

Patient-reported dyspnea and health predict waitlist mortality in patients waiting for lung transplantation in Japan

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Research

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Abstract

Background

Waitlist mortality due to donor shortage for lung transplantation is a serious problem worldwide. Currently, the selection of recipients is mainly based on registration order in Japan. However, scientific evidence for risk stratification for waitlist mortality is needed in future. We hypothesized that patient-reported dyspnea and health would predict mortality in patients waitlisted for lung transplantation.

Methods

Using data on 203 patients who were registered as candidates for lung transplantation from deceased donors, we analyzed factors related to waitlist mortality. Dyspnea was evaluated by the modified Medical Research Council (mMRC) dyspnea scale and health status was measured with the St. George's Respiratory Questionnaire (SGRQ).

Results

Among 197 patients who met inclusion criteria, the main underlying disease was interstitial pneumonia (IP) in 99 patients. During the median follow-up period of 572 days, 72 patients on the waitlist died and 96 received lung transplantation (69 from deceased donor). Univariable competing risk analyses revealed that both mMRC dyspnea and SGRQ Total were significantly associated with waitlist mortality ($p = 0.003$ and $p < 0.001$). Multivariable competing risk analyses revealed that the mMRC and SGRQ were associated with waitlist mortality, among age, IP, arterial carbon dioxide pressure, and forced vital capacity, which were all significant factors in univariable analyses.

Conclusions

Both mMRC dyspnea and SGRQ were significantly associated with waitlist mortality regardless of patients' background, underlying disease, and pulmonary function. Patient-reported dyspnea and health should be measured not only from the perspective of multi-dimensional analysis including subjective perceptions, but also as risk stratification for waitlist mortality.

Background

While lung transplantation has been recognized as an effective treatment for patients with various end-stage pulmonary diseases, shortage of lung donors is one of the main problems worldwide. Due to the imbalance between demand for donor organs and supply, waitlist mortality remains significant [1]. The average wait time for transplantation is still more than 800 days, resulting in a considerable number of deaths while on the waitlist in Japan [2]. Urgent measures to reduce waitlist mortality need to be taken

quickly. For this purpose, appropriate risk stratification of patients waitlisted for lung transplantation is necessary.

In the U.S., the lung allocation score (LAS) system was implemented in 2005 to maximize utility of decreasing waitlist time and mortality and to improve likelihood of 1-year post-transplant survival [3]. The LAS system has been adopted by Eurotransplant [4] and is prepared to be introduced in various countries including Japan. The LAS is primarily based on multi-dimensional analyses; it is weighted based on underlying diseases and calculated mostly by physiological measures [5].

Although dyspnea and health-related quality of life (HRQL) are the main targets to be improved after lung transplantation, in addition to survival, where should we rank these subjective measures in the assessment of patients waitlisted for lung transplantation? These patient-reported measures are not included in the factors contributing to the LAS, neither does the LAS reflect them [6]. This means that they should be assessed separately from the LAS.

Assessment of dyspnea and HRQL using questionnaires in respiratory diseases has developed mainly through the preceding experience and information in studies of chronic airway diseases such as asthma and chronic obstructive pulmonary disease (COPD). Dyspnea is the main symptom in these patients and is the major contributor to poor health. Assessment of dyspnea [7] and health status [8] significantly provided useful prognostic information of mortality in COPD, which contributed to the development of subsequent multi-dimensional analysis not solely based on pulmonary function [9, 10].

Therefore, we hypothesized that patient-reported dyspnea and HRQL would predict waitlist mortality in patients waitlisted for lung transplantation in Japan, even though their underlying diseases are heterogeneous. This may provide useful information in better stratifying patients at risk of mortality during limited waiting time. We then assessed the relationship between baseline variables including patient-reported outcomes at registration of lung transplantation and waitlist mortality.

Methods

Patients

A total of 203 patients who were registered as candidates for lung transplantation from deceased donors were consecutively recruited from 3 facilities (Kyoto University Hospital, Okayama University Hospital, and Tohoku University Hospital) in Japan between March 2009 and June 2015 [11]. Inclusion criteria included 1) new registration in the Japan Organ Transplant Network, 2) age over 18 years, and 3) no uncontrolled comorbidities such as malignant, cardiac, and cerebrovascular diseases. Exclusion criteria included 1) necessity of heart-lung transplantation, and 2) refusal to participate in the study. Patients' background, pulmonary function, arterial blood gas, and patient-reported measurements of dyspnea, HRQL and psychological status were assessed at study entry. Comorbidity was objectively assessed by the Charlson comorbidity index [12]. Patients underwent spirometry to measure their forced vital capacity (FVC) and forced expiratory volume in one second (FEV₁). Predicted values were based on the

recommendation by the Japanese Respiratory Society guidelines. Approval of the study protocol (E554) was obtained from the Ethics Committee of Kyoto University and each of the other facilities that were involved in this research. Written informed consent was obtained from all patients.

Patient-reported Outcomes

Dyspnea was evaluated using the Japanese version of the modified Medical Research Council (mMRC) dyspnea scale [8,9]. This is a 5-point scale (0–4) based on degrees of various physical activities that precipitate dyspnea, and higher scores indicate a worse status.

Health status or HRQL was assessed by the Japanese version of the St. George's Respiratory Questionnaire (SGRQ) [8,13]. The SGRQ was originally developed for patients with chronic airflow limitations such as asthma or COPD, but it has been validated for use in other respiratory diseases including pulmonary fibrosis, bronchiectasis, lymphangiomyomatosis (LAM), pulmonary hypertension, and bronchiolitis obliterans (BO). Therefore, it is regarded as the only frequently employed respiratory-specific HRQL instrument in lung transplantation [14]. It consists of 50 items divided into 3 components: Symptoms, Activities, and Impacts. The Total SGRQ score was calculated, with scores ranging from 0 (best) to 100 (worst).

Psychological status was evaluated using the Japanese version of the Hospital Anxiety and Depression Scale (HADS) [11,15], which consists of 14 items: 7 for anxiety and 7 for depression. Each item is scored from 0 to 3, where a score of 3 represents a state corresponding to the worst anxiety or depression. The sum of these items produces 2 subscale scores, each ranging from 0 to 21.

Lung Allocation Score

The LAS of each patient was calculated using the LAS calculator on the Organ Procurement and Transplantation Network (OPTN) website (<http://optn.transplant.hrsa.gov/resources/allocation-calculators/las-calculator/>) in September 2020. The LAS in this study was calculated using the data at the time of first study registration.

Statistical Analysis

Results are presented as the median with interquartile range, unless otherwise stated. Relationships between the LAS and patient-reported measures were analyzed by Spearman's rank correlation coefficient tests. The duration from entry to the time of waitlist death (event), transplantation date including transplantations both from deceased and living donors (competing risk), or confirmation of survival without transplantation up to 5 years were recorded. Patients who withdrew from the study or remained on the waitlist were censored. We truncated the time-varying curves when fewer than 10 subjects were at risk.

Univariable and multivariable competing risk regressions with the Fine–Gray model [16] were performed to investigate the relationship between clinical measurements and waitlist mortality based on previous

analyses [7,8,17]. FVC (%predicted), interstitial pneumonia (IP), mMRC dyspnea, SGRQ, and HADS were included in the multivariable analyses based upon clinical experience even if they were not significant in the univariable analyses. Other than these variables, those with p values <0.05 were included in the multivariable analyses. Clinical measurements were defined as continuous variables with the exception of gender, smoking status, use of home oxygen therapy, and kinds of primary underlying diseases (IP or not). Results of the regression analysis were presented in terms of the estimated hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Competing risk regression with the Fine–Gray model was used to evaluate waitlist mortality in the groups with lower versus higher mMRC dyspnea, lower versus higher SGRQ, and lower versus higher LAS based on the median score. P values of less than 0.05 were considered to be statistically significant. Statistical analyses were performed using statistical software EZR (Saitama Medical Center, Jichi Medical University, Japan).

Results

Patients

Among 203 patients enrolled, 6 patients were excluded, of which 4 were unavailable for follow-up and 2 were transferred to other hospitals just after registration. Therefore, 197 patients (102 males) who met the inclusion criteria were analyzed, and their baseline characteristics are presented in Table 1. The study population had a median age of 47 (38–54) years and low body mass index (BMI) of 19.0 (16.7–21.7) kg/m^2 . The primary underlying diseases were IP (99 patients, 50.3%), BO (21 patients, 10.7%), pulmonary hypertension (15 patients, 7.6%), LAM (15 patients, 7.6%), COPD (12 patients, 6.1%), bronchiectasis (11 patients, 5.6%), and lung injury after hematopoietic stem cell transplantation (10 patients, 5.1%). Long-term oxygen therapy (LTOT) was prescribed for 174 patients and noninvasive ventilation (NIV) was used for 11 patients. FVC and FEV_1 values were low at 46.4 (36.1–61.6) %predicted and 40.8 (24.5–55.8) %predicted, respectively.

Prospective Survival Study

During the median follow-up period of 572 days (range: 1–1987 days), 96 patients (48.7%) received lung transplantation. Among them, 27 patients underwent living-donor lung lobar transplantation because they could not wait for a deceased donor. Regarding 69 patients who underwent lung transplantation from a deceased donor, the median time from registration to lung transplantation was 752 days (range: 38–1979 days). Of note, 72 patients on the waitlist (36.5%) expired: 49 had IP, and 23 had other respiratory diseases. With regard to the cause of death, 70 (97.2%) patients died because of worsening of the original respiratory diseases, 1 patient died because of pneumonia, and 1 patient died because of pulmonary hemorrhage.

Univariable competing risk regressions with the Fine-Gray model were performed to investigate the relationships between clinical measurements and waitlist mortality (Table 2). Higher age, IP, higher arterial carbon dioxide pressure (PaCO_2), and lower FVC were significantly related to waitlist mortality

($p < 0.05$). Regarding patient-reported measures, mMRC dyspnea was significantly related to waitlist mortality (HR=1.46, 95% CI=1.13-1.87, $p=0.003$). For patients classified according to the median mMRC (3), cumulative incidence curves between lower and higher mMRC score groups (score 0-2, $n=79$; score 3 or 4, $n=115$; missing, $n=3$) are presented ($p=0.011$) (Figure 1). Regarding HRQL, Symptoms, Activities, Impacts, and Total scores of the SGRQ had strong associations with waitlist mortality (HR=1.02, 95% CI=1.01-1.04, $p=0.0014$; HR=1.03, 95% CI=1.01-1.05, $p=0.002$; HR=1.03, 95% CI=1.02-1.04, $p < 0.001$; and HR=1.04, 95% CI=1.02-1.05, $p < 0.001$, respectively). For patients classified according to the median SGRQ Total (67.3), cumulative incidence curves between higher and lower SGRQ Total groups ($n=97$ and $n=98$, respectively; missing, $n=2$) are presented ($p < 0.001$) (Figure 2). HADS anxiety and depression also had weak but significant relationship with waitlist mortality (HR=1.07, 95% CI=1.02-1.13, $p=0.013$; and HR=1.05, 95% CI=1.01-1.10, $p=0.024$). Other variables such as gender, BMI, smoking history, comorbidities, LTOT, FEV₁, and 6-minute walk distance were not significant ($p > 0.05$).

Multivariable competing risk regression with the Fine–Gray model was performed using age, IP, PaCO₂, FVC (%predicted), and mMRC (Model I: dyspnea) or SGRQ Total (Model II: HRQL) or HADS (Model III: psychological status) as explanatory variables, all of which were significant factors in the univariable analyses (Table 3). We divided them into these three groups because SGRQ Total includes the evaluation of dyspnea and psychological status. In Model I, age, IP, FVC, and mMRC dyspnea were significantly related to waitlist mortality (HR=1.04, $p=0.007$; HR=2.41, $p=0.002$; HR=0.98, $p=0.016$; and HR=1.36, $p=0.037$, respectively). In Model II, age, IP, and SGRQ Total were significantly related to waitlist mortality (HR=1.03, $p=0.010$; HR=2.24, $p=0.003$; and HR=1.03, $p=0.0014$, respectively). In Model III, age, IP and FVC were significant factors related to waitlist mortality, and HADS was not. We also analyzed the data excluding patients who underwent living-donor lobar lung transplantation after registration in this study. We found that the SGRQ total and mMRC dyspnea remained significantly related to waitlist mortality after multivariable analysis (Additional file 1: Table S1).

Finally, we analyzed data regarding the LAS. It ranged from 32.6 to 71.2 with a median score of 40.1. LAS was significantly but weakly related to mMRC (Spearman's rank correlation coefficient (Rs)= 0.27, $p < 0.001$), SGRQ Total (Rs=0.36, $p < 0.001$), and HADS anxiety (Rs=0.17, $p=0.030$) and depression (Rs=0.22, $p=0.004$). Scatter plots between the LAS, mMRC, and SGRQ are shown in Additional file 2 and 3 (Figure S1 and Figure S2). Univariable competing risk analysis revealed that the LAS was significantly related to waitlist mortality (HR=1.04; 95% CI=1.01–1.07, $p=0.004$). Cumulative incidence curves for the groups with lower versus higher LAS are presented ($n=87$ and $n=86$, respectively) ($p=0.025$) (Additional file 4: Figure S3). We subsequently analyzed whether its significant relationship with waitlist mortality was independent of patient-reported measures. Therefore, multivariable competing risk analysis was performed to investigate the relationships with waitlist mortality between the LAS and (a) Model I: mMRC score (dyspnea), (b) Model II: SGRQ Total (HRQL), and (c) Model III: HADS anxiety and depression (psychological status). In Model III, only the LAS was significant ($p=0.012$); in Model I, both the LAS and the mMRC were significantly related with waitlist mortality ($p=0.039$ and 0.038 , respectively); and in Model II, the SGRQ was significant ($p < 0.001$) but the LAS was not ($p=0.11$) (Additional file 5: Table S2).

Discussion

In the present study, we analyzed factors related to waitlist mortality in patients waiting for lung transplantation in Japan, focusing on patient-reported outcomes. The most important novel finding was that mMRC dyspnea and HRQL assessed with the SGRQ were significantly associated with waitlist mortality regardless of age, underlying disease (IP or non-IP) and pulmonary function.

It is noteworthy that the patient-reported dyspnea and health were significantly associated with waitlist mortality in patients waiting for lung transplantation in multivariable models. Now, some aspects of these sensory symptoms and experience can be objectively measured using questionnaires, which enables us to differentiate between patients with better or worse status (discriminative property) and assess how much they change e.g. in response to medical intervention (evaluative property) [18]. Subsequent studies reported that they can predict future outcomes such as mortality in COPD (predictive property) [7, 8]. Regarding idiopathic pulmonary fibrosis (IPF), most prevalent original disease in the present study, mMRC dyspnea [19] and SGRQ [20, 21] also predicted mortality, although well-known multi-dimensional severity scoring for IPF such as CPI (composite physiologic index) [22] or GAP (gender, age and physiology) [23] didn't include these measures.

However, we firstly demonstrated that the predictive properties of both the mMRC and SGRQ were advantageously maintained in this heterogeneous group of patients with various advanced lung disorders and targeted for lung transplantation. This information will help us to better stratify patients at risk for waitlist mortality using these data, and to better cope with this serious problem. In addition, it is easy to assess patients' dyspnea and HRQL using appropriate questionnaires, while these patients are often so severe that they cannot perform important physiological tests such as diffusing capacity or 6-minute walk. Dyspnea and health can reflect systemic as well as local comprehensive effects of the disease on patients, differently from pulmonary function [7, 8].

Unfortunately, waitlist mortality remains still significant [1]. According to U.S. reports [1, 24], approximately 20% of waitlisted patients die on the lung transplantation waitlist or are removed because they become too sick to transplant; nevertheless, this seems to be much lower than the 36.5% mortality rate in the present study. Since the long wait time for lung transplantation is a serious problem in Japan, as well as in many other countries, waitlist mortality should be reduced as much as possible. The selection of lung transplantation recipients in Japan is currently based on a "first come, first served" system, in addition to blood type compatibility, organ size, and other factors. The LAS system in the U.S. seems to function beneficially, and many countries including Japan try to develop such systems similar to the LAS depending on their specific circumstances for lung transplantation. Since it will take some time before Japan and other countries to make the local LAS-like system, the present study was conducted to show some scientific evidence in organ allocation with regard to risk stratification.

We calculated the LAS as a reference value, despite some missing values. It was significantly but weakly related with patient-reported measures, indicating that they evaluate different aspects of the patients. Interestingly, the mMRC was significantly related to mortality independently of the LAS, and the SGRQ

was more predictive of waitlist mortality than the LAS. Thus, these subjective measures may add values to the existing lung allocation system in terms of patient risk stratification as well as patient perception. However, further prospective studies are needed to examine this hypothesis.

IP was significantly associated with waitlist mortality in different multivariable model. Among 99 IP patients enrolled, 49 patients on the waitlist (49.5%) expired. This is consistent with historical evidence [4] that patients with IPF have a higher waitlist mortality than patients with other common indications for transplantation, with mortality reported between 18% and 67%. In the U.S., the primary indications are fibrotic lung disorders, now accounting for more than 57% of cases [1]. Similarly, IP accounted for 50.3% of the 197 analyzed patients in the present Japanese study. Thus, IP occupies a significant place in lung transplantation regarding incidence and waitlist mortality, which should be solved in future.

Some limitations of the present study should be mentioned. Firstly, the present study was conducted in Japan where the LAS system is not used and waitlist time is long. In Japan, allocation is solely based on waiting time. In contrast, in the Eurotransplant region and the U.S., an allocation system is in place, stratifying patients based on medical urgency and anticipated 1-year survival. In addition, underlying diseases of enrolled patients may differ between countries. Therefore, the results may be specific to our country. Moreover, because of the small number of patients, we were unable to perform an analysis based on each underlying disease. Our findings were only adjusted depending on the presence or absence of interstitial pneumonia through multivariable analysis. Further study for generalization is needed. Secondly, we used mMRC and SGRQ as dyspnea and HRQL measures, respectively, both of which are well-known questionnaires in the respiratory field. However, as they are not specific to patients with severe diseases, the median and whole scores tended to skew to worse ends. Lung transplant specific instruments such as the recent Lung Transplant Quality of Life (LT-QOL) [25] might generate better predictive feature.

Conclusions

We demonstrated that patient-reported dyspnea and health were significantly associated with waitlist mortality in patients waiting for lung transplantation, independently of patients' age, underlying disease and physiological measures. These outcomes are not included and reflected in the LAS. Thus, patient-reported dyspnea and health should be measured not only from the perspective of multi-dimensional analysis including subjective perceptions, but also as risk stratification for waitlist mortality when a new allocation system is developed in Japan.

Declarations

Ethics approval and consent to participate

Approval of the study protocol (E554) was obtained from the Ethics Committee of Kyoto University and each of the other facilities that were involved in this research.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest and Funding

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Authors' contributions

MI and TO had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MI, TO, TFC-Y, and HD contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors contributed to acquiring study data and drafting the manuscript for important intellectual content.

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Not applicable

References

1. Ahya VN, Diamond JM. Lung transplantation. *Med Clin N Am* 2019;103:425-33.
2. Date H. Current status and problems of lung transplantation in Japan. *J Thorac Dis* 2016;8(Suppl 8):S631-6.
3. Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, et al. Development of the new lung allocation system in the United States. *Am J Transplant* 2006;6:1212-27.
4. Smits JM, Nossent GD, de Vries E, Rahmel A, Meiser B, Strueber M, et al. Evaluation of the lung allocation score in highly urgent and urgent lung transplant candidates in Eurotransplant. *J Heart Lung Transplant* 2011;30:22-8.
5. George PM, Patterson CM, Reed AK, Thillai M. Lung transplantation for idiopathic pulmonary fibrosis. *Lancet Respir Med* 2019;7:271-82.
6. Chen F, Oga T, Yamada T, Sato M, Aoyama A, Chin K, et al. Lung allocation score and health-related quality of life in Japanese candidates for lung transplantation. *Interact Cardiovascular Thorac Surg*

- 2015;21:28-33.
7. Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest* 2002;121:1434-40.
 8. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T. Analysis of the factors related to mortality in chronic obstructive pulmonary disease: role of exercise capacity and health status. *Am J Respir Crit Care Med* 2003;167:544-9.
 9. Global initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. (2021 report). [Accessed on December 21, 2020]. Available from: <https://goldcopd.org/2021-gold-reports/>
 10. Celli BR, Cote CG, Marin JM, Casanova C, de Oca MM, Mendez RA, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med* 2004;350:1005-12.
 11. Tokuno J, Chen-Yoshikawa TF, Oga T, Oto T, Okawa T, Okada Y, et al. Analysis of optimal health-related quality of life measures in patients waitlisted for lung transplantation. *Can Respir J* 2020;2020:4912920.
 12. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;40:373-83.
 13. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145:1321-7.
 14. Singer J, Chen J, Blanc PD, Leard LE, Kukreja J, Chen H. A thematic analysis of quality of life in lung transplant: the existing evidence and implications for future directions. *Am J Transplant* 2013;13:839-50.
 15. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983;67:361-70.
 16. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
 17. Aihara K, Handa T, Oga T, Watanabe K, Tanizawa K, Ikezoe K, et al. Clinical relevance of plasma prostaglandin F_{2α} metabolite concentrations in patients with idiopathic pulmonary fibrosis. *PLoS ONE* 2013;8:e66017.
 18. Oga T, Nishimura K, Tsukino M, Sato S, Hajiro T, Ikeda A, et al. Health status measured with the CRQ does not predict mortality in COPD. *Eur Respir J* 2002;20:1147-51.
 19. Nishiyama O, Taniguchi H, Kondoh Y, Kimura T, Kato K, Kataoka K, et al. A simple assessment of dyspnoea as a prognostic indicator in idiopathic pulmonary fibrosis. *Eur Respir J* 2010;36:1067-72.
 20. Case AH, Hellkamp AS, Neely ML, Bender S, Dilling DF, Gulati M, et al. Associations between patient-reported outcomes and death or lung transplant in idiopathic pulmonary fibrosis. *Ann Am Thorac Soc* 2020;17(6):699-705.

21. Furukawa T, Taniguchi H, Ando M, Kondoh Y, Kataoka K, Nishiyama O, et al. The St. George's Respiratory Questionnaire as a prognostic factor in IPF. *Respir Res* 2017;18:18.
22. Wells AU, Desai SR, Rubens MB, Goh NSL, Cramer D, Nicholson AG, et al. Idiopathic pulmonary fibrosis: A composite physiologic index derived from disease extent observed by computed tomography. *Am J Respir Crit Care Med* 2003;167:962-9.
23. Ley B, Ryerson CJ, Vittinghoff E, Ryu JH, Tomassetti S, Lee JS, et al. A multidimensional index and staging system for idiopathic pulmonary fibrosis. *Ann Intern Med* 2012;156:684-91.
24. Valapour M, Lehr CJ, Skeans MA, Smith JM, Uccellini K, Goff R, et al. OPTN/SRTR 2018 Annual Data Report: Lung. *Am J Transplant* 2020;20(Suppl s1):427-508.
25. Singer JP, Soong A, Chen J, Shrestha P, Zhuo H, Gao Y, et al. Development and preliminary validation of the Lung Transplant Quality of Life (LT-QoL) Survey. *Am J Respir Crit Care Med* 2019;199:1008-19.

Tables

Table 1. Baseline characteristics of 197 patients waiting for lung transplantation

Characteristics	Median or number	IQR
Gender, male/female	102/95	
Age, years	47	38-54
BMI, kg/m ²	19.0	16.7-21.7
Smokers, number	94 (47.7%)	
Charlson comorbidity index	0	0-1
PaO ₂ , mmHg	74.5 (n=195)	62.0-88.9
PaCO ₂ , mmHg	45.1 (n=195)	40.1-51.5
FVC, L	1.7 (n=191)	1.2-2.3
FVC, %predicted	46.4 (n=191)	36.1-61.6
FEV ₁ , L	1.2 (n=191)	0.7-1.7
FEV ₁ , %predicted	40.8 (n=191)	24.5-55.8
6-minute walk distance, m	300 (n=179)	208-389
mMRC dyspnea (0-4)	3	2-4
SGRQ Symptoms (0-100)	69.6	56.2-80.7
SGRQ Activities (0-100)	86.4	77.2-92.5
SGRQ Impacts (0-100)	57.5	43.3-70.1
SGRQ Total (0-100)	67.3	56.5-76.7
HADS anxiety (0-21)	5	2-8
HADS depression (0-21)	6	3-9

IQR, interquartile range, *BMI*, body mass index; *PaO₂*, arterial partial pressure of oxygen; *PaCO₂*, arterial partial pressure of carbon dioxide; *FVC*, forced vital capacity; *FEV₁*, forced expiratory volume in one second; *mMRC*, modified Medical Research Council; *SGRQ*, St. George's Respiratory Questionnaire; *HADS*, Hospital Anxiety and Depression Scale.

Table 2. Univariable competing risk analysis with the Fine-Gray model in 197 patients waiting for lung transplantation

Characteristics	HR	95% CI	P value
Gender, male	1.08	0.68-1.71	0.76
Age, years	1.04	1.02-1.06	<0.001
BMI, kg/m ²	1.00	0.94-1.05	0.90
Smoking history	1.01	0.64-1.62	0.96
Charlson comorbidity index	1.01	0.75-1.37	0.96
Interstitial pneumonia	2.75	1.70-4.44	<0.001
Long-term oxygen therapy	0.80	0.43-1.52	0.50
PaO ₂ , mmHg	1.01	1.00-1.02	0.14
PaCO ₂ , mmHg	1.02	1.00-1.04	0.041
FVC, L	0.58	0.43-0.80	<0.001
FVC, %predicted	0.98	0.97-0.99	<0.001
FEV ₁ , L	0.92	0.68-1.25	0.61
FEV ₁ , %predicted	1.00	0.99-1.01	0.89
6-minute walk distance, m	1.00	1.00-1.00	0.55
mMRC dyspnea	1.46	1.13-1.87	0.003
SGRQ Symptoms	1.02	1.01-1.04	0.0014
SGRQ Activities	1.03	1.01-1.05	0.002
SGRQ Impacts	1.03	1.02-1.04	<0.001
SGRQ Total	1.04	1.02-1.05	<0.001
HADS anxiety	1.07	1.02-1.13	0.013
HADS depression	1.05	1.01-1.10	0.024

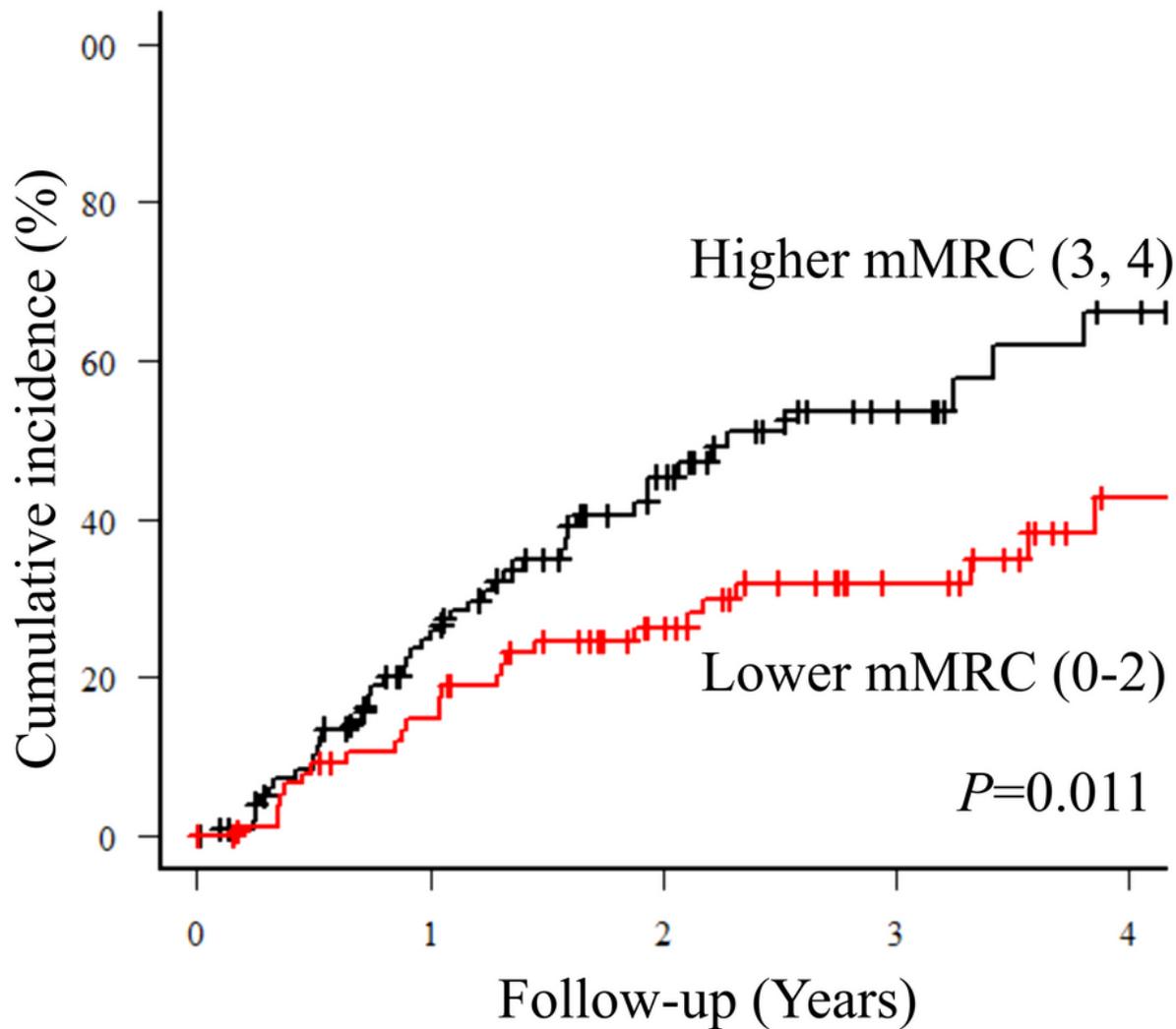
HR, hazard ratio; *CI*, confidence interval; *BMI*, body mass index; *PaO₂*, arterial oxygen pressure; *PaCO₂*, arterial carbon dioxide pressure; *FVC*, forced vital capacity; *FEV₁*, forced expiratory volume in one second; *mMRC*, modified Medical Research Council; *SGRQ*, St. George's Respiratory Questionnaire; *HADS*, Hospital Anxiety and Depression Scale.

Table 3. Multivariable competing risk analysis with the Fine-Gray model to analyze the relationship between patient-reported outcomes and mortality in patients waiting for lung transplantation

	Model I (dyspnea)			Model II (HRQL)			Model III (psychological status)		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age, years	1.04	1.01-1.06	0.007	1.03	1.01-1.06	0.010	1.04	1.01-1.06	0.002
IP	2.41	1.38-4.21	0.002	2.24	1.32-3.78	0.003	2.10	1.26-3.51	0.005
PaCO ₂ , mmHg	1.00	0.97-1.03	0.950	1.00	0.97-1.04	0.840	1.00	0.96-1.03	0.830
FVC, %predicted	0.98	0.96-1.00	0.016	0.99	0.97-1.01	0.150	0.98	0.96-0.99	0.002
mMRC dyspnea	1.36	1.02-1.81	0.037						
SGRQ Total				1.03	1.01-1.05	0.0014			
HADS anxiety							1.05	0.95-1.15	0.330
HADS depression							1.00	0.93-1.07	0.970

HRQL, health-related quality of life; *HR*, hazard ratio; *CI*, confidence interval; *IP*, interstitial pneumonia; *PaCO₂*, arterial carbon dioxide pressure; *FVC*, forced vital capacity; *mMRC*, modified Medical Research Council; *SGRQ*, St. George's Respiratory Questionnaire; *HADS*, Hospital Anxiety and Depression Scale.

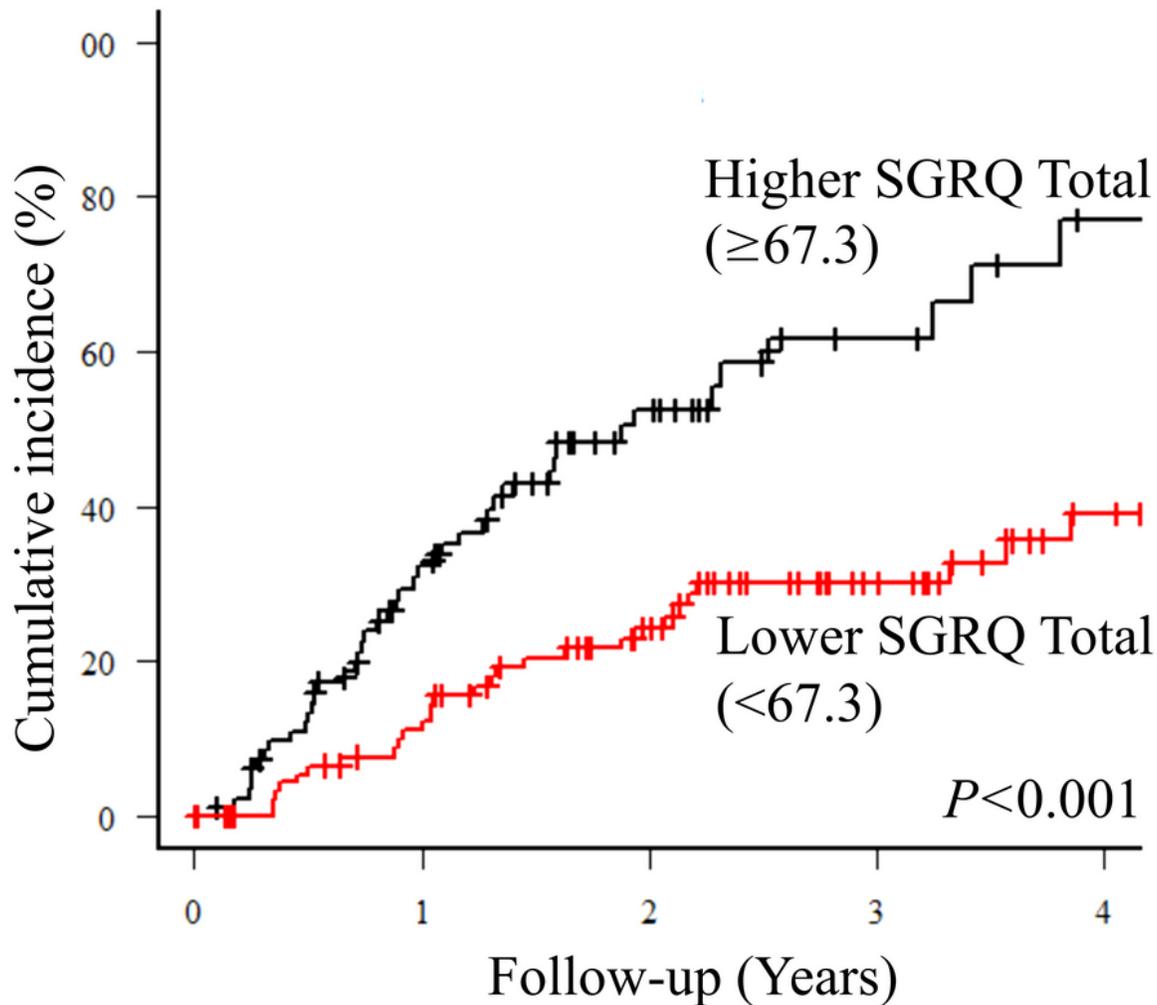
Figures



	0 year	1 year	2 years	3 years	4 years
Higher mMRC dyspnea					
Number at risk	115	64	33	15	7
Upper 95% CI		0.33	0.55	0.64	0.78
Lower 95% CI		0.16	0.33	0.40	0.47
Lower mMRC dyspnea					
Number at risk	79	62	43	25	12
Upper 95% CI		0.23	0.36	0.42	0.56
Lower 95% CI		0.06	0.15	0.20	0.26

Figure 1

Cumulative incidence on the waiting list comparing groups with higher and lower mMRC dyspnea based on the median score. The group with higher mMRC score (mMRC= 3 or 4) showed significantly worse waitlist mortality than that with lower mMRC score (mMRC= 0-2) ($p=0.011$). mMRC, modified Medical Research Council.



	0 year	1 year	2 years	3 years	4 years
Higher SGRQ Total					
Number at risk	97	48	22	9	3
Upper 95% CI		0.42	0.63	0.73	0.88
Lower 95% CI		0.21	0.39	0.45	0.54
Lower SGRQ Total					
Number at risk	98	78	55	32	17
Upper 95% CI		0.17	0.33	0.40	0.51
Lower 95% CI		0.04	0.15	0.19	0.25

Figure 2

Cumulative incidence on the waiting list comparing groups with higher and lower SGRQ Total score based on the median score. The group with higher SGRQ Total score showed significantly worse waitlist mortality than that with lower SGRQ Total score ($p < 0.001$). SGRQ, St. George's Respiratory Questionnaire.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1TableS1.docx](#)
- [Additionalfile2FigureS1.tif](#)
- [Additionalfile3FigureS2.tif](#)
- [Additionalfile4FigureS3.tif](#)
- [Additionalfile5TableS2.docx](#)