



# Risk factors for respiratory failure after tuberculosis-destroyed lung surgery and increased dyspnea score at 1-year follow-up

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**Background:** Although pneumonectomy is an important surgical treatment for tuberculosis-destroyed lung (TDL), few studies have investigated long-term postoperative TDL prognosis. Here, risk factors were determined for postoperative secondary respiratory failure and modified British Medical Research Council (mMRC  $\geq 1$ ) at discharge and at 1-year post-surgical follow-up.

**Methods:** A two-way cohort study was conducted of 116 patients admitted to our thoracic surgery department for surgical TDL treatment from January 2001 to June 2020. General clinical data were collected then patient postoperative mMRC scores were monitored for 1 year. Dyspnea-associated factors (mMRC  $\geq 1$ ) were identified then risk factors for postoperative respiratory failure and compromised long-term respiratory function were identified using multivariate adjusted logistic regression analysis.

**Results:** Of 116 patients, 27.6% (32/116) developed respiratory failure secondary to surgery. Multifactorial logistic regression analysis revealed that preoperative serum albumin of  $< 30$  g/L [adjusted odds ratios (aOR) 6.613, 95% confidence intervals (CI): 1.064–41.086] and intraoperative bleeding of  $> 1,000$  mL (aOR 6.876, 95% CI: 1.236–38.243) were risk factors for subsequent respiratory failure only in patients experiencing postoperative secondary respiratory failure. Sorting of patient mMRC dyspnea index scores into two groups (mMRC = 0, mMRC  $\geq 1$ ) followed by logistic regression analysis revealed that risk factors for 1-year postoperative dyspnea included mMRC score  $\geq 1$  at discharge (aOR 14.446, 95% CI: 1.102–189.361) and postoperative respiratory failure occurrence (aOR 9.946, 95% CI: 1.063–93.034).

**Conclusions:** TDL patient preoperative hypoalbuminemia and extensive intraoperative bleeding were risk factors for postoperative secondary respiratory failure. Postoperative secondary respiratory failure and high mMRC ( $\geq 1$ ) at discharge were associated with reduced postoperative long-term recovery of respiratory function.

**Keywords:** Tuberculosis-destroyed lung (TDL); surgical treatment; postoperative; respiratory failure; modified British Medical Research Council (mMRC)

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## Introduction

Although treatments with highly effective anti-tuberculosis (TB) drugs have improved pulmonary tuberculosis cure rates, challenges of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are of increasingly concern, as are co-infections with aspergillus or (1-3). Consequently, 40.3% to 66.7% of TB patients will develop extensive pulmonary damage detected as lung structural changes (4,5). Of these patients, 1.3% will develop TB-destroyed lung (TDL) manifesting as extensive destruction of lung parenchyma, irreversible lung function deficits, and reduced ventilation/perfusion ratio (6). TDL patients are commonly hypoxic and prone to secondary infections and recurrent hemoptysis which, in severe cases, lead to significantly impaired lung function and respiratory distress (7,8). As an additional challenge, chemotherapeutic treatment for TDL is ineffective (9). However, surgical treatment can benefit some TDL patients, including those with recurrent positive test results for sputum TB bacilli that either fail to revert to negative or repeatedly revert from negative to positive. In addition, emergency surgical treatment is administered to TDL patients with life-threatening hemoptysis.

Rates of postoperative complications of surgical treatment of TDL range from 5% to 33.3% (10-14), with postoperative mortality rates ranging from 0 to 7.7% (10-12,14,15) associated mainly with deaths due to respiratory failure (16,17). The purpose of this study was to clarify factors influencing the occurrence of respiratory failure soon after TDL surgery as well as respiratory distress occurring during the long-term postoperative period. These results should be useful for preventing and treating postoperative respiratory failure while also preserving or restoring long-term respiratory function. Therefore, we retrospectively analyzed risk factors for postoperative secondary respiratory failure in a population of 116 patients with postoperatively confirmed TDL pathology from January 2001 to June 2020 at Beijing Chest Hospital Affiliated with Capital Medical University based on prospective follow-up modified British Medical Research Council (mMRC) measured at discharge and at 1-year post-surgical follow-up for each patient. We present the following article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-22-610/rc>).

## Methods

### *Study design and participants*

This ambidirectional cohort study was conducted using retrospective data obtained from the electronic medical records system of Beijing Chest Hospital, Capital Medical University for TDL patients treated surgically in the thoracic surgery department from January 2001 to June 2020. In addition, prospective data were obtained from all TDL patients at discharge and at 1-year postoperative follow-up during the period from Jan 2001 to Jun 2021 (from the date when the first patient in the study was discharged to the date of completion of 1-year follow-up for the last discharged patient). In this study, TDL was defined as a pulmonary disease induced by TB sequelae involving destruction of one or more lobes of the lungs. TDL is diagnosed based on X-rays or chest computed tomography (CT) scan findings of coexistent fibrotic cavities and caseous foci with or without segmental atelectasis or bronchiectasis (12,18). Patients were diagnosed with respiratory failure based on partial pressure of oxygen readings of <60 Torr (1 Torr =0.133 kPa) and/or partial pressure of carbon dioxide (PaCO<sub>2</sub>) readings of >50 Torr accompanied by significant clinical symptoms of respiratory failure (19,20). Exclusion criteria included a medical history of bronchial asthma, chronic obstructive pulmonary disease, malignancy, and/or chronic cardiac insufficiency. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Beijing Chest Hospital (No. IORG0006551) and informed consent was taken from all the patients.

Patients were assigned to two groups, a respiratory failure group and a no respiratory failure group, based on post-surgical development of respiratory failure. Respiratory function was evaluated in all TDL patients at the end of the 1-year postoperative follow-up period based on mMRC criteria (21,22). Thirty-eight patients who were lost to follow-up or who did not respond to requests for follow-up were excluded from the final analysis, leaving 78 patients who completed follow-up in the prospective cohort; these patients were assigned to two groups with mMRC =0 (no respiratory distress group) and mMRC ≥1 (presence of respiratory distress) at the end of the 1-year postoperative follow-up period.

Importantly, TDL patients were evaluated to determine

whether they were afflicted with TB disease (caused by *Mycobacterium tuberculosis*) or lung infections with NTM. Diagnosis of mycobacterial infection was confirmed based on any of the following criteria: (I) positive result indicating the presence of acid-fast bacilli (AFB) in sputum; (II) sputum positive for *M. tuberculosis*; (III) pathological biopsy results of tissue samples showing granulomatous inflammation with caseous necrosis or positive histopathological examination results revealing the presence of AFB. A TB diagnosis was confirmed (and NTM infection ruled out) using standard methods, including growth on p-nitrobenzoic acid (PNB) identification medium and detection of MPT64 antigen, a key protein secreted by *M. tuberculosis*.

Surgical indications of TDL included: TDL located in the unilateral lung; sputum smear and/or sputum culture that were repeatedly positive for *Mycobacterium tuberculosis*; severe hemoptysis; repeated secondary infection associated with TDL; multidrug resistant pulmonary tuberculosis; and patient inability to tolerate anti-tuberculosis treatment. Routine preoperative clinical management included preoperative nutritional treatment, infusion of albumin and/or suspended red blood cells as necessary, adjustments of preoperative plasma albumin level to  $>30$  g/L and hemoglobin to  $>9$  g/L, as well as atomization and physical measures to promote sputum excretion. A panel of experts comprised of radiology, thoracic surgery, and anesthesiology specialists decided whether to carry out surgical treatment after discussing each patient's clinical status (23). All preoperative ancillary examinations were completed within 24 to 60 hours prior to surgery.

### **Retrospective data collection**

Demographic information included gender, age, BMI, smoking status, comorbidities, and mMRC score. BMI was based on the World Health Organization criteria for the Asia-Pacific region (24), which stipulates that a BMI of  $<18.5$  corresponds to low weight, a BMI of 18.5 to 24.9 corresponds to normal weight, and a BMI of  $\geq 25$  corresponds to obese weight status. Main comorbidities included hypertension (8 cases), coronary artery disease (8 cases), and diabetes mellitus (6 cases). Second-line antituberculosis regimens administered to patients included the following: Group A: fluoroquinolones (including levofloxacin, moxifloxacin, gatifloxacin) and clarithromycin. Group B: second-line injectable drugs, including amikacin, capreomycin, and streptomycin. Group C: other core second-line drugs, including cycloserine, prothiouracil, ethionamide,

clofazimine, and linezolid. Group D: bedaquiline, delamanid, para-aminosalicylic acid, amoxicillin-clavulanic acid potassium, aminothiurea, imipenem-cilastatin sodium, and meropenem.

For general clinical assessments, patients were assessed for the following: dyspnea at admission and at discharge according to mMRC score followed by patient assignments to two groups based on mMRC =0 and mMRC  $\geq 1$ ; adverse drug reactions experienced while taking anti-TB drugs; TDL accompanied by chronic co-infection with aspergillus presenting as chronic pulmonary aspergillosis (30 cases) or co-infection with NTM (3 cases).

Preoperative ancillary testing included chest CT scan analysis, pulmonary function testing, routine laboratory testing, and arterial blood gas analysis that were conducted 24 to 60 hours prior to surgery. For interpretation of chest CT scan results, patients were assigned to two groups based on the presence or absence of lesions in the contralateral lung. Pulmonary function was measured using a Master Screen-IOS and MasterScreen-PFT System (Jäger, Germany), while pulmonary diffusion function was measured using the one-breath diffusion method. Surgery-related information that was collected included intraoperative bleeding volume, operation time (duration), scope of surgery, and surgical approach. Intraoperative bleeding was assessed based on  $\leq 1,000$  and  $>1,000$  mL cutoff values; surgical duration was based on  $\geq 4$ -hour or  $<4$ -hour cutoffs; lesion resection type was scored as left or right lobe; lobectomy type was scored as with or without pleural dissection; pneumonectomy type was scored as left or right whole lung with pleural dissection; surgical approach was thoracoscopic in only one case, while all other cases involved thoracotomy.

### **Prospective data collection**

Follow-up observational data were collected through telephone interrogation by a health care provider after discharge. Written informed consent was obtained from each participant before follow-up. Follow-up assessments of respiratory function of all participants in the retrospective cohort were completed by the deadline of June 30, 2021. Ultimately, 34 patients were lost during the follow-up period because calls made to reach them using phone numbers they had provided were not successful after  $\geq 3$  attempts, for a loss rate of 30.3% (34/112), while 78 patients aged  $39.3 \pm 13.2$  years completed follow-up, including 33 males and 45 females.

### Statistical analysis

Means and standard deviations of normally distributed continuous variables were calculated and the numbers and proportions of categorical variables were tabulated. Univariate logistic regression models were used to compare correlations between different demographic characteristics, clinical examination findings, surgical information, and postoperative secondary respiratory failure status. Multivariate logistic regression models were used to analyze effects of risk factors of TDL patient postoperative respiratory failure and perioperative respiratory failure on patient postoperative long-term respiratory function. All statistical analysis procedures were completed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA).

## Results

### General demographic and clinical characteristics

A total of 116 patients with TDL were included as the retrospective cohort in this study, including 51 males and 65 females aged  $39.1 \pm 13.6$  years. It was 27.6% (32/116; 19 men, 13 women; ages  $42.8 \pm 15.5$  years) of the total number of patients that experienced secondary postoperative respiratory failure and 11.2% (13/116) required ventilatory support for severe respiratory failure secondary to surgery. For the latter group, duration of mechanical ventilation ranged from 12 to 360 hours and the mortality rate was 3.5% (4/116). Upon admission, dyspnea assessments based on mMRC scores revealed that 12 patients had mMRC scores of 0 (no dyspnea) and 104 patients had mMRC scores of  $\geq 1$  (dyspnea).

### Risk factors linked to postoperative respiratory failure in TDL patients

Univariate logistic regression analysis revealed that as compared to the group without postoperative respiratory failure, the respiratory failure group possessed higher proportions of males, current and/or former smokers, patients co-infected with chronic aspergillus or NTM, and patients receiving anti-tuberculosis treatments ( $P=0.015$ ,  $0.009$ ,  $0.008$ , and  $0.014$ , respectively) (Table 1). As compared to the group without postoperative respiratory failure, the respiratory failure group had higher preoperative C-reactive protein (CRP) values, lower preoperative values of albumin, and lower preoperative values of hemoglobin ( $P=0.025$ ,  $0.008$ , and  $0.014$ , respectively) (Table 2).

Blood transfusions were conducted for 64.7% (75/116) of patients using blood volumes ranging from 200 to 8,400 mL, for an average blood transfusion volume of 750 mL. Intraoperative blood loss of  $>1,000$  mL was noted in 32.8% (38/116) of patients, with intraoperative bleeding of  $>1,000$  mL observed in a greater proportion of patients in the respiratory failure group than in the no respiratory failure group ( $P=0.001$ ) (Table 3).

Based on results obtained using multivariate logistic analysis, risk factors for respiratory failure after TDL included a preoperative serum albumin level of  $<30$  g/L [adjusted odds ratios (aOR) 6.613, 95% confidence intervals (CI): 1.064–41.086] and an intraoperative bleeding volume of  $>1,000$  mL (aOR 6.876, 95% CI: 1.236–38.243) (Table 4).

### Perioperative death and follow-up

Three of four perioperative deaths occurring secondary to surgery resulted from postoperative bleeding leading to multiple organ failure, while one patient died from severe postoperative pulmonary infection. Seventy-eight patients completed a 1-year postoperative telephone follow-up interview by Jun 30, 2021. Of these patients, none died during the 1-year postoperative follow-up period, while 49 patients (62.8%, 49/78) had mMRC scores of 0 and 29 (37.2%, 29/78) patients had mMRC scores of  $\geq 1$ .

### Risk factors for dyspnea at the end of the 1-year follow-up period after TDL surgery

Results of multivariate logistic regression analysis revealed risk factors for occurrence of dyspnea at 1-year post-TDL surgery that included an mMRC score of  $\geq 1$  at discharge (aOR 14.446, 95% CI: 1.102–189.361) and the occurrence of respiratory failure after surgery (aOR 9.946, 95% CI: 1.063–93.034) (Table 5).

## Discussion

TDL, a typical outcome of severe pulmonary TB (8,10), poses treatment challenges due to the lack of treatment guidelines and expert consensus on optimal TDL management practices. Here our results indicated an incidence of respiratory failure after TDL surgery of 27.6% (32/116), which is similar to that reported in the literature (13). TDL surgery aims to improve patient quality of life by addressing massive hemoptysis, cavitation, co-infections with aspergillus or NTM, and ineffective

**Table 1** Univariate analysis of demographic and clinical characteristics of TDL patients stratified by respiratory failure

Variables	Total (n=116)	Non-respiratory failure group (n=84)	Respiratory failure group (n=32)	Crude OR (95% CI)	P value
Sex					
Female	65	53 (81.5)	12 (18.5)	Ref	
Male	51	31 (60.8)	20 (39.2)	2.849 (1.228–6.612)	0.015
Age group (years)					
≤60	113	83 (73.5)	30 (26.5)	Ref	
>60	3	1 (33.3)	2 (66.7)	5.533 (0.484–83.262)	0.169
BMI (kg/m <sup>2</sup> )					
18.5–24.9	78	59 (75.6)	19 (24.4)	Ref	
<18.5	25	14 (56.0)	11 (44.0)	2.440 (0.949–6.270)	0.064
≥25	13	11 (84.6)	2 (15.4)	0.565 (0.115–2.777)	0.482
Smoking history					
No	100	77 (77.0)	23 (23.0)	Ref	
Yes	16	7 (43.8)	9 (56.2)	4.304 (1.444–12.828)	0.009
Comorbidities					
No	94	71 (75.5)	23 (24.5)	Ref	
Yes	22	13 (59.1)	9 (40.9)	2.137 (0.809–5.645)	0.125
Second-line drugs	11	8 (72.7)	3 (27.3)	2.250 (0.304–16.632)	0.055
CPA/NTM					
No	83	66 (79.5)	17 (20.5)	Ref	
Yes	33	18 (54.5)	15 (45.5)	3.235 (1.358–7.708)	0.008
Take anti-TB drugs					
No	107	81 (75.7)	26 (24.3)	Ref	
Yes	9	3 (33.3)	6 (66.7)	6.231 (1.455–26.685)	0.014
mMRC (preoperative)					
0	12	9 (75.0)	3 (25.0)	Ref	
1	37	24 (64.9)	13 (35.1)	1.625 (0.373–7.702)	0.518
2	40	31 (77.5)	9 (22.5)	0.871 (0.194–3.914)	0.857
3	27	20 (74.0)	7 (26.0)	1.050 (0.220–5.020)	0.951

Data are presented as n (%), univariate logistic regression analysis was utilized. TDL, tuberculosis destroyed lung; OR, odds ratio; CI, confidence interval; BMI, body mass index, CPA/NTM, chronic pulmonary aspergillosis/non-tuberculous mycobacteria; TB, tuberculosis; mMRC, modified British Medical Research Council; Ref, reference.

ventilation leading to pulmonary-systemic shunts. Surgical resection of pulmonary tissue infected with large numbers of *M. tuberculosis* is helpful for preventing spread of bacilli in infected sputa to the opposite lung to prevent TB recurrence (25). Moreover, surgical removal of TB lesions

eliminates lesion-associated ineffective alveolar ventilation, improves the ventilation/perfusion ratio, alleviates tissue and organ hypoxia, and relieves dyspnea symptoms.

High intraoperative bleeding was the most prominent risk factor associated with subsequent development of

**Table 2** Univariate analysis of preoperative examination on TDL patients stratified to respiratory failure

Variables	Total (n=116)	Non-respiratory failure group (n=84)	Respiratory failure group (n=32)	Crude OR (95% CI)	P value
Contralateral pulmonary disease					
No	32	21 (65.6)	11 (34.4)	Ref	
Yes	84	63 (75.0)	21 (25.0)	0.636 (0.264–1.538)	0.315
Spinal scoliosis					
No	84	64 (76.2)	20 (23.8)	Ref	
Yes	32	20 (62.5)	12 (37.5)	1.920 (0.801–4.602)	1.444
Electrocardiogram					
Normal	70	51 (72.9)	19 (27.1)	Ref	
Abnormal	46	33 (71.7)	13 (28.3)	1.057 (0.461–2.426)	0.895
Leukocyte					
Normal	105	78 (74.3)	27 (25.7)	Ref	
Abnormal	11	6 (54.5)	5 (45.5)	2.407 (0.680–8.529)	0.173
Creatinine					
Normal	105	77 (73.3)	28 (26.7)	Ref	
Decreased	11	7 (63.6)	4 (36.4)	1.571 (0.427–5.78)	0.496
CRP					
Normal	37	32 (86.5)	5 (13.5)	Ref	
Increased	79	52 (65.8)	27 (34.2)	3.323 (1.162–9.505)	0.025
Albumin					
Normal	83	66 (79.5)	17 (20.5)	Ref	
Decreased	33	18 (54.5)	15 (45.5)	3.235 (1.358–7.708)	0.008
Hemoglobin					
Normal	107	81 (75.7)	26 (24.3)	Ref	
Decreased	9	3 (33.3)	6 (66.7)	6.231 (1.455–26.685)	0.014
Blood glucose					
Normal	101	76 (75.2)	25 (24.8)	Ref	
Increased	15	8 (53.3)	7 (46.7)	2.660 (0.876–8.075)	0.084
FEV <sub>1</sub> (%pred)		58.0±17.3	53.0±20.4	1.00 (0.956–1.013)	0.274
FEV <sub>1</sub> /FVC		77.1±11.6	70.0±15.3	0.96 (0.918–0.994)	0.024
Normal	111	81 (73.0)	30 (27.0)	Ref	
Increased	5	3 (60.0)	2 (40.0)	1.342 (0.535–3.362)	0.531
PaO <sub>2</sub> (Torr)					
Normal	102	74 (72.5)	28 (27.5)	Ref	
Decreased	14	10 (71.4)	4 (28.6)	1.057 (0.306–3.647)	0.930

Table 2 (continued)

**Table 2** (continued)

Variables	Total (n=116)	Non-respiratory failure group (n=84)	Respiratory failure group (n=32)	Crude OR (95% CI)	P value
PaCO <sub>2</sub> (Torr)					
Normal	89	67 (75.3)	22 (24.7)	Ref	
Increased	27	17 (63.0)	10 (37.0)	1.791 (0.716–4.485)	0.213

Data are presented as n (%), univariate logistic regression analysis was utilized. TDL, tuberculosis destroyed lung; OR, odds ratio; CI, confidence interval; CRP, C-reaction protein, reference value 0–5 mg/L; Albumin, reference value 35–55 g/L; Hemoglobin, reference value 110–150 g/L; pH value, reference value 7.35–7.45; PaO<sub>2</sub>, reference value 80–100 Torr; PaCO<sub>2</sub>, reference value 35–45 Torr; FEV<sub>1</sub> % pred, forced expiratory volume in one second of predicted; FEV<sub>1</sub>/FVC, the ratio of forced expiratory volume in one second to forced vital capacity; PaO<sub>2</sub>, partial pressure of oxygen; PaCO<sub>2</sub>, partial pressure of carbon dioxide; Ref, reference.

**Table 3** Univariate analysis of TDL patients during operation stratified to respiratory failure

Variables	Total (n=116)	Non-respiratory failure group (n=84)	Respiratory failure group (n=32)	Crude OR (95% CI)	P value
Operation time (hour)					
≤4	66	50 (76.8)	16 (23.2)	Ref	
>4	50	34 (60.0)	16 (40.0)	1.471 (0.649–3.334)	0.356
Bleeding volume (mL)					
≤1,000	78	64 (82.1)	14 (17.9)	Ref	
>1,000	38	20 (52.6)	18 (47.4)	4.114 (1.7421–9.724)	0.001
Surgical excision range					
Lobectomy of lungs	35	23 (65.7)	12 (34.3)	Ref	
Pneumonectomy with or without pleura	81	61 (75.3)	20 (24.7)	0.628 (0.266–1.487)	0.291

Data are presented as n (%), univariate logistic regression analysis was utilized. TDL, tuberculosis destroyed lung; OR, odds ratio; CI, confidence interval; Ref, reference.

**Table 4** Multivariate analysis of postoperative respiratory failure in patients with TDL

Variables	Adjusted OR (95% CI)	P value
Sex (male)	2.285 (0.225–23.230)	0.485
Age, years	0.996 (0.922–1.077)	0.924
BMI, kg/m <sup>2</sup>	0.734 (0.530–1.018)	0.064
Smoking (yes)	0.999 (0.082–12.151)	1.000
Albumin (yes)	6.613 (1.064–41.086)	0.043
Hemoglobin (yes)	0.833 (0.009–75.955)	0.937
CRP (yes)	1.551 (0.156–15.409)	0.708
FEV <sub>1</sub> (%pred)	1.010 (0.966–1.056)	0.656
DLCO (%pred)	1.006 (0.970–1.043)	0.757
PaO <sub>2</sub> (Torr)	0.989 (0.963–1.015)	0.403
Operation time (>4 hours)	0.457 (0.060–3.456)	0.448
Bleeding volume (>1,000 mL)	6.876 (1.236–38.243)	0.028

TDL, tuberculosis destroyed lung; OR, odds ratio; CI, confidence interval; BMI, body mass index; CRP, C-reaction protein; FEV<sub>1</sub> %pred, forced expiratory volume in one second of predicted; DLCO %pred, lung diffusion capacity of predicted; PaO<sub>2</sub>, partial pressure of oxygen.

**Table 5** Risk factors for dyspnea at the end of one year after TDL surgery

Variables	mMRC =0 group (n=49)	mMRC ≥1 group (n=29)	Crude OR (95% CI)	Adjusted OR (95% CI)
Sex				
Female	29 (59.2)	15 (51.7)	Ref	Ref
Male	20 (40.8)	14 (48.3)	1.353 (0.537–3.412)	1.357 (0.222–8.280)
Age (years)	37.0±12.7	40.3±14.9	1.034 (0.998–1.073)	1.057 (0.992–1.125)
Smoking history				
No	40 (81.6)	24 (82.8)	Ref	Ref
Yes	9 (18.4)	5 (17.2)	0.926 (0.278–3.089)	0.095 (0.005–1.847)
mMRC on discharge				
0	15 (30.6)	2 (6.9)	Ref	Ref
≥1	34 (69.4)	27 (93.1)	5.956 (1.252–28.329)	14.446 (1.102–189.361)
FEV <sub>1</sub> (%pred)	58.9 (50.2, 71.2)	51.4 (47.2, 64.6)	0.995 (0.966–1.025)	1.019 (0.971–1.070)
DLCO (%pred)	65.1 (51.0, 75.8)	57.1 (50.8, 77.4)	0.989 (0.963–1.016)	0.985 (0.954–1.016)
CPA or NTM				
No	33 (67.3)	19 (65.5)	Ref	Ref
Yes	16 (32.7)	10 (34.5)	1.086 (0.411–2.866)	0.356 (0.037–3.390)
Bleeding volume (mL)				
≤1,000	31 (63.3)	18 (36.7)		Ref
>1,000	22 (75.9)	7 (24.1)	0.548 (0.196–1.535)	0.212 (0.031–1.431)
Albumin				
Normal	35 (71.4)	21 (72.4)		Ref
Decreased	14 (28.6)	8 (27.6)	0.952 (0.342–2.650)	0.977 (0.150–6.378)
Respiratory failure				
No	37 (75.5)	19 (65.5)		Ref
Yes	12 (24.5)	10 (34.5)	1.623 (0.594–4.434)	9.946 (1.063–93.034)

Data are presented as n (%) or mean ± SD or interquartile range, univariate logistic regression analysis was utilized. TDL, tuberculosis destroyed lung; mMRC, modified British Medical Research Council; OR, odds ratio; CI, confidence interval; FEV<sub>1</sub> %pred, forced expiratory volume in one second of predicted; DLCO %pred, lung diffusion capacity of predicted; CPA or NTM, chronic pulmonary aspergillosis or non-tuberculosis mycobacteria; Ref, reference.

respiratory failure in this study cohort, as reflected by high OR values, while exudation of plasma components was also a potential risk factor, as reported previously (26). Intraoperative bleeding volume depends on the size of the region associated with surgical trauma and the severity of tissue adhesions, both of which are exacerbated in TDL patients. More specifically, TDL lesions often harbor severe, extensive adhesions resulting from recurrent infections. Moreover, lesions are surrounded by highly fragile edematous, exuding tissues that make intraoperative

adhesiolysis difficult, due to increased risk of serious blood loss that has been reported to be closely associated with increased risk of postoperative infection (27–29). Meanwhile, in clinical practice, intraoperative hemorrhage has been shown to frequently occur in association with transfusion therapy, with whole blood transfusion shown to significantly decrease lymphocyte proliferation, significantly increase the CD4<sup>+</sup>/CD8<sup>+</sup> ratio, and increase interleukin-6 levels, while also elevating the risk of postoperative infection (30). Furthermore, results of a study by AC Bernard and



colleagues showed that transfusion of 1 unit of whole blood significantly increased risks of 30-day mortality, pneumonia, and sepsis/shock (31). In addition, TDL surgical treatment may cause a certain percentage of patients to experience major bleeding requiring extensive blood transfusions that, in turn, may increase postoperative respiratory failure risk. Therefore, reducing intraoperative bleeding is an important strategy for reducing postoperative complications, especially with regard to postoperative secondary respiratory failure.

Due to the fact that albumin is the main plasma component responsible for maintaining colloid osmotic pressure, hypoproteinemia can cause pulmonary interstitial edema leading to postoperative respiratory failure. Here, our results were consistent with this fact by revealing that preoperative lower-than-normal serum albumin level was another risk factor for postoperative secondary respiratory failure, as reported previously (14). Meanwhile, chronic *M. tuberculosis* infection has been shown to be an important correlate of poor patient nutritional status and reduced body mass index (32). In fact, nutritional status in turn has been shown to influence TB disease course and prognosis (33), which mechanistically may be due to reduced cellular immune function (34) and hypoalbuminemia in malnourished patients that increase risks of secondary postoperative infections (35) and respiratory failure (36). Therefore, improving preoperative nutritional status and correcting preoperative hypoalbuminemia may help to reduce the incidence of postoperative respiratory failure.

Follow-up monitoring of patient respiratory function after TDL surgery in this study revealed that risk factors of postoperative secondary respiratory failure and mMRC score of  $\geq 1$  at discharge were associated with increased likelihood of having a mMRC score of  $\geq 1$  at 1-year post-surgical follow-up, suggesting that postoperative secondary respiratory failure can adversely affect long-term recovery of respiratory function in surgically treated TDL patients.

Our study had several limitations. First, this study was conducted as a two-way cohort study of a small number of cases selected retrospectively. The small case number resulted from low awareness of clinicians regarding use of surgical treatment for TDL, due to the absence of clinical treatment guidelines and other influential factors that exerted small effects that may have biased our results. Nevertheless, this study included all TDL cases admitted to our center over the course of 19 years as the largest sample size of surgically treated TDL patients to date. However, despite standardized training programs, levels of expertise of thoracic surgeons differ as a factor that could not be ignored

when correlating surgical measures (e.g., extent of surgical resection of the diseased lung, operation time, intraoperative bleeding) with the occurrence of postoperative respiratory failure. Thus, we still could not completely ignore potential biases related to surgical technique and slight differences in preoperative clinical management on our assessment of risks related to respiratory failure. Finally, although prospective follow-up of TDL respiratory function and investigational analysis of the effect of postoperative respiratory failure on long-term dyspnea were conducted in this study, lifestyle and psychiatric factors were not considered in the analysis, warranting further study.

In conclusion, our findings revealed that preoperative hypoalbuminemia and high intraoperative bleeding in TDL patients were independent risk factors for postoperative secondary respiratory failure. Moreover, postoperative secondary respiratory failure and mMRC score of  $\geq 1$  at discharge were associated with greater risk of acquiring a respiratory function-related mMRC score of  $\geq 1$  at the end of the 1-year postoperative follow-up period. Correcting preoperative hypoproteinemia and reducing intraoperative bleeding may help reduce secondary respiratory failure after TDL surgery to ultimately improve recovery of long-term postoperative respiratory function, thus improving long-term patient prognosis.

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## Footnote

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*Ethical Statement:* The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of Beijing Chest Hospital (No. IORG0006551) and informed consent was taken from all the patients.

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