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Original article

Clinical characteristics of Japanese candidates for lung transplant for interstitial lung disease and risk factors for early death while on the waiting list

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ABSTRACT

Background: Lung transplants have produced very favorable outcomes for patients with interstitial lung disease (ILD) in Japan. However, because of the severe donor lung shortage, patients must wait approximately 2.5 years before they can undergo transplantation and many candidates die before allocation. We reveal the clinical characteristics of Japanese patients with ILD who are candidates for lung transplants and the risk factors for early death while on the waiting list.

Methods: We retrospectively reviewed the clinical data of patients registered in the Japan Organ Transplant Network from Okayama University Hospital who are candidates for cadaveric lung transplants for ILD between 1999 and 2015.

Results: Fifty-three patients with ILD were included (24 patients with idiopathic pulmonary fibrosis and 29 others). They had severe pulmonary dysfunction and low exercise tolerability. The median waiting time for transplantation was 462 days, and 22 patients died before allocation. Patients who died before 462 days without undergoing transplantation had more severe dyspnea, shorter 6-minute walk distance (6MWD), and lower performance status than those who waited $\geq$462 days.

Abbreviations: ILD, interstitial lung disease; 6MWD, 6-minute walk distance; ISHLT, the International Society for Heart and Lung Transplantation; FVC, forced vital capacity; DLco, diffusing capacity of lung carbon monoxide; LAS, lung allocation score; IPF, idiopathic pulmonary fibrosis; LTOT, long-term oxygen therapy; mMRC, modified Medical Research Council; PS, Performance status.

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Conclusions: Japanese candidates for cadaveric lung transplants for ILD have severe pulmonary dysfunction. Severe dyspnea, short 6MWD, and low performance status are risk factors for early death while on the waiting list.

1. Introduction

Lung transplantation in Japan shows very favorable outcomes with a 73.7% 5-year survival rate, which is better than that reported by the International Society for Heart and Lung Transplantation (ISHLT) registry [1,2]. It is a very powerful treatment for patients with fatal lung disease. However, Japanese candidates for cadaveric lung transplants must wait considerably longer than those in other countries would because of a severe donor lung shortage. The mean waiting time is approximately 2.5 years in Japan versus 4 months in the United States [3,4].

We have used some challenging lung transplantation methods to shorten the long waiting period. We have succeeded in transplanting marginal donor lungs, including a damaged lung that was rejected by all other transplant centers [5]. Furthermore, we have performed a hybrid lung transplant, which is a simultaneous lung transplant from a cadaveric and living donor, when only one cadaveric donor lung is available [6]. However, the long waiting period remains a big problem, particularly for those with interstitial lung disease (ILD), and patients with ILD waiting for transplants have a high mortality rate [7]. We must identify the characteristics of patients who cannot wait for a long time and prioritize them for lung transplantation to decrease the number of deaths during the waiting period.

The ISHLT published recipient selection guidelines in 2015 and proposed the waiting list criteria for patients with ILD [8]. The listing criteria are a decrease in forced vital capacity (FVC) $\geq$10% in 6 months, decline in diffusing capacity of lung carbon monoxide (DLco) $\geq$15% in 6 months, desaturation to $<$88% or distance $<$250 m on the 6-minute walk test or $>$50 m decline in 6-minute walk distance (6MWD) over a 6-month period, pulmonary hypertension and hospitalization because of respiratory decline, and pneumothorax or acute exacerbation. In addition, a lung allocation score (LAS) system has been implemented in the United States and European countries to prioritize more urgent patients. This score ranges from 0 to 100 and predicts 1-year post-transplant survival and mortality rates on the waiting list. Higher scores indicate a greater priority for lung transplantation. The LAS system has decreased waiting list mortality and waiting time in the United States [9–11]. However, such recipient selection criteria and lung allocation system should be established individually in each country because lung transplant circumstances differ significantly among countries.

The characteristics of patients on the waiting list and their clinical course must be understood to determine the appropriate registration time and lung allocation system. However, no study has provided the detailed characteristics of Japanese candidates registered with the Japan Organ Transplant Network. In this study, we revealed the clinical characteristics of Japanese candidates for lung transplantation for ILD and risk factors for death while on the waiting list.

2. Patients and methods

2.1. Study population

We retrospectively reviewed the clinical data of patients who had ILD and were registered in the Japan Organ Transplant Network from Okayama University Hospital who were candidates for cadaveric lung transplants between 1999 and 2015. The study protocol was approved by the Institutional Review Board of Okayama University Hospital (approval date: 18 March 2016, approval #1603-504).

2.2. Data collection

Patient data were obtained from the clinical records of Okayama University Hospital. The LAS was calculated for each patient using a LAS calculator at the Organ Procurement and Transplantation Network website.

2.3. Statistical analysis

Statistical analyses were performed using STATA ver. 11.0 software (Stata Corp., College Station, TX). Data are presented as mean$\pm$standard deviation or median. Patient characteristics were compared using Student's *t*-test and Fisher's exact test. We estimated overall survival with the Kaplan–Meier method and compared each group with the log-rank test. Hazard ratio (HR) and 95% confidence interval (CI) were estimated using a stratified Cox regression model. *P*-values$<$0.05 were considered significant.

3. Results

3.1. Patient characteristics

Fifty-three patients were included in this study. Table 1 shows the classification of their ILD. Among the 53 patients, 24 had idiopathic pulmonary fibrosis (IPF), 14 had idiopathic interstitial pneumonias other than IPF, 11 had connective tissue disease-associated ILD, 2 had chronic hypersensitivity pneumonitis, 1 had hard metal lung disease, and 1 had drug-induced pneumonia. The patient characteristics at registration are shown in Table 2. Mean age at registration was 43.7 years. All patients received long-term oxygen therapy (LTOT). Mean flow rate was 2.3 L/min during rest and 3.9 L/min during exertion. Mean modified Medical Research Council

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