

Peer Review File

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Reviewer A

1. Abstract:

Please clarify the background in more detail in the text. The conclusion is similar to the results in the abstract. In addition, there are some grammatical improprieties in the abstract

Reply1: Thanks for your constructive suggestion. We rewrote it according to your suggest, the changed part has been displayed in red font. See line 31-33, 35-42, 43-51.

Changes in the text:

① Objectives 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 dyspnea (mMRC ≥ 1) at discharge and at 1-year post-surgical follow-up, (See Page2, line 31-33).

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 (aOR 6.613, 95% CI: 1.064-41.086) and intraoperative bleeding of >1000 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 ≥ 1) followed by logistic regression analysis revealed that risk factors for 1-year postoperative dyspnea included mMRC score ≥ 1 at discharge (aOR 14.446, 95% CI: 1.102-189.361) and postoperative respiratory failure occurrence (aOR 9.946 %CI: 1.063 to 93.034). ③ We have asked a native language polish expert to check the revision again.

2. Methods:

Some study results were described in this section. Please rewrite this section. Torr is preferred to describe the oxygen partial pressure instead of Torr. How did the authors identify Mycobacterium tuberculosis? Please clarify the identification methodology

(PCR or DNA-DNA hybridization or Mass spectrometry?). Similarly, the authors clarify the approach to identification of NTMs.

Reply2: Thanks a lot for your constructive comments. We modified the method section, please see the red font. "Torr" has been changed in the paper, (see line 98-99). Identification of Mycobacterium tuberculosis diagnosis was based on postoperative pathological diagnosis, consistent with tuberculosis. The PCR diagnosis test was carried out in our hospital in 2015, and only 16 patients in this study underwent this test. Identification of NTMs diagnosis was based on postoperative pathological diagnosis, consistent with NTMs.

Changes in the text:

- ① **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 score ≥ 1) were identified then risk factors for postoperative respiratory failure and compromised long-term respiratory function were identified using multivariate adjusted logistic regression analysis.
- ② "Torr" has been changed in the paper, (See Page5, line 106-107).

3.Results:

Table 1

There is no detail about the comorbidities in the main text. Please clarify "Second-line drugs".

Reply3: Thanks a lot for your constructive comments.

We added the comorbidities in the main text (See Page 6, line 135-136).

We added second-line drugs in the article. (See Page 6, line 136-142).

Changes in the text:

- ① Main comorbidities include hypertension (8 cases), coronary artery disease (8 cases) and diabetes Mellitus (6 cases).
- ② Second-line antituberculosis as followings: Group A: fluoroquinolones (including

levofloxacin, moxifloxacin, gatifloxacin), and clarithromycin. Group B: the second-line injectable drugs, including amikacin, capreomycin and streptomycin for injection. Group C: the other core second-line drugs, including cycloserine, prothiouracil, ethionamide, clofazimine, and linezolid. Group D: including bedaquiline, delamanid, para-aminosalicylic acid, amoxicillin clavulanic acid potassium, aminothiourea, imipenem-cistatin sodium, and meropenem.

4. Table 4

In multivariate analysis, age was not included. Age and gender are mandatory for the statistical analysis. The most important thing to remember is that the number of patients included for this study was not high enough to obtain relevant conclusions.

Reply 4: Thanks a lot for your constructive comments. We added variables to the table. We agree with you that "the number of patients included was not high enough", as we have described in the limitations of the paper, and that the low number of cases, that may have affected our results.

Changes in the table 4:

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/m²	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
FEV₁, %pred	1.010(0.966-1.056)	0.656
DLCO, %pred	1.006(0.970-1.043)	0.757
P_aO₂, Torr	0.989(0.963-1.015)	0.403
Operation time(>4 hour)	0.457(0.060-3.456)	0.448
Bleeding volume(> 1000ml)	6.876(1.236-38.243)	0.028

Note: TDL, tuberculosis destroyed lung; BMI, body mass index; CRP, C-reaction protein; FEV₁, %pred, forced expiratory volume in one second of predicted; DLCO, %pred, lung diffusion capacity of predicted.

Reviewer B

The authors have evaluated the factors associated with respiratory failure and dyspnea 1 year after surgery in patients with TB-destroyed lung. They found that low preoperative serum albumin level (<30 g/L) and high intraoperative bleeding volume (>1000 mL) were risk factors for post-surgical secondary respiratory failure. They also found that postoperative secondary respiratory failure and high mMRC \geq 1 at discharge were associated with high mMRC \geq 1 at 1-year post-surgical follow-up.

Major:

1. Table 1. Provide the indications for lung resection surgery.

Reply1: Thanks a lot for your constructive comments. Surgical indications of TDL see Page 6, line 124-127.

Changes in the text:

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.

2. The authors did not show FEV1 %pred, which is known to be one of the most important risk factors for postoperative pulmonary complications. This value should be included in Table 2.

Reply2: Thanks a lot for your constructive comments. we have modified our text as advised, (See Table 2, in red font).

Changes in the Table 2:

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	104	77(72.5)	27(27.5)	Ref	
Decreased	11	6(54.5)	5(45.5)	2.377(0.671-8.422)	0.180
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 ₁ %pred		58.0±17.3	53.0±20.4	1.00(0.956-1.013)	0.274
FEV ₁ /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
PaO₂ (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
PaCO₂ (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

Note: TDL, tuberculosis destroyed lung; 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; PaO₂, reference value 80-100 Torr; PaCO₂, reference value 35-45 Torr.

3. Please also add FEV₁/FVC ratio in Table 2.

Reply3: Thanks a lot for your constructive comments. we have modified our text as advised, (See Table 2, in red font).

Changes in the text: See the above table 2.

- The authors seem to choose variables for a multivariable analysis based on the univariable analysis. I don't think this is correct. They should also consider the biological mechanism. Thus, I'd like to recommend including age, smoking, BMI, PaO₂, FEV₁%pred, DLco, and surgical extension in the multivariable analysis for predicting postoperative respiratory failure. All these factors are well known to be associated with postoperative pulmonary complications.

Reply4: Thanks for your constructive comments. we have modified table 4.

Changes in the table 4:

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/m²	0.734(0.530-1.018)	0.064
Smoking(Yes)	0.999(0.082-12.151)	1.000
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Bleeding volume(>1000ml)	6.876(1.236-38.243)	0.028

Note: TDL, tuberculosis destroyed lung; BMI, body mass index; CRP, C-reaction protein; FEV₁, %pred, forced expiratory volume in one second of predicted; DLCO, %pred, lung diffusion capacity of predicted.

- Please re-analyze risk factors predicting dyspnea 1 year after surgery using 1) preoperative and intraoperative factors as well as 2) postoperative status. This result would be very useful for clinicians to predict long-term dyspnea in patients with TB-destroyed lung who will undergo surgical resection. Clinically important factors that are known to be associated with dyspnea after surgery should be included in the multivariable analysis even though these are not significant in univariable analysis (e.g. pulmonary function, age, etc.).

Reply: Thanks a lot for your constructive comments. we have modified table 5.

Changes in the table 5:

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 ₁ , %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)				
≤1000	35(63.6)	14(60.9)		Ref
>1000	20(36.4)	9(39.1)	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)

Note: TDL, tuberculosis destroyed lung; mMRC, modified British Medical Research Council; CPA or NTM, chronic pulmonary aspergillosis or nontuberculosis mycobacteria; CRP, C-reaction protein.

Minor

1. Definition of TB-destroyed lung - TB destroyed lung is usually defined to have 1 or

more lobes. Please consider adding the extent of lung involvement in the definition of TB-destroyed lung.

Reply 1: Thanks for your constructive comments. we have modified (See Page4, line 64-66, in red font)

Changes in the text:

TB-destroyed lung (TDL) manifesting as extensive destruction of lung parenchyma, irreversible lung function deficits, and reduced ventilation/perfusion ratio.

2. Cut-off values - The authors should provide the cut-off values for CRP, albumin, Hb, pH, PaO₂, PaCO₂, etc.

Reply2: Thanks for your constructive comments. we have modified our text as advised, (See Table 2, in red font).

Changes in the Table 2:

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; PaO₂, reference value 80-100 Torr; PaCO₂, reference value 35-45 Torr.

3. Table 4. Clarify whether albumin, CRP, and Hb were continuous variables or categorical variables. The authors included these factors as categorical variables in the univariable analyses.

Reply3: Thanks for your constructive comments. Albumin, CRP, and Hb were categorical variables. we have modified our text as advised, (See Table 4).

Changes in the Table 4:

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
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DLCO, %pred	1.006(0.970-1.043)	0.757
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Bleeding volume(> 1000ml)	6.876(1.236-38.243)	0.028
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Note: TDL, tuberculosis destroyed lung; BMI, body mass index; CRP, C-reaction protein; FEV1, %pred, forced expiratory volume in one second of predicted; DLCO, %pred, lung diffusion capacity of predicted.

4. Univariable analysis for predicting dyspnea 1 year after surgery was not provided.

Reply 4: Thanks for your constructive comments. we have modified our text as advised.

(See Table 5)

Changes in the Table 5:

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
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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)				
≤1000	35(63.6)	14(60.9)		Ref
>1000	20(36.4)	9(39.1)	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-	0.977(0.150-6.378)

2.650)

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)

Note: TDL, tuberculosis destroyed lung; mMRC, modified British Medical Research Council; CPA or NTM, chronic pulmonary aspergillosis or nontuberculosis mycobacteria; CRP, C-reaction protein.