Title: Long-term outcomes of lung transplantation requiring renal replacement therapy: a single-center experience

Word count: 2896 words

Author names and affiliations

Yasuaki Tomioka, [a, b] Seiichiro Sugimoto, [a, b] Toshio Shiotani, [a, b] Kei Matsubara, [a, b] Haruki Choshi, [a, b] Megumi Ishihara, [b] Shin Tanaka, [a, b] Kentaroh Miyoshi, [a] Shinji Otani [a, c], Shinichi Toyooka, [a]

[a] *Department of General Thoracic Surgery and Breast and Endocrinological Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan*

[b] *Department of General Thoracic Surgery and Organ Transplant Center, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan*

[c] *Department of Cardiovascular and Thoracic Surgery, Ehime University Medical School, 454 Shizugawa, Toon, Ehime 791-0295, Japan*

Corresponding author: Seiichiro Sugimoto, MD, PhD

Department of General Thoracic Surgery and Organ Transplant Center, Okayama University Hospital

2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

E-mail: sugimo-s@cc.okayama-u.ac.jp

Tel: +81-86-235-7265, FAX: +81-86-235-7269

Abstract

Background: Life-long immunosuppressive therapy after lung transplantation (LT) may lead to end-stage renal disease (ESRD), requiring renal replacement therapy (RRT). We aimed to investigate the characteristics and long-term outcomes of patients undergoing LT and requiring RRT.

Methods: This study was a single-center, retrospective cohort study. The patients were divided into the RRT (n = 15) and non-RRT (n = 170) groups. We summarized the clinical features of patients in the RRT group and compared patient characteristics, overall survival, and chronic lung allograft dysfunction (CLAD)-free survival between the two groups.

Results: The cumulative incidences of ESRD requiring RRT after LT at 5, 10, and 15 years were 0.8%, 7.6%, and 25.2%, respectively. In the RRT group, all 15 patients underwent hemodialysis but not peritoneal dialysis, and two patients underwent living-donor kidney transplantation. The median follow-up period was longer in the RRT group than in the non-RRT group ($P < 0.001$). The CLAD-free survival and overall survival did not differ between the two groups. The 5-year survival rate even after the initiation of hemodialysis was 53.3%, and the leading cause of death in the RRT group was infection.

Conclusions: Favorable long-term outcomes can be achieved by RRT for ESRD after LT.

Key words: lung transplantation, dialysis, living-donor kidney transplantation, end-stage renal disease, renal replacement therapy

Abbreviations:

BMI, body mass index; CLAD, chronic lung allograft dysfunction; CNI, calcineurin inhibitor; ESRD, end-stage renal disease; FEV1, forced expiratory volume in 1 second; HD, hemodialysis; ICU, intensive care unit; ISHLT, International Society for Heart and Lung Transplantation; KT, kidney transplantation; LAS, lung allocation score; LDKT, living-donor kidney transplantation; LDLLT, living-donor lobar lung transplantation; LT, lung transplantation; OS, overall survival; PGD, primary graft dysfunction; RRT, renal replacement therapy.

Introduction

Lung transplantation (LT) is the only effective and standard therapeutic option for various end-stage lung diseases [1]. Life-long immunosuppressive therapy is required to prevent chronic lung allograft dysfunction (CLAD), which is the main cause of late mortality after LT [2-4]. However, long-term immunosuppression is associated with an increased likelihood of end-stage renal disease (ESRD), because calcineurin inhibitor (CNI) is a nephrotoxic agent [5-9]. ESRD increases the risk of mortality by four-to-five-fold after LT [6]. According to the registry report from the International Society for Heart and Lung Transplantation (ISHLT), ESRD requiring renal replacement therapy (RRT), which includes dialysis and kidney transplantation (KT), develops in 1.4%, 3.3%, and 9.9% of patients within 1 (1.4% on dialysis), 5 (2.8% on dialysis), and 10 years (6.4% on dialysis) after LT, respectively [10].

ESRD and dialysis in recipients of LT may result in intricate and pivotal clinical consequences. Fluid retention accompanied by ESRD has limited tolerability in lung allografts especially among patients undergoing dialysis [6, 11], possibly leading to lung allograft failure [12]. Denervated lung allografts lack the potential to autoregulate blood flow and drain excess alveolar fluid through the lymphatic system [12]. Therefore, KT has been more aggressively implemented in the management of ESRD after LT than long-term dialysis in the United States and Europe [12-14]. In contrast, patients with ESRD can readily access dialysis due to its coverage by the national healthcare system in Japan [15]. Japan has the second largest prevalence of dialysis per population [16]. Additionally, ethnic differences, which are represented by single-nucleotide polymorphisms (SNPs), may affect the long-term development of ESRD after LT [6, 17]. The number of long-term survivors of ESRD after LT has been increasing with a growing number of LT in Japan. However, the clinical characteristics and outcomes of patients with ESRD requiring

RRT after LT remains unknown in the chronic phase after LT in Japan. To date, only the outcomes of patients who required RRT for acute kidney injury in the early phase after LT have been reported in Japan [18]. In this study, we investigated the clinical characteristics and outcomes of patients with ESRD who required RRT in the chronic phase after LT.

Patients and methods

Patients

This retrospective cohort study included 204 recipients who underwent LT at Okayama University Hospital between October 1998 and March 2020, excluding 19 recipients who died within 1 year. The remaining 185 recipients were grouped into recipients who required RRT in the chronic phase after LT (RRT group, n = 15) and those who did not require RRT in the chronic phase after LT (non-RRT group, n = 170). The pre-, intra-, and postoperative characteristics of the recipients were retrospectively collected from the institutional database and medical records on March 31, 2021. Information on the following preoperative characteristics of the recipients were collected: patient age, sex, body mass index (BMI), diagnosis, lung allocation score (LAS), cytomegalovirus mismatch, lung donor type (living donor, deceased donor, or hybrid, which is simultaneous living-donor LT and cadaveric LT on each side), and pre-transplant creatinine level. Information on intraoperative recipient characteristics, including the lung transplant procedure (single or bilateral), operative time, ischemic time, and cardiopulmonary bypass use, were obtained. Information collected on postoperative recipient characteristics included the maximum grade of primary graft dysfunction (PGD), incidence of acute rejection, incidence of antibody-mediated rejection, overall survival (OS), and CLAD after LT. Additionally, information on pre- and postoperative comorbidities (diabetes mellitus, hypertension, dyslipidemia and hyperuricemia), initial dialysis (scheduled or emergency), time to dialysis after LT, survival after dialysis, and KT after LT, were obtained. To establish the preoperative condition of the recipients, the LAS of each patient was calculated retrospectively using information provided during registration on the LT waiting list. The tool used for calculating the LAS was the lung composite allocation score (CAS) calculator, which was published on the Organ Procurement and Transplantation Network (OPTN) website (https://optn.transplant.hrsa.gov/data/allocation-calculators/lung-cas-calculator/) in July 2020. PGD grades were assigned based on the definition of PGD proposed in the consensus report of the ISHLT [19]. CLAD was diagnosed using the classification system proposed by ISHLT [20]. CLAD-free survival was defined as the time from LT to CLAD diagnosis, and the data were censored at the date of death. OS was defined as the time from LT to the date of death. This study was conducted with the approval of the Institutional Review Board of Okayama University Hospital (No. 2109-003). Patients provided informed consent by indicating their decision to participate or withdraw on a website. All methods were performed according to relevant guidelines and regulations.

Procedure

The organ donation allocation system for brain-dead donors is mainly based on waiting time, because Japan has not yet applied the LAS system. Critically ill patients who cannot afford to wait for cadaveric LT require living-donor lobar lung transplantation (LDLLT). Patients with LDLLT must be <70 years of age and meet conventional criteria for cadaveric LT. Patients requiring cadaveric LT are registered with the Japan Organ Transplantation Network. Our institution only accepts third-degree blood relatives or spouses as living donors. The sizematching protocol and transplant procedures have been described previously [21]. Graft ischemic time was defined as the ischemic time of the second transplanted lung.

Postoperative care

Postoperative management, including immunosuppressive and prophylactic treatments for viral and fungal infections, has been previously described [22]. Immunosuppressive therapy comprised the use of CNI (including tacrolimus and cyclosporine), mycophenolate mofetil or azathioprine, and corticosteroids. The CNI was first administered by the enteric route through a nasogastric tube between 1998 and 2010, and by intravenous administration between 2011 and 2021, followed by oral administration [23, 24]. Target trough levels for tacrolimus and cyclosporine were 10–15 ng/ml and 250–350 ng/ml, respectively, in the first 3 months after LT, 8–12 ng/ml and 200–300 ng/ml, respectively, in the subsequent 3 months, and 7–10 ng/ml and 150–250 ng/ml, respectively, thereafter. Diabetes mellitus after LT was treated in accordance with the treatment guidelines for type 2 diabetes mellitus [25], and vigilant monitoring was required for potential drug-drug interactions and infections associated with immunosuppressive therapy. For the treatment of hypertension, amlodipine and nifedipine were preferred. Dyslipidemia was treated with statin therapy to decrease cardiovascular risk. Hyperuricemia was treated with xanthine oxidase inhibitors, such as febuxostat and allopurinol.

According to the definition proposed by the ISHLT, PGD grades were determined upon intensive care unit (ICU) admission after LT and 24, 48, and 72 hours after admission [19]. Acute rejection episodes were defined as episodes requiring intravenous corticosteroid infusion therapy for three consecutive days. CLAD was diagnosed by a decline in the forced expiratory volume in 1 second (FEV1) to 80% of the baseline, as defined by the ISHLT classification system [20]. The baseline FEV_1 value was approximated as the mean of the two best FEV_1 values measured at least 3 weeks apart [20]. For the differential diagnosis of CLAD, chest radiography, chest computed tomography, pulmonary function tests, blood examinations, electrocardiography, lung ventilation scintigraphy [26], and lung perfusion scintigraphy [27] were also performed.

Statistical analyses

We performed a univariate analysis between patients in the two groups. Categorical variables were expressed as the number of cases and percentages, whereas continuous variables were expressed as medians and ranges. Categorical variables were compared using Fisher's exact probability test, and continuous variables were compared using the Mann-Whitney U test. CLAD-free survival and OS were analyzed using the Kaplan–Meier method and compared using the log-rank test. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [28]. More precisely, it is a modified version of the R commander that incorporates additional statistical functions frequently used in biostatistics. All *P*-values were two-sided, and statistical significance was set at $P < 0.05$.

Results

Of the 185 patients, 15 (8.1%) patients developed ESRD requiring chronic dialysis. The cumulative incidence of ESRD requiring dialysis at 5, 10, and 15 years were 0.8%, 7.6%, and 25.2%, respectively (**Fig. 1**). The characteristics of patients in the two groups are presented in **Table 1**. The graft ischemic time was shorter in the RRT group than in the non-RRT group (P = 0.041) due to the relatively higher rate of LDLLT in the RRT group. The percentages of known risk factors for CKD, including diabetes mellitus, hypertension, dyslipidemia and hyperuricemia, did not differ between the two group in the preoperative phase, during the admission for LT, and in the chronic phase after LT, except for the percentage of preoperative hyperuricemia. There was no significant difference in the use of CNI between two groups.

The clinical characteristics of the RRT group are summarized in **Table 2**. In the RRT group, all 15 patients underwent chronic hemodialysis (HD) but not peritoneal dialysis. Whereas six patients underwent emergency HD, the remaining nine patients underwent scheduled HD. The median interval between LT and the initiation of HD was 11.5 (4.4–17.7) years. Nine (60.0 %) recipients developed CLAD, and seven (46.7 %) patients developed CLAD before the initiation of HD. Two patients (Cases 2 and 15) underwent living-donor KT (LDKT). The intervals between LT and KT were 13.5 years in Case 2 and 18.5 years in Case 15. The intervals between hemodialysis and KT were 1.9 years in Case 2 and 4.0 years in Case 15. Six patients died during the observation period; five (83.3%) of these patients died of infective causes, such as sepsis, pneumonia, and aspergillosis. Twelve (80.0%) patients mainly underwent follow-up at a local hospital after LT.

The 5-, 10-, and 15-year CLAD-free survival rates of the RRT group were 73.3%, 57.0%, and 47.5%, respectively. These rates were similar to those of the non-RRT group (P = 0.473) (**Fig. 2**). As shown in **Fig. 3**, no difference in the OS rates was observed between the two groups (P = 0.694). The 5-, 10-, and 15-year OS rates in the RRT group were 100%, 79.0%, and 63.2%, respectively. Additionally, the 1-, 3-, and 5-year survival rates after the initiation of HD in the RRT group were 93.3%, 77.8%, and 53.3%, respectively (**Fig. 4**). The survival rates after the initiation of HD did not differ between the patients who underwent emergency and scheduled HD (P = 0.805, **Supplementary Fig. S1**).

Discussion

In this study, we found that long-term survivors of LT might develop ESRD as a chronic complication, necessitating RRT. However, the patients with RRT demonstrated favorable CLAD-free survival and OS similar to the patients without RRT after LT. The 5-year survival rate even after the initiation of HD showed a favorable outcome, and the leading cause of death was infection among patients with RRT. Our results suggest that even when the recipients of LT require RRT for ESRD in the chronic phase, RRT with careful monitoring for infection may provide favorable long-term outcomes in Japan.

The cumulative incidence of ESRD requiring RRT at 10 years after LT in our study (7.6%) tended to be lower than that in the ISHLT registry report (9.9%) [10]. Our results might be corroborated by the fact that Asians have a lower risk of ESRD requiring RRT than Caucasians [6]. With respect to patient characteristics, the RRT group had significantly shorter ischemic time and longer follow-up period than the non-RRT group after LT in our study. These results were reflected by the relatively high rate of LDLLT in the RRT group, because LDLLT was aggressively performed before the revision of the Organ Transplant Act in 2010 in Japan and the survivors of LDLLT tended to have long follow-up period. ESRD has been shown to develop over time after LT [6], and long-term survival rates after LT in Japan are known to be better than those of the ISHLT registry report [1, 29]. Accordingly, the number of long-term survivors of LT with ESRD are increasing in Japan. Physicians should pay attention to the introduction of RRT for ESRD in the chronic phase after LT.

Therapeutic intervention for CKD after LT includes the management of known risk factors for CKD, such as diabetes mellitus, hypertension, dyslipidemia, and hyperuricemia, and the patient education regarding salt and fluid intake as well as the avoidance of nonsteroidal anti-inflammatory drugs [12, 29]. In the present study, the prevalence of known risk factors for CKD did not differ between the two groups, except for preoperative hyperuricemia. Our results might be attributed to our strategy of early intervention for known risk factors for CKD after LT. In the patients with CKD after LT, we minimize the use of nephrotoxic agents and reduce the dose of CNI with increasing the dose of mycophenolate mofetil if possible [12, 29]. Furthermore, m-TOR inhibitors, including sirolimus and everolimus, would be a therapeutic option, if they were covered for immunosuppressive agents after LT by the national health insurance program in Japan [29].

Only two of 15 recipients undergoing chronic HD after LT underwent LDKT and remain alive in our study. Compared with dialysis, KT improves survival in patients with ESRD [30, 31] with or without non-renal organ transplantation [6, 14]. Moreover, LDKT after LT has been shown to offer better long-term survival [12]. Since the average waiting time for KT from deceased donors is more than 14 years due to the severe donor shortage in Japan [32], LDKT may be a feasible option for patients who develop ESRD after LT, particularly for those who have stable lung allograft function. Especially, the availability of living-donors for LDKT would be limited for the survivors of LDLLT due to the history of living lung donation. ABO blood type-incompatible LDKT, which is commonly performed for LDKT, might be a solution to this issue.

While nine of 15 (60.0 %) patients with RRT developed CLAD, the CLAD-free survival did not differ between the RRT and non-RRT groups after LT. Notably, four of seven recipients had already developed CLAD before the initiation of HD and died during the observation period. The initiation of HD might negatively affect the disease progression of CLAD due to limited tolerability for fluid retention in denervated lung allografts [6, 11]. Attention should be paid to fluid overload especially in the initiation of HD for the patients with CLAD after LT [33]. Our results might lend a support that survival of patients on the waiting list for KT after LT is determined by the progression of lung disease but not renal pathology [13]. Therefore, despite further deterioration of renal function, immunosuppressive therapy should be maintained to prevent disease progression of CLAD. Given the increasing number of patients with ESRD and CLAD after LT, concurrent lung and kidney transplantations from deceased donors should be considered for implementation in Japan as in the other countries.

No significant difference in the OS was observed between the RRT and non-RRT groups after LT in our study. Furthermore, the 5-year survival rate even after the initiation of HD showed a favorable outcome (53.3%), compared with the previous results of a median survival of 5 months [34] or 37.1 months [14] after LT for patients requiring dialysis after LT. Our results would be attributed to the unique situation of dialysis in Japan, where the national health insurance system covers most costs of dialysis treatment [15] and the survival rate of dialysis patients is the highest in the world [35]. Although the emergency introduction of HD is associated with a poor prognosis [36], patients undergoing emergency HD had similar survival after the initiation of HD to patients undergoing scheduled dialysis in our study. Nevertheless, careful follow-up and early prophylactic HD for patients with ESRD would lead to lower mortality and better quality of life [36].

Consistent with previously reported results [37], infection was the leading cause of death in patients undergoing RRT after LT in our study. Impairment of the typical response of the innate and adaptive immune systems in ESRD is associated with increased susceptibility to infections and poor vaccine response [37, 38]. Moreover, chronic immune activation leads to a proinflammatory milieu [39-41], contributing to the progression of atherosclerosis and cardiovascular diseases [42]. Notably, the three oldest patients in our study (Cases 10, 13, and 14) died within 2 years of the initiation of HD. In addition to the ESRD-induced immune changes, our results might lend support to age-based changes in immune responses, i.e. immuno-senescence, in elderly patients [43-45], including replicative senescence, weakened thymic function, and modified cytokine secretion patterns [46].

This study had several limitations. First, the number of LT recipients was small in this study. Therefore, a nationwide study will be required in the future. Second, most of the patients did not receive KT due to the severe donor shortage and easy access to HD in Japan. Therefore, the outcomes of LT may vary when the number of KT increase. Third, the RRT group better corresponded to the long-term survivors of LT who had longer follow-up periods than the non-RRT group, leading to a potential bias for survival analysis. However, since this study is the first report of long-term outcomes of patients who undergo RRT for ESRD after LT in Japan, our results would provide essential information for long-term management after LT.

Conclusions

Long-term survivors of LT might develop ESRD requiring RRT. However, the CLAD-free survival and OS were similar between the RRT and non-RRT groups. Favorable long-term outcomes can be achieved by RRT even in patients developing ESRD after LT. Additionally, patients undergoing RRT after LT should be carefully monitored to prevent development of infections.

Funding

This study was supported by a Grant-in-Aid for Scientific Research (Grant No. 23K08294) from the Japan Society for the Promotion of Science.

Author contributions

Y.T. and S.S. designed the study. Y.T. analyzed the data and performed statistical analyses. Y.T. and S.S. drafted and revised the manuscript. All authors critically edited and approved the final version of the manuscript.

Data Availability

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

Conflict of interest

The authors have no conflicts of interest.

Acknowledgements

We would like to thank all this study participants for their cooperation and International Medical Information Center (www.imic.or.jp) for their assistance with English-language editing.

Appendix A. Supplementary data

Supplementary data to this article can be found online.

References

[1] Chambers DC, Perch M, Zuckermann A, Cherikh WS, Harhay MO, Hayes D Jr, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-eighth adult lung transplantation report - 2021; Focus on recipient characteristics. J Heart Lung Transplant. 2021;40:1060-72. https://doi:org/10.1016/j.healun.2021.07.021. PMID: 34446355.

[2] Korom S, Boehler A, Weder W. Immunosuppressive therapy in lung transplantation: state of the art. Eur J Cardiothorac Surg. 2009;35:1045-55. https://doi:org/10.1016/j.ejcts.2009.02.035. PMID: 19349186.

[3] Scheffert JL, Raza K. Immunosuppression in lung transplantation. J Thorac Dis. 2014;6:1039-53. https://doi:org/10.3978/j.issn.2072-1439.2014.04.23. PMID: 25132971.

[4] Sugimoto S, Yamamoto H, Kurosaki T, Otani S, Okazaki M, Yamane M, et al. Impact of chronic lung allograft dysfunction, especially restrictive allograft syndrome, on the survival after living-donor lobar lung transplantation compared with cadaveric lung transplantation in adults: a single-center experience. Surg Today. 2019;49:686-93. https://doi:org/10.1007/s00595-019-01782-0. PMID: 30790054.

[5] Fisher NC, Nightingale PG, Gunson BK, Lipkin GW, Neuberger JM.Chronic renal failure following liver transplantation: a retrospective analysis. Transplantation. 1998;66:59-66. https://doi:org/10.1097/00007890-199807150-00010. PMID: 9679823.

[6] Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. New England Journal of Medicine. 2003;349:931-40. https://doi:org/10.1056/NEJMoa021744. PMID: 12954741.

[7] Pattison JM, Petersen J, Kuo P, Valantine V, Robbins RC, Theodore J. The incidence of

renal failure in one hundred consecutive heart-lung transplant recipients. American journal of kidney diseases. 1995;26:643-8. https://doi:org/10.1016/0272-6386(95)90602-9. PMID: 7573020.

[8] Wilkinson AH, Cohen DJ. Renal failure in the recipients of nonrenal solid organ transplants. J Am Soc Nephrol. 1999;10:1136-44. https://doi:org/10.1681/ASN.V1051136. PMID: 10232701.

[9] Sugimoto S, Date H, Miyoshi K, Otani S, Ishihara M, Yamane M, et al . Long-term outcomes of living-donor lobar lung transplantation. J Thorac Cardiovasc Surg. 2022;164:440-8. https://doi:org/10.1016/j.jtcvs.2021.08.090. PMID: 34895720.

[10] Chambers DC, Cherikh WS, Harhay MO, Hayes D Jr, Hsich E, Khush KK, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult lung and heart-lung transplantation Report-2019; Focus theme: Donor and recipient size match. J Heart Lung Transplant. 2019;38:1042-55. https://doi:org/10.1016/j.healun.2019.08.001. PMID: 31548030.

[11] Bloom RD, Doyle AM. Kidney disease after heart and lung transplantation. Am J Transplant. 2006;6:671-9. https://doi:org/10.1111/j.1600-6143.2006.01248.x. PMID: 16539623.

[12] Otani S, Levvey BJ, Westall GP, Paraskeva M, Whitford H, Williams T, et al. Long-term successful outcomes from kidney transplantation after lung and heart-lung transplantation. Ann Thorac Surg. 2015;99:1032-8. https://doi:org/10.1016/j.athoracsur.2014.11.023. PMID: 25624053.

[13] Osho AA, Hirji SA, Castleberry AW, Mulvihill MS, Ganapathi AM, Speicher PJ, et al. Long-term survival following kidney transplantation in previous lung transplant recipients-

An analysis of the unos registry. Clin Transplant. 2017;31. https://doi:org/10.1111/ctr.12953. PMID: 28295652.

[14] Lonze BE, Warren DS, Stewart ZA, Dagher NN, Singer AL, Shah AS, et al. Kidney transplantation in previous heart or lung recipients. Am J Transplant. 2009;9:578-85. https://doi:org/10.1111/j.1600-6143.2008.02540.x. PMID: 19260837.

[15] Hanafusa N, Fukagawa M. Global Dialysis Perspective: Japan. Kidney360. 2020;1:416-9. https://doi:org/10.34067/KID.0000162020. PMID: 35369370.

[16] United States Renal Data System. 2022 Annual Data Report. End Stage Renal Disease: International Comparisons. [cited 2023 August 15]. Available online: https://usrds-adr.niddk.nih.gov/2022/end-stage-renal-disease/11-international-comparisons.

[17] Tomioka Y, Sugimoto S, Yamamoto H, Tomida S, Shiotani T, Tanaka S, et al. Identification of genetic loci associated with renal dysfunction after lung transplantation using an ethnic-specific single-nucleotide polymorphism array. Sci Rep. 2023;13:8912. https://doi:org/10.1038/s41598-023-36143-y. PMID: 37264212.

[18] Katahira M, Hirama T, Eba S, Suzuki T, Notsuda H, Oishi H, et al. Impact of Postoperative Continuous Renal Replacement Therapy in Lung Transplant Recipients. Transplant Direct. 2020;6:e562. https://doi:org/10.1097/TXD.0000000000001013. PMID: 33062846.

[19] Snell GI, Yusen RD, Weill D, Strueber M, Garrity E, Reed A, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading-A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant. 2017;36:1097-103. https://doi:org/10.1016/j.healun.2017.07.021. PMID: 28942784.

[20] Verleden GM, Glanville AR, Lease ED, Fisher AJ, Calabrese F, Corris PA, et al. Chronic

lung allograft dysfunction: Definition, diagnostic criteria, and approaches to treatment-A consensus report from the Pulmonary Council of the ISHLT. J Heart Lung Transplant. 2019;38:493-503. https://doi:org/10.1016/j.healun.2019.03.009. PMID: 30962148.

[21] Date H, Aoe M, Nagahiro I, Sano Y, Matsubara H, Goto K, et al. How to predict forced vital capacity after living-donor lobar-lung transplantation. J Heart Lung Transplant. 2004;23:547-51. https://doi:org/10.1016/j.healun.2003.07.005. PMID: 15135369.

[22] Sugimoto S, Yamane M, Otani S, Kurosaki T, Okahara S, Hikasa Y, et al. Airway complications have a greater impact on the outcomes of living-donor lobar lung transplantation recipients than cadaveric lung transplantation recipients. Surg Today. 2018;48:848-55. https://doi:org/10.1007/s00595-018-1663-6. PMID: 29680912.

[23] Date H, Aoe M, Sano Y, Nagahiro I, Miyaji K, Goto K, et al. Improved survival after living-donor lobar lung transplantation. J Thorac Cardiovasc Surg 2004;128:933-40. https://doi:org/10.1016/j.jtcvs.2004.07.032. PMID: 15573079.

[24] Hirano Y, Sugimoto S, Mano T, Kurosaki T, Miyoshi K, Otani S, et al. Prolonged Administration of Twice-Daily Bolus Intravenous Tacrolimus in the Early Phase After Lung Transplantation. Ann Transplant 2017;22:484-92. https://doi:org/10.12659/aot.904225. PMID: 28798289.

[25] Shivaswamy V, Boerner B, Larsen J. Post-Transplant Diabetes Mellitus: Causes, Treatment, and Impact on Outcomes. Endocr Rev 2016;37:37-61. https://doi:org/10.1210/er.2015-1084. PMID: 26650437

[26] Shinya T, Sato S, Kato K, Gobara H, Akaki S, Date H, et al. Assessment of mean transit time in the engrafted lung with 133Xe lung ventilation scintigraphy improves diagnosis of bronchiolitis obliterans syndrome in living-donor lobar lung transplant recipients. Ann Nucl

Med. 2008;22:31-9. https://doi:org/10.1007/s12149-007-0078-z. PMID: 18250985.

[27] Yamamoto H, Sugimoto S, Kurosaki T, Miyoshi K, Otani S, Okazaki M, et al. Lung perfusion scintigraphy to detect chronic lung allograft dysfunction after living-donor lobar lung transplantation. Sci Rep. 2020;10:10595. https://doi:org/10.1038/s41598-020-67433-4. PMID: 32601414.

[28] Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452-8. https://doi:org/10.1038/bmt.2012.244. PMID: 23208313.

[29] Sugimoto S, Matsubara K, Tanaka S, Miyoshi K, Ishihara M, Toyooka S. Long-term management and outcome of lung transplantation in Japan. J Thorac Dis 2023. https://doi:org/10.21037/jtd-22-1679. PMID: 37868843.

[30] Schnuelle P, Lorenz D, Trede M, Van Der Woude FJ. Impact of renal cadaveric transplantation on survival in end-stage renal failure: evidence for reduced mortality risk compared with hemodialysis during long-term follow-up. J Am Soc Nephrol. 1998;9:2135-41. https://doi:org/10.1681/ASN.V9112135. PMID: 9808102.

[31] Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. N Engl J Med. 1999;23:1725-30. https://doi:org/10.1056/NEJM199912023412303. PMID: 10580071.

[32] The Japan Organ Transplant Network. Organ donation and transplantation data book 2017. https://www.jotnw.or.jp/datas/databook/. [Accessed August 1 2023].

[33] Shimizu D, Miyoshi K, Sugimoto S, Toma T, Matsuda Y, Tomioka Y, et al. Acute Pulmonary Edema Due to Arteriovenous Shunt Placement After Lung Transplantation. Ann Thorac

Surg 2022;114:e245-e7. https://doi:org/10.1016/j.athoracsur.2021.12.017. PMID: 35007504

[34] Mason DP, Solovera-Rozas M, Feng J, Rajeswaran J, Thuita L, Murthy SC, et al. Dialysis after lung transplantation: prevalence, risk factors and outcome. J Heart Lung Transplant. 2007;26:1155-62. https://doi:org/10.1016/j.healun.2007.08.006. PMID: 18022082.

[35] Goodkin DA, Bragg-Gresham JL, Koenig KG, Wolfe RA, Akiba T, Andreucci VE, et al. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). J Am Soc Nephrol. 2003;14:3270-7. https://doi:org/10.1097/01.asn.0000100127.54107.57. PMID: 14638926.

[36] Bian Z, Gu H, Chen P, Zhu S. Comparison of prognosis between emergency and scheduled hemodialysis. J Int Med Res. 2019;47:1221-31. https://doi:org/10.1177/0300060518807092. PMID: 30704325.

[37] Kato S, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, et al. Aspects of immune dysfunction in end-stage renal disease. Clin J Am Soc Nephrol. 2008;3:1526-33. https://doi:org/10.2215/CJN.00950208. PMID: 18701615.

[38] Syed-Ahmed M, Narayanan M. Immune Dysfunction and Risk of Infection in Chronic Kidney Disease. Adv Chronic Kidney Dis. 2019;26:8-15. https://doi:org/10.1053/j.ackd.2019.01.004. PMID: 30876622.

[39] Witko-Sarsat Vr, Friedlander M, Khoa TN, Capeillère-Blandin C, Nguyen AT, Canteloup S, et al. Advanced Oxidation Protein Products as Novel Mediators of Inflammation and Monocyte Activation in Chronic Renal Failure1, 2. The Journal of Immunology. 1998;161:2524-32. PMID: 9725252.

[40] Arici M, Walls J. End-stage renal disease, atherosclerosis, and cardiovascular mortality: is C-reactive protein the missing link? Kidney Int. 2001;59:407-14. https://doi:org/10.1046/j.1523-1755.2001.059002407.x. PMID: 11168922.

[41] Girndt M, Ulrich C, Kaul H, Sester U, Sester M, Kohler H. Uremia-associated immune defect: the IL-10-CRP axis. Kidney Int Suppl. 2003:S76-9. https://doi:org/10.1046/j.1523-1755.63.s84.14.x. PMID: 12694315.

[42] Girndt M, Kaul H, Sester U, Ulrich C, Sester M, Georg T, et al. Anti-inflammatory interleukin-10 genotype protects dialysis patients from cardiovascular events. Kidney Int. 2002;62:949-55. https://doi:org/10.1046/j.1523-1755.2002.00504.x. PMID: 12164877.

[43] Aw D, Silva AB, Palmer DB. Immunosenescence: emerging challenges for an ageing population. Immunology. 2007;120:435-46. https://doi:org/10.1111/j.1365-2567.2007.02555.x. PMID: 17313487.

[44] Gruver AL, Hudson LL, Sempowski GD. Immunosenescence of ageing. J Pathol. 2007;211:144-56. https://doi:org/10.1002/path.2104. PMID: 17200946.

[45] Tomioka Y, Tanaka S, Otani S, Shiotani T, Yamamoto H, Miyoshi K, et al. Elderly lung transplant recipients show acceptable long-term outcomes for lung transplantation: A propensity score-matched analysis. Surg Today. 2023. Jun 3. doi: 10.1007/s00595-023-02699-5. Epub ahead of print. https://doi:org/10.1007/s00595-023-02699-5. PMID: 37269338.

[46] Pawelec G, Barnett Y, Forsey R, Frasca D, Globerson A, McLeod J, et al. T cells and aging, January 2002 update. Front Biosci. 2002;7:d1056-183. https://doi:org/10.2741/a831. PMID: 11991846.

Table 1. Characteristics of recipients in the RRT and non-RRT groups

Variables	Non-RRT (N = 170)	RRT (N = 15)	*P* value
Preoperative variables			
Age, years, median (range)	35.5 (1.0-68.0)	32.0 (16.0-64.0)	0.807
Sex (female), n (%)	102 (60.0%)	12 (80.0%)	0.169
Body mass index, kg/m^2, median (range)	17.7 (10.5-28.8)	18.3 (14.7-29.0)	0.494
Diagnoses			0.081
Interstitial lung disease	51 (30.0%)	2 (13.3%)	
Pulmonary hypertension	32 (18.8%)	6 (40.0%)	
Pulmonary graft-versus-host disease	30 (17.6%)	1 (6.7%)	
Lymphangioleiomyomatosis	13 (7.6%)	4 (26.7%)	
Chronic obstructive pulmonary disease	10 (5.9%)	0 (0.0%)	
Other diseases	24 (14.1%)	2 (13.3%)	
Lung allocation score, median (range)	40.8 (22.1-100.0)	38.4 (30.2-72.2)	0.442
CMV mismatch (recipient negative/donor positive)	17 (10.0%)	0 (0.0%)	0.368
Lung donor			0.093
Living donor	75 (44.1%)	10 (66.7%)	
Deceased donor	93 (54.7%)	5 (33.3%)	
Hybrid	2 (1.2%)	0 (0.0%)	
Pretransplant creatinine (mg/dl), median (range)	0.58 (0.10-1.72)	0.55 (0.32-0.89)	0.736
Preoperative diabetes mellitus, yes	16 (9.4%)	1 (6.7%)	1
Preopeartive hypertension, yes	35 (20.6%)	1 (6.7%)	0.310
Preoperative dyslipidemia, yes	12 (7.1%)	2 (13.3%)	0.316
Preoperative hyperuricemia, yes	6 (3.5%)	3 (20.0%)	0.027
Intraoperative variables			
Lung transplant procedure			0.740
Single	36 (21.2%)	1 (6.7%)	
Bilateral	134 (78.8%)	14 (93.3%)	
Operative time (min), median (range)	460.0 (219.0-1174.0)	478.5 (252.0-563.0)	0.939
Ischemic time (min), median (range)	332.0 (74.0-787.0)	192.0 (89.0-665.0)	0.041
Cardiopulmonary bypass use, yes	133 (78.2%)	14 (93.3%)	0.314
Postoperative variables			
Maximum grade of PGD (0-72h), median (range)	2 (0-3)	2 (0-3)	0.845
Acute rejection, yes	74 (43.5%)	8 (53.3%)	0.281
Antibody-mediated rejection, yes	12 (7.1%)	2 (13.3%)	0.316
Diabetes mellitus during the admission for LT, yes	39 (22.9%)	1 (6.7%)	0.198
Hypertension during the admission for LT, yes	139 (81.8%)	13 (86.7%)	1
Dyslipidemia during the admission for LT, yes	33 (19.4%)	5 (33.3%)	0.197
Hyperuricemia during the admission for LT, yes	11 (6.5%)	2 (13.3%)	0.284
Calcineurin inhibitor			0.317
Tacrolimus	136 (80.0%)	10 (66.7%)	
Cyclosporine	34 (20.0%)	5 (33.3%)	
Diabetes mellitus in the chronic phase, yes	29 (17.1%)	3 (20.0%)	0.727
Hypertension in the chronic phase, yes	127 (74.7%)	14 (93.3%)	0.125
Dyslipidemia in the chronic phase, yes	43 (25.3%)	7 (46.7%)	0.124
Hyperuricemia in the chronic phase, yes	31 (18.2%)	4 (26.7%)	0.490
Kidney transplantation after lung transplantation, yes	0 (0.0%)	2 (13.3%)	0.006

Data are presented as n, median (range) or n (%). CMV, cytomegalovirus; LT, lung transplantation; PGD, primary graft dysfunction; RRT, renal replacement therapy

Table 2. Characteristics of LT recipients requiring RRT

Case	Age	Sex	Diagnosis	Type of LT	Procedure type	CNI	Scheduled or emergency HD for initial HD	Follow-up period after initial LT (y)	Time to HD after initial LT (y)	Survival after HD (y)	KT	CLAD	Onset of CLAD before or after HD	CLAD-free survival (y)	Outcome	Cause of death	Follow-up hospital
1	29	F	GVHD	LDLLT	Bilateral	TAC	Scheduled	20.9	17.7	3.2	No	Yes	Before	15.7	Alive		Transplant center
2	23	F	LAM	LDLLT	Bilateral	TAC	Emergency	20.5	11.5	8.9	Yes	No	No	20.5	Alive		Local hospital
3	25	F	CF	LDLLT	Bilateral	CYA	Scheduled	18.9	15.4	3.5	No	Yes	Before	7.0	Dead	Pneumonia	Local hospital
4	38	F	PH	LDLLT	Bilateral	TAC	Scheduled	12.1	6.8	5.4	No	Yes	Before	4.1	Dead	Sepsis	Local hospital
5	30	F	LAM	CLT	Bilateral	CYA	Scheduled	17.5	14.2	3.3	No	Yes	After	16.1	Alive		Local hospital
6	35	F	PH	LDLLT	Bilateral	TAC	Scheduled	15.6	13.2	2.5	No	No	No	15.6	Alive		Local hospital
7	32	F	PH	LDLLT	Bilateral	TAC	Emergency	12.7	8.6	4.1	No	Yes	Before	7.6	Dead	Heart failure, CLAD	Local hospital
8	32	F	LAM	LDLLT	Bilateral	TAC	Emergency	14.2	13.2	1.1	No	No	No	14.2	Alive		Local hospital
9	16	F	PH	LDLLT	Bilateral	TAC	Scheduled	14.2	6.5	7.7	No	Yes	Before	2.1	Alive		Transplant center
10	40	F	LAM	CLT	Single	TAC	Scheduled	7.6	6.0	1.6	No	No	No	7.6	Dead	Hemoptysis from native lung (Aspergillosis)	Local hospital
11	33	F	LCH	LDLLT	Bilateral	CYA	Scheduled	14.0	13.5	0.5	No	Yes	After	13.9	Alive		Local hospital
12	32	F	ILD	CLT	Bilateral	CYA	Emergency	10.4	6.9	3.5	No	Yes	Before	0.6	Alive		Transplant center
13	57	M	PH	CLT	Bilateral	TAC	Scheduled	6.4	4.4	2.0	No	Yes	Before	6.4	Dead	Sepsis	Local hospital
14	64	M	ILD	LDLLT	Bilateral	TAC	Emergency	5.8	5.5	0.3	No	No	No	5.8	Dead	Sepsis	Local hospital
15	23	M	CLAD	CLT	Bilateral	CYA	Emergency	19.9	14.5	5.4	Yes	No	No	6.2	Alive		Local hospital

Data are presented as n, median (range) or n (%). CF, cystic fibrosis; CLAD, chronic lung allograft dysfunction; CLT, cadaveric lung transplantation; CMV, cytomegalovirus; CNI, calcineurin inhibitor; CYA, cyclosporine; F, female; GVHD, graft-versus-host disease; HD, hemodialysis; ILD, interstitial lung disease; KT, kidney transplantation; LAM, lymphangioleiomyomatosis; LCH, langerhans cell histiocytosis; LDLLT, living-donor lobar lung transplantation; M, male; PGD, primary graft dysfunction; PH, pulmonary hypertension; RRT, renal replacement therapy;TAC, tacrolimus

Figure legends

Figure 1. Cumulative incidence of end-stage renal disease (ESRD) requiring dialysis. The cumulative incidences of ESRD at 5, 10, 15, and 20 years after lung transplantation were 0.83%, 7.6%, 25.2%, and 35.0%, respectively.

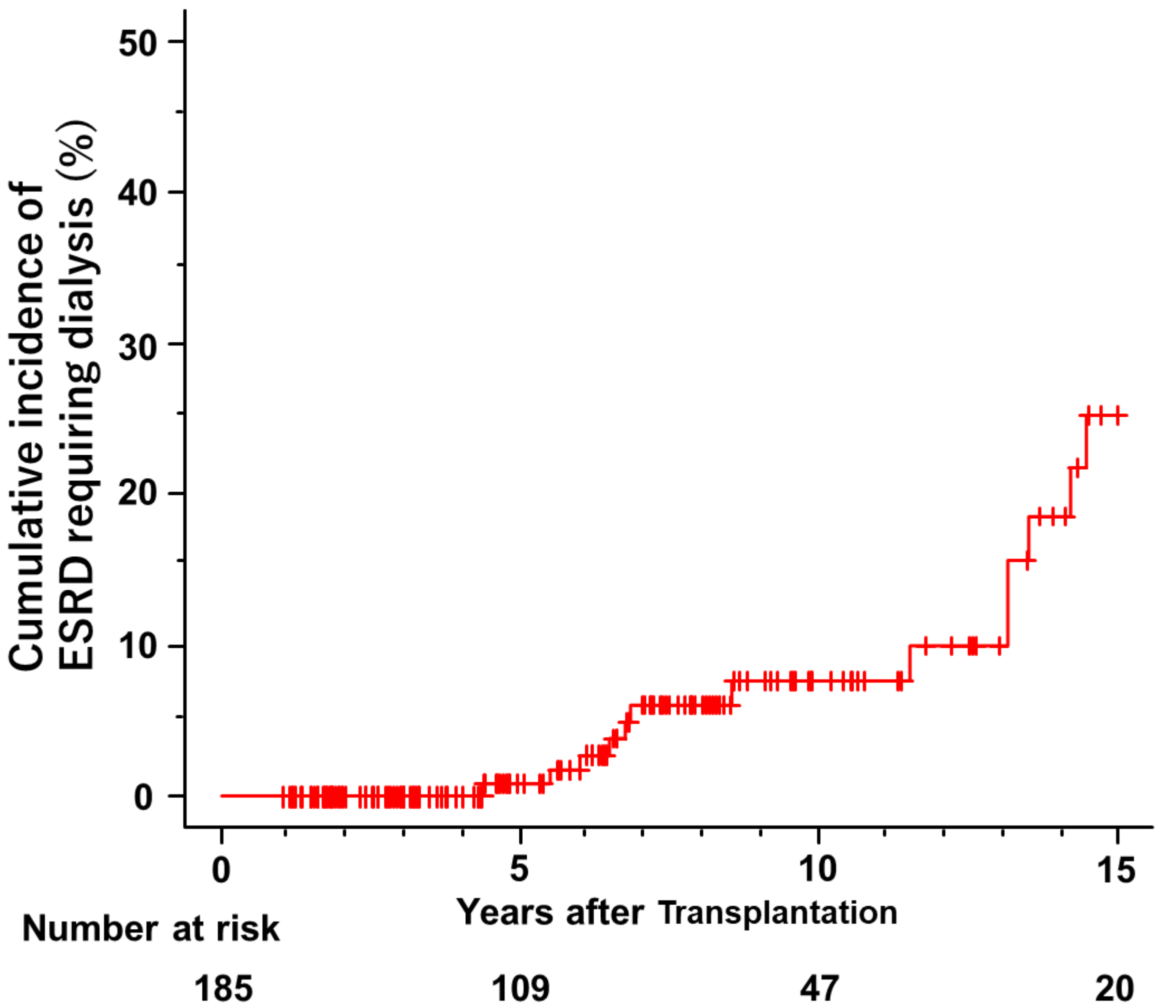


Figure 2. Kaplan–Meier curve for the overall survival rate in the renal replacement therapy (RRT) group and the non-RRT group after lung transplantation. No difference was observed between the two groups (p = 0.694).

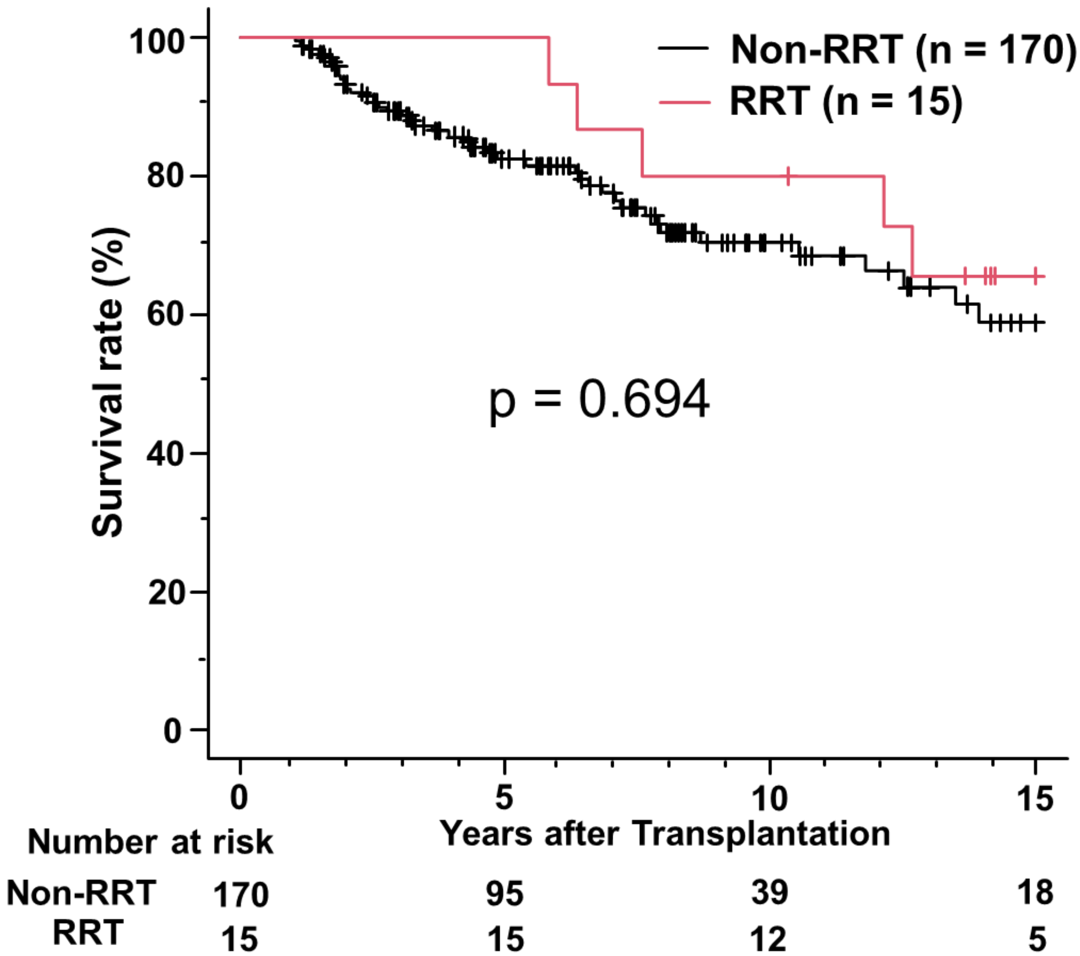


Figure 3. Kaplan–Meier curves for chronic lung allograft dysfunction (CLAD)-free survival rate in the renal replacement therapy (RRT) group and non-RRT group after lung transplantation. No difference was observed between the two groups (p = 0.473).

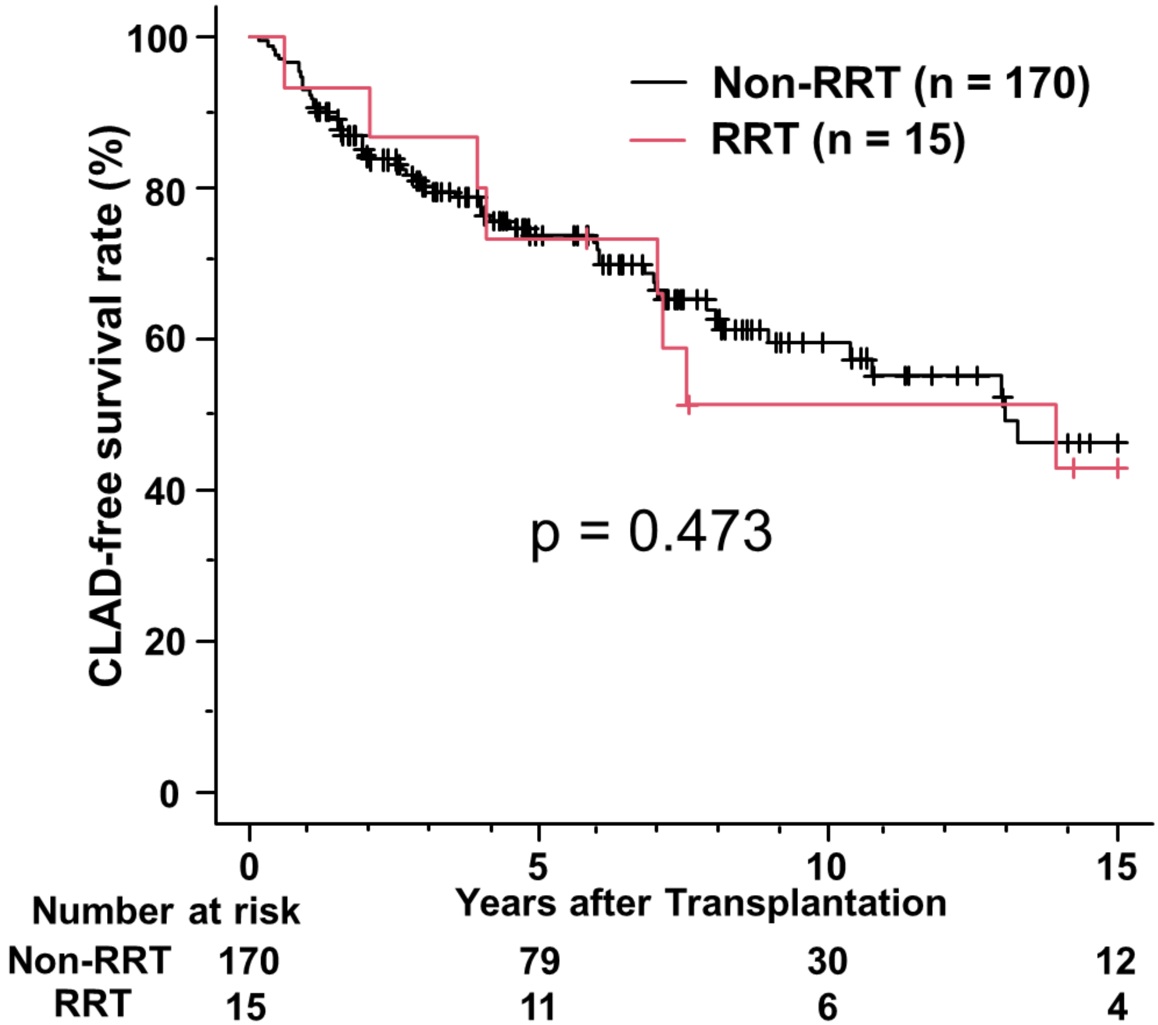
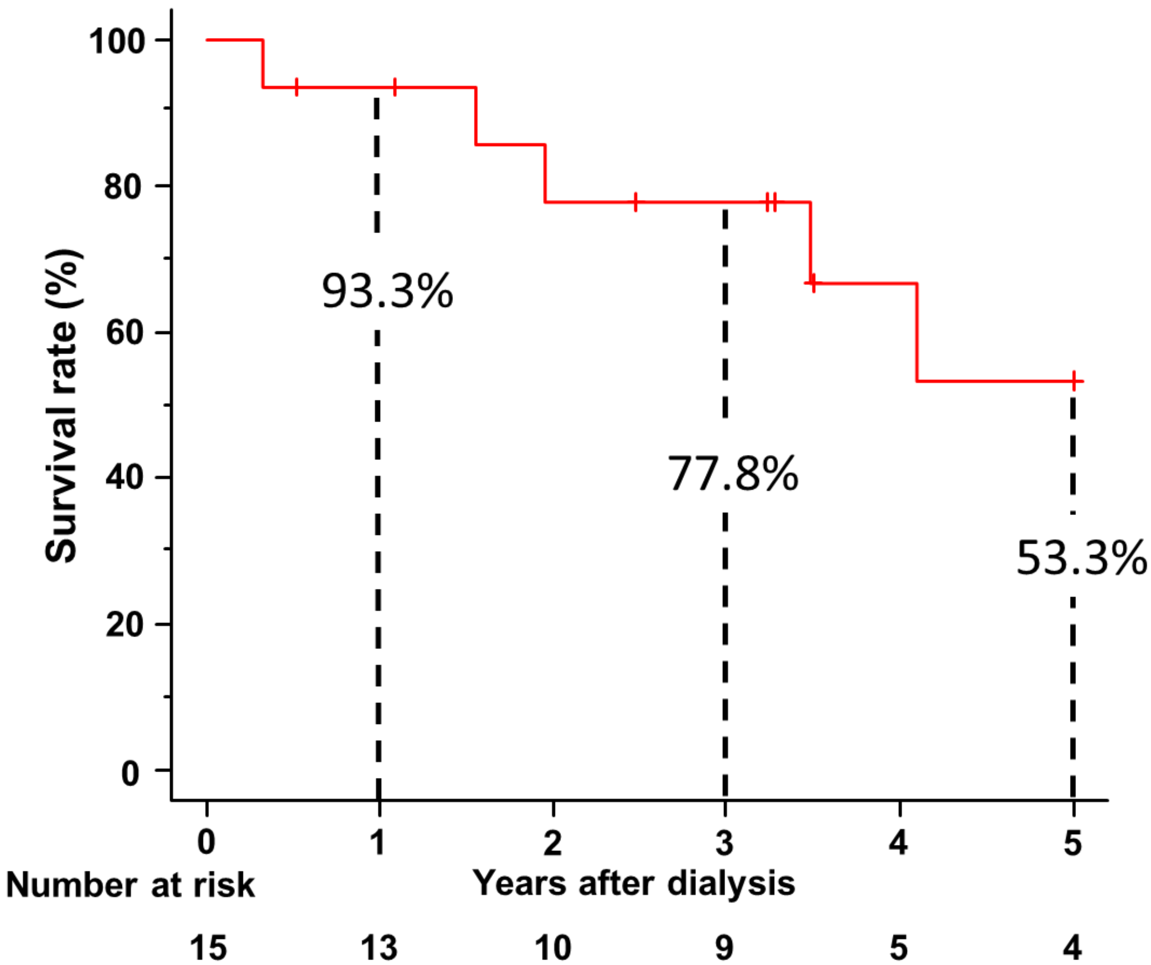


Figure 4. Kaplan–Meier curve for the survival rate after the initiation of hemodialysis in lung transplant recipients with end-stage renal diseases. The 1-, 3-, and 5-year survival rates were 93.3%, 77.8%, and 53.3%, respectively.



Supplementary Figure S1. Kaplan–Meier curve for the survival rate in lung transplant recipients with end-stage renal disease (ESRD) requiring dialysis according to the scheduled dialysis group or emergency dialysis group. The survival rate was not different between the two groups ($p = 0.805$).