccine-induced immunity against tuberculosis [13]. Li et al., revealed that in HIV-negative TB patients, the proportion of CD8 T cells, rather than CD4 T cells, was positively associated with the prevalence of disseminated infection [14]. However, the association between CD8 T cell count and the severity of Pulmonary TB (PTB) has not been elucidated.

In this study, we sought to determine the risk factors (including CD8 T cells count) are associated with severe PTB, gaining better knowledge and timely identifying the high-risk patients to surveillance more intensively.

MATERIALS AND METHODS

Study design and severe pulmonary tuberculosis definition

Patients, admitted to a tertiary hospital from January 2013 to December 2017 and diagnosed with tuberculosis diseases with T cells subtypes tested, were screened for analysis. All participants were over the age of 18 and diagnosed as pulmonary tuberculosis with lung parenchymal involvement. Those without chest CT images during enrolled admission, with latent tuberculosis infection and obsolete pulmonary tuberculosis were excluded. Patients with repeated hospitalizations were analyzed with the first admission. The pulmonary tuberculosis was bacteriologically diagnosed (with sputum/bronchoalveolar lavage fluid/lung tissue confirmed tuberculosis nucleic acid and/or those sample culture positive) or clinically diagnosed by clinical symptoms and chest images after excluding other pulmonary diseases.

Severe pulmonary tuberculosis was defined if the patient met any one of the followings criteria:

1. At least three lung lobes involvement on CT scan.
2. With tuberculosis meningitis.
3. With hematogenous pulmonary tuberculosis.
4. The diameter of lung cavity over 4 centimeters, no matter the lung cavity numbers.
5. With hypoxemia respiratory failure (PaO_2/FiO_2<300 mmHg).

This study was approved by the ethics committee of the hospital and followed the principles of the declaration of Helsinki. And the written informed consent was waived by the ethics committee of West China Hospital of Sichuan University to use anonymized and retrospective data.

Clinical data collection

We collected the basic information including age, sex, Body Mass Index (BMI, calculated by weight (kg)/height (m^2)), the previous history of tuberculosis, the history of *Bacillus* Calmette-Guérin (BCG) vaccine, tobacco, and alcohol use. Underlying comorbidities, such as diabetes, chronic kidney diseases, hepatitis and liver cirrhosis, other infective and non-infective lung diseases (including chronic obstructive lung diseases, bronchitis, emphysema, interstitial lung diseases, bacteria pneumonia, fungal pneumonia, obstructive sleep apnea, nontuberculous mycobacteria, paragonimus, pneumoconiosis), HIV, autoimmune diseases, organ transplants, tumor history, and medications of steroids and immune-suppressants using were also recorded. In addition, patient's clinical symptoms, cavity size and numbers in chest computed tomography, laboratory tests of complete blood count, the ratio of neutrophil to lymphocyte (NLR) albumin, T cells subtypes and the status of sputum smear were included for analysis.

The lymphocyte subsets were measured by the BD FACSCanto II Flow Cytometer [Becton Dickinson (BD) Biosciences, Heidelberg, Germany], including $CD3^+$ T cell, $CD4^+$ T cell, $CD8^+$ T cell. Peripheral blood samples were obtained from each participant in the morning after fasting from midnight. Blood samples were transported to the laboratory shortly after acquiring and analyzed by board-certified laboratory technicians who were blind to the clinical information in the department of laboratory medicine of West China hospital, Sichuan University.

Statistics

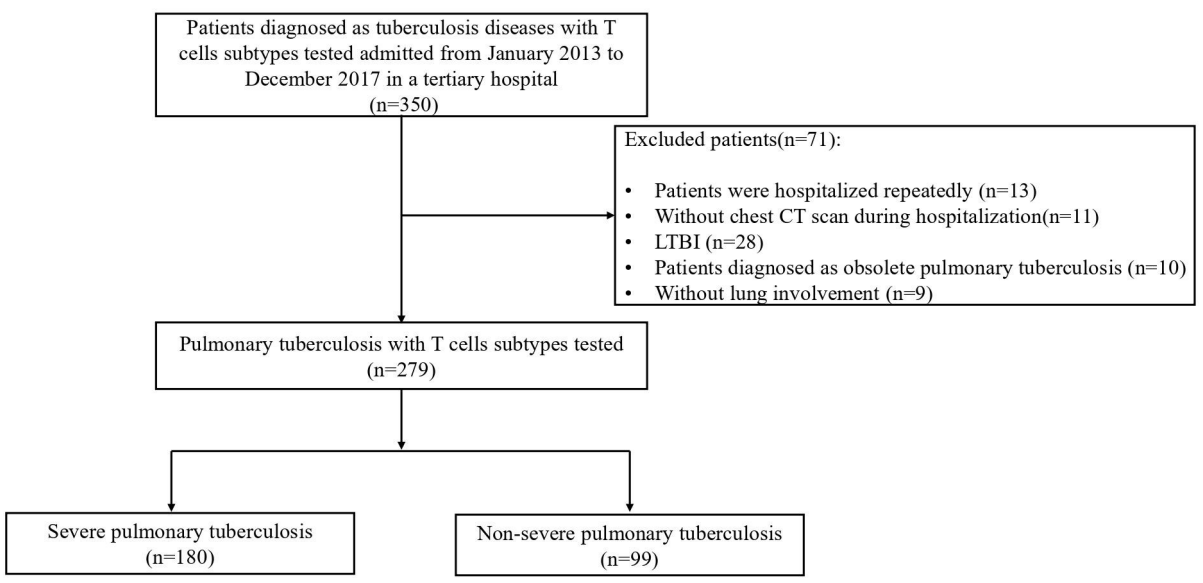
All statistics were analyzed by R software version 4.2.2 (https://www.r-project.org). Categorical variables were presented as counts with percentages, while non-normally and normally distributed continuous variables were expressed as medians with Interquartile Ranges (IQRs) or mean with Standard Deviations (SDs). Two group comparisons of continuous variables were using t-test or Wilcoxon rank sum test for normally distributed variables and non-normally distributed variables, respectively. Categorical variables were compared with the Chi-square test or Fisher's exact test. Variables included in the regression models were fewer than 1% of the subjects. We carried out the mean imputation for the missing BMI, and the median imputation for white blood cell count, lymphocyte count, and neutrophil count. To further evaluate the risk factors associated with severe pulmonary tuberculosis, variables in univariable analysis with P-value>0.1 were entered multi-variable logistic regression analysis after the exclusion of multi-collinearity of all covariates and the Box-Tidwell method used to test the linear relationship between continuous independent variables and dependent variable logit conversion values. All P-values were two-tailed with a significance level of 0.05.

RESULTS

Demographics of severe PTB and non-severe PTB

Of the 279 patients enrolled for analysis, 180 were severe pulmonary tuberculosis (64.5%) and 99 were non-severe pulmonary tuberculosis (35.5%) (Figure 1).

Figure 1. The flow chart of patient enrollment.



Among the severe PTB, there were 23 patients with comorbid tuberculosis meningitis, and 5 patients with hematogenous tuberculosis (data not shown). The median age of enrolled patients was 41 years old (Table 1), and there were 19 older patients (age ≥ 65) (6.8%).

Table 1. The characteristics of severe PTB and non-severe PTB.

Variables	Overall (n=279)	Severe PTB (n=180)	Non-severe PTB (n=99)	p-value
Age (years)	41 (28-51)	42 (29-52)	40 (27-48.5)	0.231
Age ≥ 65(%)	19 (6.8)	13 (7.2)	6 (6.1)	0.904
Female (%)	90 (32.3)	55 (30.6)	35 (35.4)	0.492
BMI (kg/m^2)	20.52 (18.42-22.04)	20.22 (18.05-21.30)	20.76 (19.42-22.69)	0.002
Previous TB (%)	51 (18.3)	35 (19.4)	16 (16.2)	0.605
Relapse (%)	51 (18.3)	33 (18.3)	18 (18.2)	1.0
BCG history (%)	112 (40.1)	72 (40.0)	40 (40.4)	1.0
Tobacco use (%)	110 (39.4)	79 (43.9)	31 (31.3)	0.054
Alcohol use (%)	39 (14.0)	31 (17.2)	8 (8.1)	0.054
Comorbidities (%)				
Diabetes (%)	35 (12.5)	27 (15.0)	8 (8.1)	0.139
CKD (%)	40 (14.3)	19 (10.6)	21 (21.2)	0.024
Hepatitis (%)	33 (11.8)	23 (12.8)	10 (10.1)	0.639
Liver cirrhosis (%)	9 (3.2)	6 (3.3)	3 (3.0)	1.0
Lung diseases (%)	38 (13.6)	32 (17.8)	6 (6.1)	0.011
HIV	59 (21.1)	38 (21.1)	21 (21.2)	1.0
Autoimmune diseases (%)	35 (12.5)	21 (11.7)	14 (14.1)	0.683
Malignancy (%)	10 (3.6)	9 (5.0)	1 (1.0)	0.168
Organ transplants (%)	17 (6.1)	7 (3.9)	10 (10.1)	0.07
Steroids & immune-supressants use (%)	55 (19.7)	31 (17.2)	24 (24.2)	0.21

Note: TB=Tuberculosis; PTB=Pulmonary Tuberculosis; BMI=Body Mass Index; BCG=*Bacillus* Calmette-Guerin vaccination; CKD=Chronic Kidney Disease; HIV=Human Immunodeficiency Virus.

Among all the participants, the male took up the majority (67.7%). The median BMI in severe PTB patients was lower than that in non-severe PTB (20.22 kg/m^2 *vs.* 20.76 kg/m^2, P=0.002). And compared with non-severe PTB patients, severe PTB patients were more associated with other lung diseases (38% *vs.* 21%, P=0.011). While the non-severe group with higher percentages of CKD diseases (10.6% *vs.* 21.2%, P=0.024). There was no significant difference in age, gender, history of previous TB, relapse rate, BCG, tobacco use, alcohol use, diabetes, hepatitis and liver cirrhosis, HIV, autoimmune diseases, tumor history, organ transplants, steroids and immune suppressants between the severe and non-severe PTB patients (p>0.05).

Clinical manifestations in severe PTB and non-severe PTB

Comparing the clinical symptoms between severe and non-severe PTB (Table 2), we found that severe PTB patients presented with higher rates of fever (65.6% *vs.* 48.5%, P=0.008), fever ≥ 39°C (50.6% *vs.* 34.3%, P=0.013), cough (58.3% *vs.* 31.3%, P<0.001), sputum (27.8% *vs.* 14.1%, P=0.015), dyspnea (11.7% *vs.* 3.0%, P=0.025). Other related symptoms, like weight loss, hemoptysis, night sweating, chest pain, and chest tightness were similar in those two groups (P>0.05).

Table 2. The clinical manifestations of severe PTB and non-severe PTB.

Variables	Overall (n=279)	Severe PTB (n=180)	Non-severe PTB (n=99)	p-value
Symptoms				
Fever (%)	166 (59.5)	118 (65.6)	48(48.5)	0.008
Fever ≥ 39 °C (%)	125 (44.8)	91 (50.6)	34(34.3)	0.013
Weight loss (%)	121 (43.4)	86 (47.8)	35(35.4)	0.06
Cough (%)	136 (48.7)	105 (58.3)	31(31.3)	<0.001
Sputum (%)	64 (22.9)	50 (27.8)	14(14.1)	0.015
Hemoptysis (%)	14 (5.0)	9 (5.0)	5(5.1)	1
Night sweat (%)	12 (4.3)	9 (5.0)	3(3.0)	0.64
Chest pain (%)	19 (6.8)	13 (7.2)	6(6.1)	0.904
Chest tightness (%)	11 (3.9)	5 (2.8)	6(6.1)	0.157
Dyspnea (%)	24 (8.6)	21 (11.7)	3(3.0)	0.025
Laboratory tests				
CD3 T cell count (cell/μL)	649 (378.5-1057)	585 (336.5-971.5)	793 (500-1178)	0.007
CD4 T cell count (cell/μL)	291 (120.5-510)	249.5 (85.5-471)	339 (187.5-565.5)	0.011
CD8 T cell count (cell/μL)	281 (169-449)	265.5 (147.25-435.75)	326 (192.5-511.5)	0.036
CD4/CD8	1.10 (0.60-1.71)	1.02 (0.58-1.70)	1.24 (0.72-1.88)	0.241
Hemoglobin(g/L)	110.36 ± 25.32	106.86 ± 25.09	116.72 ± 24.61	0.002
Lymphocyte (10^9/L)	0.96 (0.66-1.29)	0.91 (0.64-1.23)	1.05 (0.72-1.35)	0.009
WBC (× 10^9/L)	5.92 (4.26-8.25)	6.20 (4.44-8.81)	5.28 (4.18-6.75)	0.012
Neutrophils (× 10^9/L)	4.10 (2.82-6.52)	4.33 (3.00-7.14)	3.57 (2.45-4.93)	0.001
NLR	4.27 (2.77-7.73)	5.37 (3.17-8.63)	3.41 (2.15-5.46)	<0.001
Albumin(g/L)	33.7 (28.6-39.2)	32 (27.53-37.35)	37.6 (32.2-41.3)	<0.001
Smear-negative (%)	189 (67.7)	115 (63.9)	74 (74.7)	0.085
Chest images				
Cavity (%)	93 (33.3)	81 (45.0)	12 (12.1)	<0.001
Cavity numbers	0 (0-1)	0 (0-2)	0 (0)	<0.001

Note: WBC=White Blood Cell; NLR= the ratio of neutrophil to lymphocyte.

As for the laboratory tests, severe PTB patients with less median CD3 T cell count (585 cell/μL *vs* 793 cell/μL, P=0.007), CD4 T cell count (249.5 cell/μL *vs* 339 cell/μL, P=0.011), CD8 T cell count (265.5 cell/μL *vs.* 326 cell/μL, P=0.036), lymphocyte count (0.91 × 10^9/L *vs.* 1.05 × 10^9/L, P=0.009), mean hemoglobin level (106.86 ± 25.09

g/L *vs.* 116.72 ± 24.61 g/L, P=0.002) and median albumin (32 g/L *vs.* 37.6 g/L, P<0.001). However, severe PTB patients with higher median white blood cell (6.20 × 10^9/L *vs.* 5.28 × 10^9/L, P=0.12), neutrophil (4.33 × 10^9/L *vs.* 3.57 × 10^9/L, P=0.001), NLR (5.37 *vs.* 3.41, P<0.001). The CD4/CD8 and the percentage of smear-negative were not different significantly between severe and non-severe PTB (1.02 *vs.* 1.24, P=0.241), (63.9% *vs.* 74.7%, P=0.085), respectively.

After a comparison of chest CT images, we found the proportion of cavities was higher in the severe PTB patients (45% *vs.* 12.1%, P<0.001). The median cavity number between these two groups was similar, but the analysis was of significant difference (0(0-2) *vs.* 0(0), P<0.001).

In the severe PTB group (data not shown), there were 41 progressed into respiratory failure (22.8%), among them, 29 patients with invasive ventilation, 5 patients with non-invasive ventilation, and 7 patients with oxygen therapy. And 28 patients with invasive ventilation were transferred to the intensive care unit. While in the non-severe PTB, one patient was received invasive ventilation and admitted to ICU due to an epilepsy attack caused by cerebral cysticercosis.

Risk factors associated with severe PTB

After the univariable analysis, factors with P<0.1 were: BMI, alcohol use, smoking, accompany other lung diseases, CKD, organ transplantation, weight loss, fever, fever ≥ 39°C, cough, sputum, dyspnea, lung cavity, lung cavity numbers, CD3 cell count, CD4 cell count, CD8 cell count, white blood cell counts, neutrophil, lymphocyte, NLR, haemoglobin, albumin and smear negative. Then, the linear relationship between continuous independent variables and dependent variable logit conversion values was tested by the Box-Tidwell method (P>0.05). While the multi-collinearity between all covariates was assessed by the Variance Inflation Factor (VIF). The primary analysis of all variates showed the VIFs of CD3, CD4, CD8 and white blood cell count, neutrophils were more than 10, which suggested the existence of multi-collinearity. According to clinical implications, we ruled out CD3 and white blood cell factors with the other factors reserved. The left factors underwent the VIF check again with all the VIFs less than 3, indicating the absence of multi-collinearity. The remaining 22 covariates were used to conduct a logistic regression model (Table 3), we found the model was statistically significant (χ^2=89.247, P<0.001). Lung cavity (aOR 4.631, 95% CI [1.798-12.853], P=0.002) and albumin (aOR 0.952, 95% CI [0.905-1.000], P=0.05) were associated with severe PTB. While CD4 T cell count (aOR 1.00, 95% CI [0.999-1.001], P=0.794), CD8 T cell count (aOR 1.00, 95% CI [0.999-1.001], P=0.973), and lymphocyte (aOR 0.82, 95% CI [0.389-1.774], P=0.603) were not associated with severe PTB after adjusting covariates.

Table 3. Multi-variable analysis of risk factors associated with severe PTB.

Variables	B	S.E.	Wald	p-value	aOR (95% CI)
Lung disease	0.451	0.576	0.612	0.434	1.57 (0.527-5.187)
CKD	-0.752	0.484	2.412	0.12	0.472 (0.18-1.213)
Organ transplants	-0.382	0.709	0.291	0.59	0.682 (0.167-2.758)
Smear-negative	-0.026	0.359	0.005	0.942	0.974 (0.48-1.973)
Weight loss	0.015	0.323	0.002	0.962	1.016 (0.536-1.914)
Fever	0.494	0.465	1.131	0.288	1.64 (0.664-4.145)
Fever ≥ 39°C	0.124	0.461	0.072	0.788	1.132 (0.452-2.776)
Alcohol use	0.865	0.531	2.653	0.103	2.374 (0.872-7.117)
Smoke use	-0.018	0.355	0.002	0.96	0.983 (0.488-1.972)
Cough	0.555	0.361	2.364	0.124	1.741 (0.862-3.567)
Sputum	0.1	0.482	0.043	0.836	1.105 (0.43-2.877)
Dyspnea	1.197	0.794	2.271	0.132	3.311 (0.772-18.623)
Cavity	1.533	0.498	9.484	0.002	4.631 (1.798-12.853)
Cavity number	0.039	0.077	0.255	0.614	1.04 (0.91-1.251)
CD4 T cell count	0	0.001	0.068	0.794	1.00 (0.999-1.001)
CD8 T cell count	0	0.001	0.001	0.973	1.00 (0.999-1.001)
Hemoglobin	-0.003	0.008	0.188	0.665	0.997 (0.982-1.012)
Neutrophils	0.068	0.071	0.922	0.337	1.07 (0.929-1.232)
Lymphocyte	-0.199	0.382	0.271	0.603	0.82 (0.389-1.774)
Albumin	-0.049	0.025	3.83	0.05	0.952 (0.905-1.000)
BMI	-0.055	0.049	1.273	0.259	0.946 (0.858-1.041)
NLR	0.041	0.045	0.805	0.369	1.042 (0.966-1.161)

Note: CKD=Chronic Kidney Disease; BMI=Body Mass Index; NLR= the ratio of neutrophil to lymphocyte.

DISCUSSION

TB continues to be a major global health threat, especially for those with disseminated diseases, lung cavities, respiratory failure, and tuberculosis meningitis, which are of poor outcomes and devastating mortality [15-17]. In this study, we analyzed the risk factors associated with severe PTB and found that the presence of lung cavity and lower albumin level were related with increased risk of severe PTB, while CD4, CD8 T cell count and lymphocytes were not with the severity of PTB.

Cavitation is a common manifestation of PTB, that was not only associated with the delayed sputum culture conversion, but also with increased the risk of disease transmission [16]. It was reported that the rate of cavitation was higher in patients with diabetes [18], but lower with HIV-positive patients [19] and renal transplants [20]. In our study, we found the existence of lung cavity significantly related to severe PTB, which was consistent with previous studies [21,22]. Some studies defined moderate or advanced diseases as the cavitation over 4 cm [23,24], which was based on the classification system of the U.S. National Tuberculosis and Respiratory Disease Association formulated nearly 50 years ago, but the latest definition of the severity of TB that targets the current PTB spectrum and image patterns was absent. The finding in our study that the presence of a lung cavity rather than a cavity up to 4 cm would provide some advice for the evaluation of severe PTB. Because the manifestation of the TB cavity is heterogeneous, patients may present with a single cavity or multiple cavities, and the adjoining small cavities would fuse into larger cavities [16].

Tuberculosis is a kind of severe wasting disease. Albumin is synthesized exclusively by the liver, playing an important role in sustaining colloidal osmotic pressure and carrying proteins. During TB infection, the high inflammatory state makes the albumin leak from the intravascular space and patients with poor appetite, causing the lower of albumin. Therefore, the lower the albumin indicating more severe the illness [25] and related to mortality. Similarly, our study found that lower albumin was associated with severe PTB.

The mechanisms of infection by M.tb to active TB disease are complex. From patients with comorbidities that modulate host immune function, like HIV infection, diabetes, and undernourishment [1], are more susceptible to TB, it is not hard to deduce lymphocytes, especially CD4 T cells and CD8 T cells act as crucial roles in the disease onset and progression. And in our study, we found the lymphocyte count, CD4 T cells count and CD8 T cells count were lower in the severe PTB group, but they were not associated with the severity of PTB after adjusting covariates. Actually, the immune response to TB infection is complicated. So it may be not appropriate to judge the outcome by the immune cell count. Flynn et al. proposed that immune cells and immune response interact with and influence the outcome of TB infection [6]. There are many types of T cells playing different functions that may contribute to the protection or exacerbation of diseases. The balance of T cell response and T cell count is effective in controlling infection and restricting inflammation [26,27]. Besides, the normal number of T cells was not equal to normal functions. The research found that chronic infections by viruses and bacteria led the continuous exposure to antigens, causing the overexpression of inhibitory receptors, such as PD-1 [28,29], CTLA-4 [30], Tim-3 [31], and Lag-3 [32] on the surface of CD4 T cells and CD8 T cells, which could reduce the release of cytokines by T cells and impair the functions of T cells [33]. The phenomenon was called T cell exhaustion, which was associated with the severity of PTB [31,32].

There are several limitations in our study. Firstly, it was a single-center retrospective observatory research, that leading the selection bias. In addition, we only assess the count of peripheral venous blood lymphocytes and T cells, the subtypes of CD4 T cells and CD8 T cells, the surface and intracellular molecular in those T cells, and even the immune cells in lung lesions can be used to analyze in the future to better understanding the complex immune responses between host and M.tb Last but not least, we did not perform the follow-up, thus, the association between T cells and outcomes, and the changes in T cells after anti-tuberculosis treatment could not be evaluated.

CONCLUSION

In our study, the different characteristics of severe PTB and non-severe PTB were compared. After adjusted covariates, lung cavity and lower albumin level were related with an increased risk of severe PTB, while CD4, CD8 T cells count and lymphocytes were not with the severity of PTB. The subtypes of CD4 T cells and CD8 T cells, the surface and intracellular molecular in those T cells could be evaluated in the future to clarify the function of T cells.

DECLARATIONS

Funding and competing interests

This work was supported by the National Natural Science Foundation of China (Grant No. 81870015) in clinical data collection and data analysis. The authors declare that there is no competing interest.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics approval and informed consent statement

This study was approved by the ethics committee of West China hospital of Sichuan University and followed the principles of the declaration of Helsinki. And the written informed consent was waived by the ethics committee of West China hospital of Sichuan University to use anonymized and retrospective data.

Author contributions

M.Q. and X.X. both contributed to the study concepts and design, clinical studies and data analysis and manuscript preparation. QX.L. and DY.T were the contributors of manuscript review and editing. JQ.H was the guarantor of the integrity of the entire study and contributed to the conception of the study and manuscript editing. All authors read and approved the final manuscript.

REFERENCES

1. Global tuberculosis report 2022. Geneva: World Health organization. 2022.
2. Houben RMGJ, et al. The global burden of latent tuberculosis infection: A re-estimation using mathematical modelling. PLoS Med. 2016;13:e1002152.
3. Liu CH, et al. Innate immunity in tuberculosis: Host defense *vs* pathogen evasion. Cell Mol Immunol. 2017;14:963-975.
4. Wang Y, et al. Systemic immune dysregulation in severe tuberculosis patients revealed by a single-cell transcriptome atlas. J Infect. 2023;86:421-438.
5. Cooper AM, et al. The protective immune response to *Mycobacterium tuberculosis*. Curr Opin Immunol. 1995;7:512-516.
6. Flynn JL, et al. Immune cell interactions in tuberculosis. Cell. 2022;185:4682-4702.
7. Jasenosky LD, et al. T cells and adaptive immunity to *Mycobacterium tuberculosis* in humans. Immunol Rev. 2015;264:74-87.
8. Regional response plan for TB-HIV 2017-2021. World Health Organization. 2017.
9. Lin PL, et al. CD8 T cells and *Mycobacterium tuberculosis* infection. Semin Immunopathol. 2015;37:239-249.
10. Silva BDS, et al. Different phenotypes of CD8+ T cells associated with bacterial load in active tuberculosis. Immunology Letters. 2014;160:23-32.
11. Mthembu M, et al. Discrepancy between Mtb-specific IFN- γ and IgG responses in HIV-positive people with low CD4 counts. EBioMedicine. 2023;90:104504.
12. Lyon SM, et al. Pulmonary tuberculosis. Microbiol Spectr. 2017:5.
13. Chen CY, et al. A critical role for CD8 T cells in a nonhuman primate model of tuberculosis. PLoS Pathog. 2009;5:e1000392.
14. Li Q, et al. The association of peripheral T lymphocyte subsets disseminated infection by *Mycobacterium tuberculosis* in HIV-negative patients: A retrospective observational study. Medicina (Kaunas). 2022;58:1606.
15. Huynh J, et al. Tuberculous meningitis: Progress and remaining questions. Lancet Neurol. 2022;21:450-464.
16. Urbanowski ME, et al. Cavitary tuberculosis: The gateway of disease transmission. Lancet Infect Dis. 2020;20:e117-e128.
17. Kim YJ, et al. Pulmonary tuberculosis with acute respiratory failure. Eur Respir J. 2008;32:1625-1630.

18. Zhang L, et al. Risk factors for pulmonary cavitation in tuberculosis patients from China. Emerg Microbes Infect. 2016;5:e110.
19. Munthali L, et al. The effect of HIV and antiretroviral therapy on characteristics of pulmonary tuberculosis in northern Malawi: A cross-sectional study. BMC Infect Dis. 2014;14:107.
20. Pereira M, et al. High-resolution CT findings of pulmonary *Mycobacterium tuberculosis* infection in renal transplant recipients. Br J Radiol. 2016;89:20150686.
21. Koo HK, et al. Cluster analysis categorizes five phenotypes of pulmonary tuberculosis. Sci Rep. 2022;12:10084.
22. Kim S, et al. Mortality and predictors in pulmonary tuberculosis with respiratory failure requiring mechanical ventilation. Int J Tuberc Lung Dis. 2016;20:524-529.
23. Sousa J, et al. *Mycobacterium tuberculosis* associated with severe tuberculosis evades cytosolic surveillance systems and modulates IL-1β production. Nat Commun. 2020;11:1949.
24. Berry MPR, et al. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. Nature. 2010;466:973-977.
25. Bhurayanontachai R, et al. Factors influencing development and mortality of acute respiratory failure in hospitalized patient with active pulmonary tuberculosis: A 10-year retrospective review. J Thorac Dis. 2016;8:1721-1730.
26. Gideon HP, et al. Variability in tuberculosis granuloma T cell responses exists, but a balance of pro- and anti-inflammatory cytokines is associated with sterilization. PLoS Pathog. 2015;11:e1004603.
27. Kauffman KD, et al. PD-1 blockade exacerbates *Mycobacterium tuberculosis* infection in rhesus macaques. Sci Immunol. 2021;6:eabf3861.
28. Lu YJ, et al. CD4 T cell help prevents CD8 T cell exhaustion and promotes control of *Mycobacterium tuberculosis* infection. Cell Rep. 2021;36:109696.
29. Singh A, et al. Programmed death-1^{+} T cells inhibit effector T cells at the pathological site of miliary tuberculosis. Clin Exp Immunol. 2017;187:269-283.
30. Cai H, et al. Immune checkpoints in viral infections. Viruses. 2020;12:1051.
31. Wang X, et al. Elevated expression of Tim-3 on CD8 T cells correlates with disease severity of pulmonary tuberculosis. J Infect. 2011;62:292-300.
32. Chen J, et al. The elevated expression of LAG-3 on CD8+T cells correlates with disease severity of pulmonary TB. Microb Pathog. 2023;179:106089.
33. Pan J, et al. Landscape of exhausted T cells in tuberculosis revealed by single-cell sequencing. Microbiol Spectr. 2023;14:e0283922.