

Peer review file

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Reviewer A

Major comments

Comment 1. I did not understand the aim of this study. I believe that the patient group is too heterogeneous and makes difficult to interpret the results. The authors should compare patients who were supported by mechanical ventilation on 30-day regardless reintubation and tracheostomy and died within 30 days with other. If the authors clarified the risk of re-intubation, the participants should patients who tried to extubation (passed the SAT and SBT) within 30-days.

Response: in this study, we investigated the preoperative risk factors for unsuccessful extubation or reintubation in LTx patients

Reply 1: The previous studies have reported that unsuccessful extubation is associated with longer intensive care and hospital stays and increased mortality (25-50%).^{1,2} This study tried to investigate the association between the preoperative factors of lung transplantation receptors and unsuccessful extubation or reintubation, which will can further help clinicians to previously distinguish those highly risk receptors and take effectively preventive measures.

In this study, the unsuccessful extubation was defined as mechanical ventilation dependent or reintubation. As the previous studies report, the term extubation failure has been used to refer to “the inability to tolerate spontaneous ventilation without

mechanical support and the need for re-intubation within 24-72 h of a planned extubation.³⁻⁵

Change in text: None.

Comment 2. The author should provide the criteria of extubation, re-intubation, and tracheostomy. Did all patients perform SAT and SBT? Please describe in method in detail.

Reply 2: The criteria of extubation, re-intubation, and tracheostomy have described in method in detail. “The extubation criteria were:1, successful spontaneous breathing trial (SBT) 120 minutes;2, hemodynamic stability;3, Glasgow coma scale score of 13 or larger; 4, without upper airway resistance and controllable secretions; 5, ameliorative imaging of chest x-ray. As reported in the previous study in detail.¹¹ The reintubation would be performed when the patients suffered from postextubation respiratory failure or severe clinical events, such as respiratory or cardiac arrest, massive aspiration, severe hemodynamic instability, and so on. In our center, a tracheostomy was performed if a patient failed to wean from the ventilator and intubation would exceed postoperative 30 days, which was evaluated by intensive care physicians.”

Change in the text: We added the “2.2 postoperative mechanical ventilation management” in methods (see Page 6, Line 115 to 124)

Comment 3. Why did the author defined successful extubation as the first successful liberation from MV within 30 days after LTx and without reintubation? Please add the appropriate references and described the research and clinical implication based on this

definition.

Reply 3: the first successful liberation from MV may be not really correct expression to this study. We have changed this expression to “the first successful extubation”.

There were two reasons to define successful extubation as the first successful extubation within 30 days after LTx and without reintubation. First, the previous studies reports have defined the term extubation failure as “the inability to tolerate spontaneous ventilation without mechanical support” or “the need for re-intubation within 24-72 h of a planned extubation”.³⁻⁵ Second, a tracheostomy was usually performed in our center, when the intubation exceed postoperative 30 days.

Change in the text: We changed the expression “the first successful liberation from MV” into “the first successful extubation”. (see Page 7, Line 141)

Comment 4. The author devided age, BMI and hypoxia for three groups. Please provide more information for the cut-off point and add the propriate references. Preoperative hypoxia was changed by FIO₂, thus I believe PaO₂/FIO₂ ratio is more appropriate than PaO₂ to assess oxygeneration.

Reply 4: In early eras, age over 65 years was the one of relative contraindications of lung transplantation. However, there are increasing numbers of centers transplanting patients over age 65 years old in recent years,⁶ which may increase the risk of extubation failure after LTx. So the age was divided to age between 45 years and 65 years, younger than 45 years, and older than 65 years.

The classification of BMI in this study is not really reasonable. According to the

previous relative study of LTx, the BMI was re-classified 3 subgroups, less than 18.5 (underweight), 18.5 to 24.9 (normal), more than 24.9 (overweight), in revised manuscript.⁷

According to the reviewer suggestion, the classification based on PaO₂ was modified as the classification based on PaO₂/FiO₂ ratio in revised manuscript. And there were 3 subgroups, PaO₂/ FiO₂ less than 150, PaO₂/ FiO₂ between 150 to 250, and PaO₂/ FiO₂ more than 250.

Change in the text: We changed the BMI classification “included between 18 and 24, less than 18, and more than 24” into “less than 18.5 (underweight), 18.5 to 24.9 (normal), more than 29.9 (overweight)” (see Page 7, Line 137)

We changed the PaO₂ classification “mild hypoxia (PaO₂ more than 50mmHg), moderate hypoxia (PaO₂ between 30mmHg and 50mmHg), and severe hypoxia (PaO₂ less than 30mmHg)” into “PaO₂/ FiO₂ less than 150, PaO₂/ FiO₂ between 150 to 250, and PaO₂/ FiO₂ more than 250” (see Page 5, Line 138-140)

Comment 5. The authors described the variables with P<0.20 were entered into further multivariate analysis. Why “hypoxia” (P=0.005 in table 2) was not included in table 2? Why “Independent sputum clearance”, “Hypoxia”, “Type of transplantation” were also not included in table 5?

Reply 5: In this study, Logistic regression models were applied for multivariate analysis using forward stepwise selection procedure. The cutoff for variable removal was set a significance level of 0.05. A probability value of P<0.05 was required for entry into the

model and $P > 0.05$ for elimination. The “Hypoxia” was removed in table 3 because of $P > 0.05$ In multivariate analysis. Those factors, “Independent sputum clearance”, “Hypoxia”, and “Type of transplantation”, were also removed in table 5 also because of $P > 0.05$ In multivariate analysis.

Change in the text: We added the detail logistic regression methods in revised manuscript. (see Page 8, Line 149-152)

Comment 6. The discussion was not based the results. The author did not understand the difference between odds ratio and risk ratio. If the authors would like to discuss the risk, please provide the result as risk ratio.

Reply 6: We have modified the inaccuracy expressions in discussion.

Change in the text: We changed “We found preoperative ECMO support was the independent risk factor of unsuccessful extubation. And the risk rate of unsuccessful extubation for patients supported by preoperative ECMO was 4.631 folds higher than those patients without preoperative ECMO support” to “We found preoperative ECMO support was an important factor for unsuccessful extubation (OR=4.631)” (see Page 12, Line 242-243).

We changed “The patients without the independent sputum clearance ability had 4.517 times risk than patients with the ability to unsuccessfully weaning from MV” to “The patients without the independent sputum clearance ability had more risk than patients with the ability to unsuccessfully weaning from MV (OR=4.517)”. (see Page 12-13, Line 249-250).

We changed “The right single LTx had the lowest risk for unsuccessful extubation after postoperative, followed by left single LTx. The unsuccessful risk rate of double LTx was 3.39 times than the right single LTx. And the heart-lung transplant receptors suffered the highest fail risk for liberating from MV, 16.579 times than right single transplant” to “the right single LTx had the lowest risk for unsuccessful extubation, followed by left single LTx and double LTx. And the heart-lung transplant receptors suffered the highest fail risk for postoperative extubation (OR=16.579, vs right single transplant).” (see Page 13, Line 262-265).

We changed “we found that the unsuccessful risk rate in older than 65 years was 4.039-fold than the age between 45-year-old and 65-year-old. Hence, for the old patients” to “we found that patients older than 65 years have higher risk of extubation failure than the age between 45-year-old and 65-year-old (OR=4.039)”. (see Page 14, Line 278-280).

Minor comments

Comment 1. L1 The title did not reflect this study. Please revise it.

Reply 1: the old title was revised as “Preoperative risk factors for successful extubation or not after lung transplantation”.

Change in the text: the old title was revised as “Preoperative risk factors for successful extubation or not after lung transplantation”. (see Page 1, Line 1)

Comment 2. L45 “Background” is preferable.

Reply 2: The “Introduce” was revised as “Background”.

Change in the text: The “Introduce” was revised as “Background”. (see Page 5, Line 84).

Comment 3. L77 Is this study “cohort study” as described in abstract or “case-control study” in method section? Which is correct?

Reply 3: This study was a retrospective case-control study. The incorrect expression in abstract has been reviewed.

Change in the text: The “cohort study” was revised as “case-control study” in abstract. (see Page 3, Line 46).

Comment 4. L86 What is “independent sputum clearance”? Please describe when, how, who assess by what definition? Please add in method section.

Reply 4: We have described “independent sputum clearance” in methods. The ability of independent sputum clearance of patients was judged by clinical physician based on whether the patients could clear sputum by spontaneous cough without medical assistance or not during being hospitalized for transplantation.

Change in the text: We have described “independent sputum clearance” in methods. (see Page 7, Line 129-132).

Comment 5. Please provide the number of patients with tracheostomy and the number of patients died in result section.

Reply 5: the number of patients with tracheostomy was added in the Subject

Demographics of result section. The 1-year mortalities of successful extubation, unsuccessful extubation and re-intubation group were presented in the Long-term outcome of result section.

Change in the text: We added the number of patients with tracheostomy in the Subject Demographics of result section. “9 patients underwent tracheostomy, because MV exceeds 30 days” (see Page 9, Line 167-168)

Reviewer B

Comment 1. The references are not in numerical order, the first reference in the introduction is #5.

Reply 1: We re-put the references in numerical order in revised manuscript.

Change in the text: We re-put the references in numerical order in revised manuscript. (see Page 17, Line 332)

Comment 2. The manuscript could use editing for proper English, there are some grammatical errors throughout the paper.

Reply 2: We have checked the grammatical errors in revised manuscript.

Change in the text: The “form” was revised “from” (see Page 3, Line 46). The “...who successfully liberated from ...” was revised “... who were successfully liberated from ...” (see Page 3, Line 52). The “...independent risk factors for reintubation” was revised “...independent risk factor for reintubation” (see Page 4, Line 66). “..., and type of transplant is the impact factor ...” was revised “..., and type of transplant were the

impact factors ...” (see Page 9, Line 176)

Comment 3. Your Table 1 should include more patient characteristics, such as co-morbidities (i.e. pre-op renal failure), surgical approach, did you use cardiopulmonary bypass during the transplant. All of these factors affect the ability for a successful post-operative extubation.

Reply 3: Because lung transplantation is a complex therapy with a significant risk of perioperative morbidity and mortality, untreatable significant dysfunction of another major organ system (e.g., heart, liver, kidney, or brain) was absolute contraindications for lung transplantation.⁸ In our center, the preoperative renal failure was contraindications for lung transplantation. the other co-morbidities (e.g., hypertension, diabetes) and surgical approach were added in Table 1. In our center, the cardiopulmonary bypass was used during heart-lung transplantation. The ECMO was used in necessity during lung transplantation.

Change in the text: the other co-morbidities (e.g., hypertension, diabetes) and surgical approach were added in Table 1. (See table 1)

Comment 4. Do you have any data on the pre-operative fragility score? This also impacts the ability of a patient to be extubated.

Reply 4: The pre-operative fragility score was not routinely recorded in our center. But we used the simpler indicator “The ability of independent sputum clearance” to represent the fragility of patients.

Change in the text: None

Comment 5. Age >65 is a high risk for transplantation, can you elaborate more on these patients? Indications, etc?

Reply 5: Age >65 years is associated with low physiologic reserve and high comorbid conditions. However, age by itself should not be considered a contraindication to lung transplantation. Sreeja Biswas Roy and associates reported that older patients up to age 74 had acceptable outcomes after lung transplantation. even older than 75 have acceptable short-term outcomes for single lung transplantation.⁹

In this study, for age > 65-years patients, the most common indication consisted of interstitial lung disease (ILD) or pulmonary fibrosis (65.4%). The second most common indication consisted of COPD (26.9%). And the other indications include Sarcoidosis (3.8%) and Silicosis (3.8%).

Change in the text: None

Comment 6. Did the patients with pre-op ECMO leave the operative room on ECMO or de-cannulated at the time of the transplant?

Reply 6: In our center, the patients with preoperative ECMO leave the operative room on ECMO. And the ECMO was de-cannulated usually in postoperative 2 to 3 days after assessing by ICU physicians.

Change in the text: None

Comment 7. Can you elaborate on post-op complications. There are many factors affecting the ability to extubate or stay extubated. For example, post-op return to the OR, blood transfusions, post-operative sepsis, acute rejection, etc.

Reply 7: We also agree the postoperative factors (e.g., second operation, blood transfusions, post-operative sepsis, acute rejection, etc.) may affect whether successfully extubate or not. However, the purpose of this study was to uncover preoperative risk factors for extubation failure or re-intubation for patients undergoing lung transplant, which may help us to find the high risk patients and take some targeted preventive measures.

Change in the text: None

Reviewer C

Comment 1. The authors should review the “proper terminology” for describing their statistical analyse which they performed, In their Abstract they describe the analyses as “univaiate and multivariate”. While in the text of the manuscript their analyses were described as “univariable amd multivariable”. These terms are not synonymous and only one set is correct. I will leave it to the authors to discuss with their coauthors which are correct. This mistake is elementary and indicates a lack in understanding or just a lapse in proof reading.

Reply 1: The wrong expression “univariate and multivariate” have been revised in abstract and methods section.

Change in the text: The wrong expression “univariate and multivariate” have been revised as “univariable and multivariable”. (see Page 3, Line 48; see Page 8, Line 148)

In line 216 of the manuscript’s Text it is written “ In my study...” , shouldn’t it read “ In our study...” to be more inclusive to all of the coauthors? (Especially since there are 13 of you listed on this paper.

The wrong expression “in my study” have been changed to “in our study”.

Change in the text: The wrong expression “in my study” have been changed to “in our study”. (see Page 13, Line 261)

Comment 2. I think some information included in this manuscript is of real importance which should be rementioned. Right single lung transplantation had the lowest risk for reintubation of any group. Pretransplant ECMO was a significant predictor of reintubation post-transplantation. I would like to ask the authors what they feel the basic causes are for these two issues.

Reply 2: In this study, we found the right single LTx had less risk for extubation failure than left single LTx (OR=1.735), although the difference was not significance in statistics (P=0.431). the more angle of right main bronchus may be potential cause leading to less extubation for right single LTx, which may decrease the postoperative infection risk of transplanted lung. Moreover, I Ben Nachum and associates reported that the left-sided bronchial anastomosis may be more vulnerable to complications.¹⁰

Patients with pretransplant ECMO often continue to keep ECMO support in early post-

transplant, which will increase the odds for some postoperative complications, such as post-operative ventilator support >48 hours, in-hospital stroke, in-hospital dialysis, in-hospital acute rejection episodes, and etc.^{11,12} Those complications may further cause re-intubation.

Change in the text: “the right single LTx” and “Pretransplant ECMO” was re-mentioned in discussion section. (see Page 13, Line 265-270; Page 14, Line 284-290)