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RESEARCH ARTICLE

Association of cardiac disease with the risk of post-lung transplantation mortality in Chinese recipients aged over 65 years

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Abstract **The current organ allocation rules prioritize elderly and urgent patients on the lung transplantation (LT) waiting list. A steady increase in the threshold at which age is taken into consideration for LT has been observed. This retrospective cohort study recruited 166 lung transplant recipients aged ⩾ 65 years between January 2016 and October 2020 in the largest LT center in China. In the cohort, subgroups of patients aged 65–70 years (111 recipients, group 65–70) and ⩾ 70 years (55 recipients, group ⩾ 70) were included. Group D restrictive lung disease was the main indication of a lung transplant in recipients over 65 years. A significantly higher percentage of coronary artery stenosis was observed in the group ⩾ 70 (30.9% vs. 14.4% in group 65–70, *P* = 0.014). ECMO bridging to LT was performed in 5.4% (group 65–70) and 7.3% (group ⩾ 70) of patients. Kaplan–Meier estimates showed that recipients with cardiac abnormalities had a significantly increased risk of mortality. After adjusting for potential confounders, cardiac abnormality was shown to be independently associated with the increased risk of post-LT mortality (HR 6.37, *P* = 0.0060). Our result showed that LT can be performed in candidates with an advanced age and can provide life-extending benefits.**

Keywords cardiac disease; mortality; aged population; lung transplantation

Background

Based on the International Society for Heart and Lung Transplantation (ISHLT) data, the ratio of recipients aged ⩾ 66 years has increased up to 19% in 2017 [1]. In the US, reports showed that the percent of recipients aged ⩾ 65 years increased to over 30% in 2019 [2]. Recent guidelines have characterized age over 65 years as a relative contraindication, but a steady increase in the threshold at which age is taken into consideration for lung transplantation has been observed [3].

Several risk factors for mortality in recipients aged ⩾ 65 years have been reported on the basis of the large multinational LT registry [4]. End-stage lung disease with concurrent cardiac abnormalities, including coronary artery disease (CAD) and cardiac valve disease, is common in the aged population. Coronary angiography-confirmed CAD, regardless of treatment with either drugs, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG), is not an absolute contraindication for lung transplantation [5]. Cardiovascular-related deaths account for 11.6% of the deaths in lung transplant recipients within the first month of LT [6], and the use of immunosuppressive therapy post-LT may accelerate the progression of atherosclerosis. Cases with concurrent or consecutive LT and cardiac surgery have been reported; however, the effect of the therapeutic strategy of CAD on LT is not adequately established. Furthermore, data are extremely lacking on LT recipients who are elderly and have cardiac diseases.

We have previously reported the outcomes of LT programs between 2015 and 2018 in China [7]. The number of LT recipients who are aged ⩾ 65 years has increased dramatically in recent years; in particular, we have performed LT in five elderly patients suffering from respiratory failure caused by COVID-19-related pulmonary fibrosis [8]. Our center maintains the largest LT program in China, with a transplant volume of approximately 150 cases/year [9]. In this study, we presented data of lung transplant recipients aged ⩾ 65

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years at our center over the past 5 years to determine the survival outcomes, risk of death, and early comorbidities.

Methods

Study population

This retrospective cohort study recruited patients who underwent lung transplantation from January 2016 to October 2020 at our center. A total of 166 recipients aged ⩾ 65 years were identified, and the study included 55 recipients who were ⩾ 70 years old and 111 recipients aged between 65 (included) and 70 (not included) years. The ratio of patients aged ⩾ 65 years in all recipients from 2016 to 2020 was about 24%.

The Institutional Ethics Committees of Wuxi People's Hospital approved the study, including our retrospective review, non-interventional design, and data analysis. All patients in our study were anonymous. The research was conducted in accordance with the *2000 Declaration of Helsinki* and the *Declaration of Istanbul 2008*. The Institutional Ethics Committee approved the transplantation procedures, and transplanted organs were obtained from volunteer donations. No lungs were obtained from executed prisoners. A written informed consent on the transplantation procedure was obtained from patients and next of kin. The transplanted organs were obtained from volunteer donations, and the next of kin voluntarily provided a written informed consent.

Data collection and clinical characteristics

Patient pre-operative demographics, donor's data, operative data, post-operative clinical features, and clinical events during the follow-up period were collected through a medical record database in our center and national lung transplantation registry database. Data collection protocol is demonstrated in supplementary methods. We collected data from recipients who had cardiovascular abnormalities (CAD and valve disease) for pre-LT evaluation, and these patients were defined as the group of patients with cardiac abnormalities.

Statistics

Demographic data related to donors, recipients, and transplants were presented as numbers and percentages for categorical variables. Continuous variables were expressed as the mean ± SD if they exhibited a normal distribution or as median (interquartile range (IQR)) if they displayed a skewed distribution. Continuous and categorical variables were compared using Student's *t*-test or the Mann–Whitney U test, Chi-square, or Fisher's exact test as appropriate. In identifying the prognostic effect of age group and cardiac abnormality on survival, cumulative survival as a function of time was investigated using Kaplan–Meier analysis and compared by log-rank tests. Univariate and multivariate Cox proportional-hazard regression models were used to test the correlation between exposure variables and post-lung transplantation survival. Regression analysis results are presented as hazard ratios (HR) and 95% confidence interval (CI). The modifications and interactions of subgroups were inspected by likelihood ration tests. Data calculations and comparisons were performed using SPSS version 25 (SPSS Inc., Chicago, IL, USA). Furthermore, R (The R Foundation) and EmpowerStats (X&Y Solutions, Inc., Boston, MA) were used to plot and model. A P value less than 0.05 was considered significant.

Results

Pre-operative characteristics

Among the entire study cohort of 166 lung transplant recipients aged ⩾ 65 years, subgroups of patients aged 65–70 years (111 recipients, group 65–70) and ⩾ 70 years (55 recipients, group ⩾ 70) were included (Table 1). A high percentage of recipients aged ⩾ 70 years were residents in Jiangsu Province, where our center is located, considering the medical insurance coverage for LT. Group D restrictive lung disease was the main indication of LT in recipients aged ⩾ 65 years, and chronic obstructive pulmonary disease (COPD) was the second most indicated underlying condition for LT. The cardiac function, as graded by the NYHA system, showed that most recipients were Grade III–IV before LT. The majority of subjects were hospitalized at the time of transplantation (97.3% and 92.8%).

For candidates with CAD, CT angiography and cardiac ultrasound were still performed when the patient was evaluated for LT and treated with drug therapy or PCI. Among patients who had a history of cardiac disease during admission to our center, six (3.6%) had PCI and stent implantation pre-LT, and one received a concomitant CABG. We also found a significantly higher percentage of coronary artery abnormalities in group ⩾ 70 compared with group 65–70 (30.9% vs. 14.4% in group 65–70, $P = 0.014$); furthermore, we found valvular structural abnormalities in both groups, ranging from 8.1% to 16.4%, which included medium-to-severe valve stenosis or regurgitation. Only data from transthoracic ultrasound were available because of limitations in time and facilities. Recipients aged ⩾ 65 years had a high mean pulmonary artery pressure level (58.2 ± 19.1 mmHg in group 65–70 vs. 54.9 ± 11.2 mmHg in group ⩾ 70). ECMO bridging to LT was performed in 5.4% (group 65–70) and 7.3% (group ⩾ 70) of patients. All bridging

Table 1 Recipient preoperative characteristics

	Group 65–70 ($N = 111$)	Group ⩾ 70 ($N = 55$)	X^2/t	P
Gender, male, *n* (%)	96 (86.5)	51(92.7)	1.413	0.305
Age (year), mean ± SD	66.3 ± 1.4	72.5 ± 2.2		
BMI at transplant (kg/m^2), mean ± SD	21.95 ± 3.8	21.81 ± 3.5	0.203	0.840
Residency in Jiangsu Province, *n* (%)	30 (27.1)	22 (40)	4.623	0.036
Pretransplant tobacco use, *n* (%)	64 (57.7)	21 (38.2)	4.593	0.028
Primary diagnosis, *n* (%)			0.886	0.368
Group A obstructive lung disease	27 (24.3)	13 (23.6)		
Group D restrictive lung disease	77 (69.4)	42 (76.4)		
Others	7 (6.3)	0		
Medical condition at transplantation, *n* (%)			2.195	0.334
In ICU	9 (8.1)	3 (5.5)		
Hospitalized but not in ICU	99 (89.2)	48 (87.3)		
Not hospitalized	3 (2.7)	4 (7.2)		
NYHA Grade, *n* (%)				
II	23 (20.7)	1 (1.8)		
III	52 (46.8)	31(56.4)		
IV	36 (32.4)	23 (41.8)		
Cardiac vascular abnormality (CTA), *n* (%)			6.282	0.014
Medium and severe	16 (14.4)	17 (30.9)		
Cardiac valve abnormality (chest echo), *n* (%)			2.593	0.118
Medium and severe	9 (8.1)	9 (16.4)		
Mean PAP (mmHg), mean ± SD	58.2 ± 19.1	54.9 ± 11.2	1.073	0.286
LVEF value (%), mean ± SD	61.2 ± 3.7	60.4 ± 3.2	0.939	0.350
Chronic steroid use, *n* (%)	13 (11.7)	13 (23.6)	3.959	0.047
ECMO bridging, *n* (%)	6 (5.4)	4 (7.3)	0.227	0.732
Group D	6 (100)	4 (100)	0.227	0.732
Mechanical ventilation bridging, *n* (%)	2 (1.8)	2 (3.6)	0.526	0.6
Creatinine (μmol/L), mean ± SD	63.1 ± 16.9	60.4 ± 14.7	0.797	0.428
ALT (U/L), mean ± SD	24.9 ± 20.1	22.9 ± 11.1	0.512	0.525
Total bilirubin (μmol/L), mean ± SD	13.8 ± 7.9	14.6 ± 6.1	0.574	0.568
Pretransplant 6MWD (m), mean ± SD	183.6 ± 98.6	217.8 ± 83.9	1.089	0.288
6MWD not tolerated, *n* (%)	83(74.8)	44(80)	0.559	0.561
Hypertension, *n* (%)	34 (30.6)	23 (41.8)	5.792	0.018
Cardiac disease history, patient-reported, *n* (%)	31 (27.9)	23 (41.8)	7.603	0.009
Cerebral vascular disease, *n* (%)	3 (2.7)	3 (5.5)	0.799	0.399
Diabetes, *n* (%)	30 (27.0)	13 (23.6)	0.220	0.709
Pre-transplant pulmonary embolism, *n* (%)	3 (2.7)	4 (7.3)	1.902	0.221
CMV-IgG positive, *n* (%)	64 (57.7)	35 (63.6)	0.546	0.504
CMV-IgM positive, *n* (%)	1 (0.9)	3 (5.5)	3.243	0.107
EB-IgG positive, *n* (%)	34 (30.6)	18 (32.7)	0.075	0.859
Pulmonary infection need admission, *n* (%)	51 (45.9)	37 (67.3)	6.715	0.013

cases were recipients that had underlying pulmonary fibrosis, and the rate was higher than the rate reported in the other registry [4]. Comorbidities, such as cardiac disease and hypertension, were more common in group ⩾ 70 recipients. A high percentage of pulmonary infection that required hospitalization in group ⩾ 70

patients was also observed. Furthermore, no significant differences in the rate of pre-LT cerebral vascular disease, diabetes, pre-transplant pulmonary embolism, or CMV/EB antibody tests were observed among the groups.

Perioperative course

In China, more lungs were donated, but donors often have a long intubation time before organ retrieval, which causes a low utilization rate [10]. Most donations were brain death donors, who had an average intubation time of 7.6 days (group 65–70) and 5.5 days (group ⩾ 70) before organ retrieval (Table 2). The average cold ischemic time was 434.6 min in group 65–70 and 395.9 min in group ⩾ 70, which were both over 6.5 h. Single lung transplantation was performed most often in both groups, and we performed more single left lateral lung transplantation in group ⩾ 70 patients, which may be due to patients primarily having pulmonary fibrosis. The strategies for the selection of the LT type were different between the two age groups and were affected by the indication and cardiopulmonary function. Intraoperative ECMO support was used in 73% of the recipients in group 65–70 and 65.5% of recipients in group ⩾ 70, and ECMO support for single lateral lung transplantation was performed in 91.7% of the recipients in group ⩾ 70. The median ICU stay post-LT was 5 days (group 65–70) and 4 days (group ⩾ 70). Post-LT infections occurred in over 90% of patients in both groups, and the rate of fungal infections was as high as 58.2% in group ⩾ 70 (Table 3). Significantly higher occurrence rates of acute rejection, cardiac arrhythmia, and pleural effusion were observed in group ⩾ 70 compared with group 65–70. In particular, we still observed residual or new-onset cardiac valvular abnormalities post-LT in 20.7% of the recipients in group 65–70 and 34.5% in group ⩾ 70 during the follow-up, although the difference did not reach statistical significance.

Outcome and survival

Using the Cox proportional-hazards regression model with cubic spline functions and smooth curve fitting, we observed that the correlation between age and death is nonlinear (Fig. S1). Kaplan–Meier estimates of the 30-day, 3-month, and 1- and 3-year survival by age groups are shown in Table S1, and the survival curves are shown in Fig. 1A. The most common cause of death post-lung transplantation was infection (47.4% vs. 44.4%), followed by multi-organ dysfunction and fatal hemorrhage (Table 3). We further compared the survival curves between patients with and without cardiac abnormality and the NYHA grading, and the result showed a significantly higher mortality risk in recipients with a cardiac abnormality ($P = 0.0093$, Fig. 1B) and a NYHA Grade of IV ($P < 0.0001$, Fig. 1C).

Multivariate and subgroup analyses using the Cox proportional-hazard regression model

In univariable analysis, assessed clinical characteristics

Table 2 Intraoperative characteristics

	Group 65–70 ($N = 111$)	Group ⩾ 70 ($N = 55$)	X^2/t	*P*
Donor age (year), mean ± SD	39.5 ± 14.5	39.4 ± 10.6	0.040	0.969
Donor/recipient gender mismatch, *n* (%)	12 (10.8)	7 (12.7)	0.2	0.788
Donor type DBD, *n* (%)	75 (67.6)	31 (56.4)	1.632	0.228
Donor intubation time before recovery, day, mean ± SD	7.6 ± 11.4	5.5 ± 6.1	1.130	0.262
Donor P/F, mean ± SD	419.7 ± 116.9	443.9 ± 70.6	1.168	0.247
OTO score[a], median (IQR)	2 (0.5,4)	3(0,4.75)		0.985
Interprovincial transportation via GCHOT, *n* (%)	73 (65.8)	37(67.3)	0.037	0.864
Cold ischemic time (min), mean ± SD	434.6 ± 113.8	395.9 ± 95.9	2.263	0.025
Transplantation type, *n* (%)			14.447	0.001
Bilateral (BLT)	38 (34.2)	5 (9.1)		
Single, left (SLLT)	34 (30.6)	30 (54.5)		
Single, right (SRLT)	39 (35.1)	20 (36.4)		
Blood loss (mL), median (IQR)	1000 (600,1250)	800 (600,1000)		0.019
With intraoperative ECMO support, *n* (%)	81 (73)	36 (65.5)	0.999	0.367
In SLT	57 (70.4)	33 (91.7)	6.368	0.016
ICU stay, day, median (IQR)	5 (3,8)	4 (3,7)		0.880

[a]Oto score, including age, smoking history, chest X-ray, secretions, and ratio of arterial oxygen tension to inspired oxygen fraction (PaO_2/FiO_2).

Table 3 Post-LT characteristics

	Group 65–70 ($N = 111$)	Group ⩾ 70 ($N = 55$)	X^2/t	P
Drug-resistant bacterial infection, *n* (%)	101 (91)	52 (94.5)	0.644	0.548
Fungal infection, *n* (%)	46 (41.4)	32 (58.2)	4.138	0.048
Bronchostenosis, *n* (%)	19 (17.1)	9 (16.4)	0.015	0.903
Acute rejection, *n* (%)	8 (7.2)	10 (18.2)	4.582	0.038
Valve abnormality post-LT (chest echo), *n* (%)	23 (20.7)	19 (34.5)	3.719	0.060
Cardiac arrhythmia, *n* (%)	51 (45.9)	36 (65.5)	5.612	0.021
Cerebral dysfunction, *n* (%)	57 (51.4)	23 (41.8)	1.339	0.254
Delirium	14 (12.6)	6 (10.9)	0.101	0.751
Depression/anxiety	10 (9)	5 (9.1)	0.000	1.000
Change on cerebral imaging/electrophysiology	20 (18)	11 (20)	0.095	0.833
PGD (⩾ grade 2 at 72 h), *n* (%)	64 (57.7)	32 (58.2)	0.004	0.949
Reintubation, *n* (%)	22 (19.8)	10 (18.2)	0.063	0.838
Pleural effusion, *n* (%)	31 (27.9)	33 (60)	15.969	0.000
Pulmonary embolism, *n* (%)	7 (6.3)	5 (9.1)	0.425	0.535
GERD, *n* (%)	12 (10.8)	1 (1.8)	4.120	0.062
Acute kidney injury, *n* (%)	29 (26.1)	17 (30.9)	0.420	0.582
Need CRRT in patients with AKI, *n* (%)	13 (44.8)	13 (76.5)	4.3672	0.064
Creatinine at 6 months (μmol/L), mean ± SD	66.7 ± 20.6	75.6 ± 13.7	0.856	0.409
Creatinine at 1 year (μmol/L), mean ± SD	98.2 ± 55.5	119.1 ± 23.3	0.871	0.398
Creatinine at 3 years (μmol/L), mean ± SD	81.3 ± 6.66	93.8 ± 18.5	1.102	0.332
Cyclosporine-based immunosuppression, *n* (%)	13 (11.7)	9 (16.4)	0.692	0.468
Tacrolimus-based immunosuppression, *n* (%)	59 (53.2)	27 (49.1)	0.243	0.742
Survival upon discharged, *n* (%)	91 (82)	45 (81.8)	0.001	0.979
Death, *n* (%)	38 (34.2)	27 (49.1)	3.407	0.091
Infection	18 (47.4)	12 (44.4)	0.054	0.816
Multiorgan dysfunction	8 (21.1)	8 (29.6)	0.626	0.561
Hemorrhage	5 (13.2)	0		0.061
Death in Diagnosis Group D, *n* (%)	25 (32.4)	21(50)	2.039	0.169
6 min walking distance (m, mean ± SD)	429 ± 82.5	370.3 ± 39.8	1.153	0.279
FEV1 (%) at 6 months, mean ± SD	63.5 ± 18.2	78.9 ± 20.5	2.408	0.021
FVC (%) at 6 months, mean ± SD	60.9 ± 16.1	67.5 ± 16.4	1.218	0.230
FEV1/FVC (%) at 6 months, mean ± SD	83.1 ± 10.5	87.5 ± 9.5	1.390	0.171
FEV1 (%) at 1 year, mean ± SD	69.1 ± 23.7	75.0 ± 16.8	0.770	0.448
FVC (%) at 1 year, mean ± SD	65.2 ± 21.1	68.2 ± 13.52	0.425	0.674
FEV1/FVC (%) at 1 year, mean ± SD	80.1 ± 11.9	84.1 ± 7.6	1.068	0.295
FEV1 (%) at 3 years, mean ± SD[a]	75.2 ± 20.2	82.1 ± 15.3	0.740	0.469
FVC (%) at 3 years, mean ± SD[a]	77.4 ± 15.2	74.5 ± 20.2	0.131	0.897
FEV1/FVC (%) at 3 years, mean ± SD[a]	76.2 ± 12.4	84.1 ± 9.2	1.280	0.219
Confirmed diagnosis of CLAD at 3 years, *n* (%)	30 (27)	12(21.8)	0.528	0.467

LT, lung transplantation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; PAP, pulmonary artery pressure; DBD, donation after brain death; PGD, primary graft dysfunction; GERD, gastroesophageal reflux disease; CRRT, continuous renal replacement therapy; AKI, acute kidney injury; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.[a]Data available in 15 patients in group 65–70 and 7 patients in group > 70.

were found to be significantly associated with mortality (Table S2). In adjusting for covariates, patients with cardiac abnormality have 93% increased risk of mortality based on an unadjusted model. After adjustment for age,

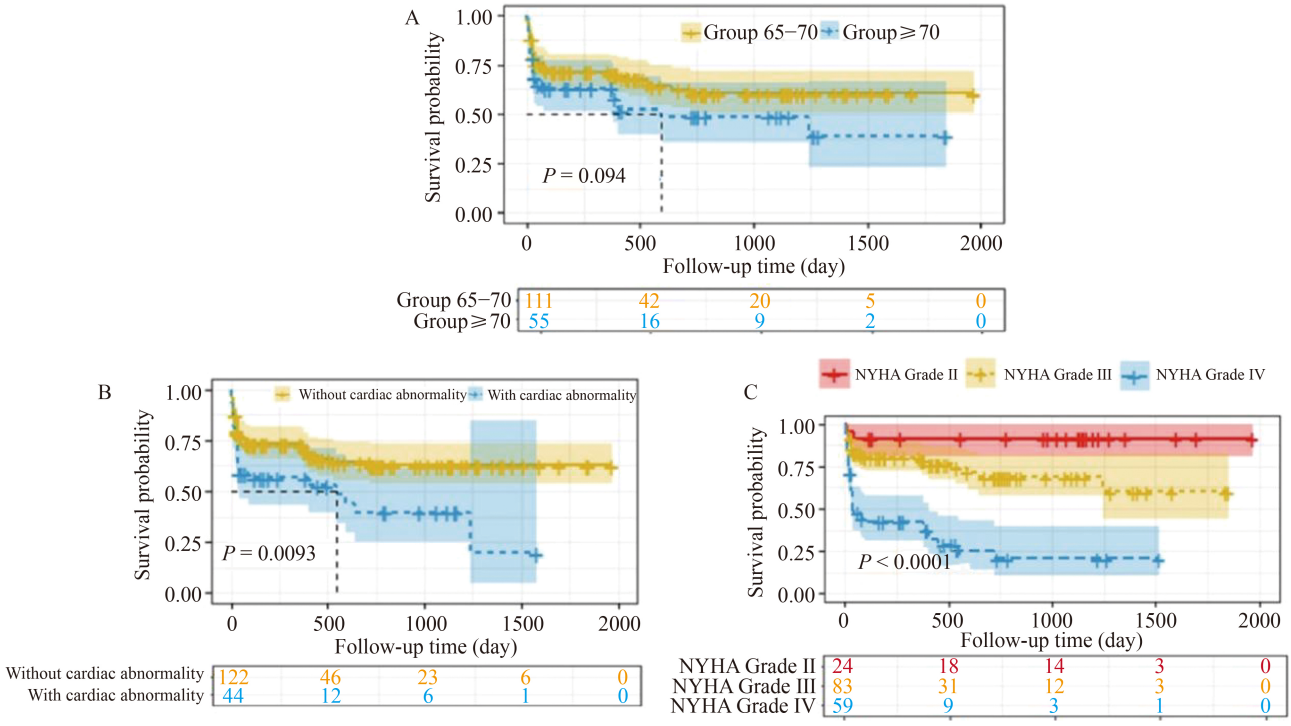

Fig. 1 Kaplan–Meier plot demonstrating time to death in lung transplant recipients stratified by age (A), cardiac abnormality (B), and NYHA Grade (C). The solid lines are the Kaplan–Meier survival estimates for each age group, and the shaded areas represent the 95% confidence bands. In the log-rank test, *P* value was used to compare the curves among the strata.

the risk was 82%, and the difference was statistically significant; furthermore, when adjusted for other demographic variables, an even higher risk was demonstrated (Table 4). We conducted stratified analysis and interaction tests in pre-defined subgroups to comprehensively understand other potential influencing factors related to cardiac disease and risk of post-lung transplantation mortality (Table 5). Interaction analysis detected that age and cardiac abnormality played an interactive role in post-lung transplantation mortality (*P* for interaction = 0.0013). The results were not statistically significant for diagnosis and transplantation type, which were the key factors when considering the transplantation strategy, thereby minimizing the risk of mortality.

Discrepancy between the hemodynamic characteristics and post-LT event risk was observed between pulmonary fibrosis recipients and COPD recipients, which need optimizing the transplantation strategy. A bilateral lung transplantation was preferred for all indicated patients without cardiac abnormalities and in patients without the need for ECMO support. In general, we performed a single lateral lung transplantation with V-V or V-A ECMO for patients with pulmonary fibrosis with cardiac abnormalities or who had the need for ECMO support after considering lung function and pulmonary hypertension; otherwise, for COPD patients, bilateral lung transplantation with V-V ECMO was performed on patients without significant cardiac abnormalities, whereas a V-A ECMO-supported single lateral lung transplantation was preferred for patients with cardiac abnormalities (Fig. 2). A statistically higher incidence of mortality events was observed in recipients with moderate-to-severe primary graft dysfunction (PGD), cardiac arrhythmia, reintubation, and acute kidney injury (Figs. S2 and S3). More events of cardiac arrhythmia, pulmonary embolism, and acute kidney injury were found in recipients with cardiac abnormalities (Table S3). A nomogram with C-statistic of 0.77 for predicting survival in recipients ⩾ 65 years was further constructed on the basis of the data set with an internal validation (Fig. S4).

Discussion

We conducted this analysis of survival outcomes and risk factors for mortality in LT recipients aged ⩾ 65 years in the largest LT center in China during the past 5 years. Since 2015, China has announced that voluntary organ donation after death is the sole source of transplantation, and the “green channel of human organ transportation” was established in 2016. We have transplanted more recipients with extreme ages and critical conditions. We published the initial results of LT outcomes in the China Lung Transplantation Registry from 2015 to 2018 [7]. When survival was stratified by age groups, we observed that patients aged 66+ years had an inferior survival probability compared with younger recipients, as reported

Table 4 Relationship between cardiac abnormality and mortality in different models

Cardiac abnormality	Crude model (HR, 95% CI, *P* value)	Model I (HR, 95% CI, *P* value)	Model II (HR, 95% CI, *P* value)	Model III (HR, 95% CI, *P* value)
No	Ref	Ref	Ref	Ref
Yes	1.93 (1.16, 3.21) 0.0109	1.82 (1.09, 3.05) 0.0225	2.14 (1.20, 3.79) 0.0094	6.37 (1.70, 23.84) 0.0060

Crude model adjusted for: None.
Model I adjusted for: age.
Model II adjusted for: age, NYHA Grade IV; chronic steroid use; transplant tobacco use, pulmonary infection need admission.
Model III adjusted for: age, NYHA Grade IV; chronic steroid use; pre-transplant tobacco use, pulmonary infection need admission; donor intubation time before recovery, hypertension and primary diagnosis, BMI.
CI, confidence interval; Ref, reference.

Table 5 Effect size of cardiac abnormality on mortality in subgroups

Variables	Cardiac abnormality (−)		Cardiac abnormality (+)		*P* for interaction
	No. of cases	HR (95% CI)	No. of cases	HR (95% CI)	
Age group (year)					0.0013
65–70	87	Ref	24	12.93 (3.12, 53.59)	
⩾ 70	35	7.35 (1.53, 35.34)	20	2.47 (0.41, 14.79)	
Primary diagnosis					0.8852
Non-Group D	24	Ref	13	4.50 (0.58, 34.83)	
Group D	88	1.83 (0.36, 9.23)	31	6.95 (1.05, 46.16)	
Transplantation type					0.9259
SLLT	42	Ref	22	2.56 (0.27, 24.63)	
SRLT	43	5.64 (0.73, 43.65)	16	12.69 (1.75, 92.21)	

The above-mentioned model adjusted for NYHA Grade IV; chronic steroid use; pulmonary infection need admission; pre-LT hypertension, pre-transplant tobacco use, cold ischemic time; donor intubation time before recovery. CI, confidence interval; Ref, reference.

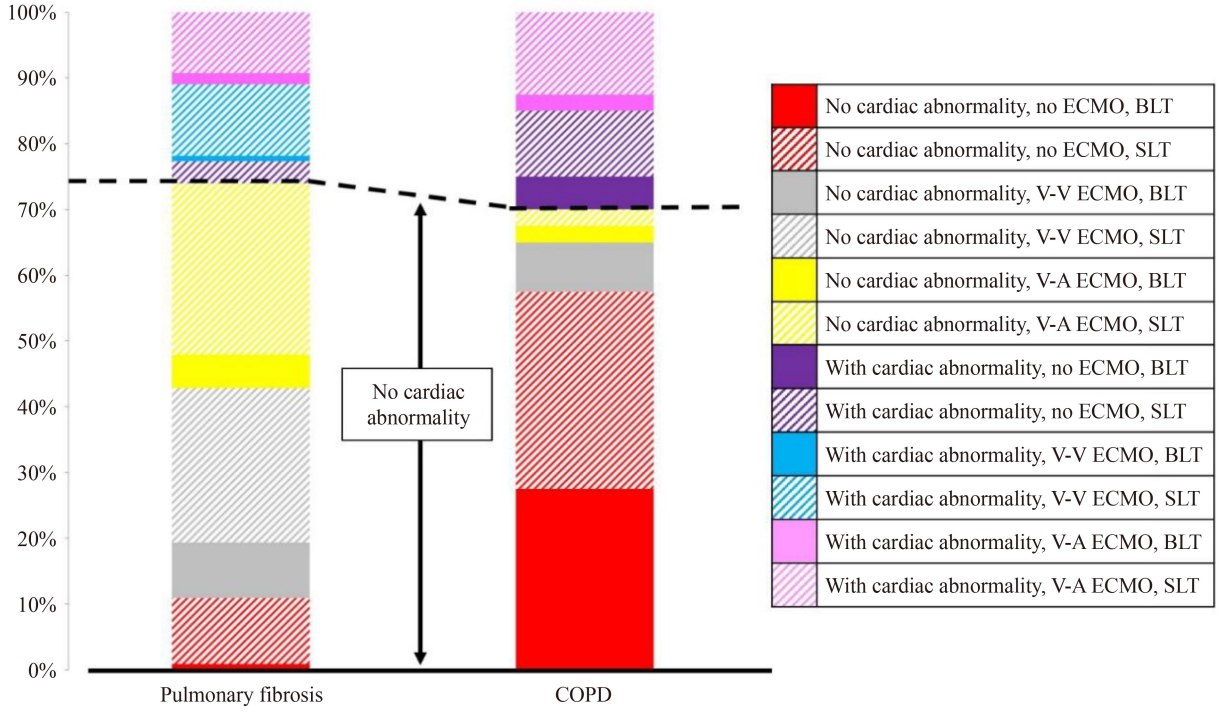

Fig. 2 Cumulative rate of transplant strategy of bilateral/single-lateral LT and ECMO when considering main indications and cardiac abnormality.

by other studies [11]. Compared with those reports from Western LT centers with long waiting lists, the utilization rate of donor lungs in China remains low [10]. Meanwhile, we had a high proportion of critical patients aged ⩾ 65 years who were reluctant to consider LT as their treatment of choice when their lung disease progressed to a late stage. When the patients were referred for LT, they always had multiple comorbidities, and they were not tolerant to full evaluation, including a 6-min walking distance, lung function, and coronary angiography by catheterization.

In our center, we have a protocol to evaluate candidates aged ⩾ 65 years, and this protocol includes a CTA for cardiac and pulmonary vascular evaluation [12]. We did not perform routine coronary angiography by left-heart catheterization in patients aged ⩾ 65 years in our center if they had already been treated with drugs and/or stents implanted in cardiac centers before they were referred for LT. However, if the candidates showed moderate or severe cardiac vascular abnormalities on CT angiography when the patients were evaluated for LT and if the patients had symptoms demonstrating an unstable cardiac status, we performed repeated PCI to determine whether further revascularization should be considered and if a LT should be performed. The cardiac function, pulmonary hypertension, pre-LT steroid use, and admission for pulmonary infection are crucial factors when considering the LT type and need for ECMO support.

Although various studies included recipients with various ages, indications, and extents of cardiac disease, cardiac disease did not compromise the survival of LT recipients. Pre-LT catheterization intervention, CABG, or concomitant CABG with LT were all feasible [13]; however, these interventions increased the post-LT complications or readmission rate because of cardiac reasons [14]. Chaikriangkai *et al*. also found that preoperative CAD did not increase the mortality risk but suggested that subsequent nonfatal cardiovascular events were increased [15]. Further studies warned of the risks of performing concomitant CABG in patients over the age of 65 years [16]. In our study, recipients who had cardiac abnormalities had inferior survival rates post-LT. Without optimizing surgical plan, recipients with cardiac abnormalities, who have a high risk of cardiac- or vascular-related events, were associated with a higher mortality. The intraoperative V-A ECMO has been used to support heart and lung function during LT; however, prolonged V-A ECMO post-LT may also increase the workload of the left heart. Its effect on the survival of recipients with advanced age and pre-LT cardiac abnormalities has not been clarified, and optimizing the post-LT care in these recipients remains to be further investigated.

In the current study, we collected preliminary data on cardiac structural abnormalities in elderly patients, and these cardiac structural abnormalities were not specified in previous reports. The high incidence of cardiac valvular stenosis or regurgitation in elderly patients also increased the risk of cardiac dysfunction and death. Transcatheter valve repair or replacement techniques helped more critical patients who were not tolerant of open-heart surgery and improved their quality of life, and these techniques have been adopted as new bridging methods in LT patients with cardiac valve abnormalities, which have been explained in recent case reports [17]. We also observed valvular abnormalities during the follow-up post LT, and these abnormalities might be related to alterations in cardiopulmonary hemodynamics or aging. We did not obtain further data to evaluate valvular diseases, and no intervention was further performed for these groups of patients. Our research revealed that for LT candidates aged ⩾ 65 years, more cardiac-related factors should be taken into consideration for pre-LT, as wells as coronary artery angiography. Pre-LT cardiac structural abnormalities, electrophysiological condition evaluations, and optimized perioperative management strategies for these patients remain to be further illustrated in future prospective studies.

In China, we have a higher proportion of patients with pulmonary fibrosis who had ECMO bridging before LT than in the ISHLT report; thus, perioperative strategies have great challenges. Our results provide several important observations regarding the outcomes of lung transplantation in recipients aged ⩾ 65 years. Bilateral transplantation is associated with improved long-term survival, whereas single lung transplantation confers a survival benefit within the first year of transplantation [18,19]. In addition, we provide evidence that the benefit of the transplantation type might be related to indications and comorbidities. Recipients with pulmonary fibrosis were in critical status with cardiac dysfunction, which might not be tolerant to long surgery durations and may have hemodynamic instability. These patients had single lateral LTs, particularly on the left side. For COPD patients without the need for ECMO, a bilateral lung transplantation was preferred. Post-LT severe pulmonary infection, such as multi-drug resistant bacteria (MDR)-related infection, has been recognized as a great risk factor for long-term outcomes. An increased risk of MDR infection was related to factors such as idiopathic pulmonary fibrosis, pre-transplant colonization and infections, and comorbidities [20]. The aged population receiving multiple drugs and immunosuppression therapy and undergoing invasive procedures was vulnerable to infection events.

Furthermore, a large proportion of recipients are supported by intraoperative and prolonged ECMO, and complications related to ECMO in elderly patients should

be considered. Apart from infection, thrombosis, and hemorrhage, which have been previously discussed, neurological complications in aged LT recipients are rarely reported. Common neurological complications related to ECMO include hypoxic-ischemic brain injury, intracranial hemorrhage, cerebral edema, and brain death [21]. We observed that 51.4% of recipients aged 65–70 years and 41.8% of recipients aged ⩾ 70 years had post-LT neurological complications in our cohort. Cerebral infarction, hemorrhage, and epilepsy had high occurrence rates, followed by delirium, depression, or anxiety. Influencing factors, including surgery, drug interactions, patient metabolism, ECMO-related factors (including rapid correction of hypercarbia and coagulation disturbance), ICU stay, and the nutritional status of patients, might contribute to adverse events. However, we still lack sufficient data to illustrate the impact of these events on recipients' post-LT survival because of limited methods of neurologic assessment and neuromonitoring.

However, this study, similar to many other studies, is limited in its statistical power because of being a single-center cohort with a relative infrequency of events. The majority of our cohort had restrictive lung disease, as it is the main indication for LT in recipients aged ⩾ 65 years. Our findings may reflect the contributions of patients with interstitial lung disease to a greater extent compared with other diseases. Our outcomes may not be broadly applicable, as factors such as surgical strategy and team experience vary in different centers. In illustrating post-LT complications, more diagnostic tools might be needed to supplement the routine monitoring protocol, such as gastroesophageal reflux disease-related manometry and pH monitoring. Outcome-related results, not only survival but also quality of life, should also be measured in detail to reflect the benefit of LT in the aged population.

Conclusions

Our experience from the largest aged LT cohort from the eastern population supported that LT can be performed in candidates with advanced chronological age and provided life-extending benefits to these patients. This analysis may help the global transplant community to expand recipient access despite a growing number of older recipients. Therefore, evaluation and treatment protocol are of great importance for recipients aged ⩾ 65 years to improve post-transplant survival in future adaptations of organ allocation.

Compliance with ethics guidelines

Guohui Jiao, Shugao Ye, Ji Zhang, Bo Wu, Dong Wei, Dong Liu, Feng Liu, Chunxiao Hu, and Jingyu Chen declare that they have no conflict of interest. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the *Helsinki Declaration* of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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