Original Article

Short-term and long-term outcomes of lung transplantation from marginal donors: a single-center retrospective study

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Background: To expand the donor pool, medical centers worldwide are applying marginal donor lungs in clinical settings. We carried out this research to reveal the short-term and long-term outcomes of marginal lung donor transplantation.

Methods: We performed retrospective research using data from patients who underwent lung transplantation (LT) in The Affiliated Wuxi People's Hospital of Nanjing Medical University, Jiangsu Province, China, between 2018 and 2022 to compare the short-term and long-term outcomes of standard donors and marginal donors.

Results: A total of 553 cases were incorporated in this study. The perioperative mortality of recipients who received marginal donor lungs was around 20.8%, compared with 13.4% in the standard donor recipients (P=0.03). There were no significant differences between the two groups in terms of mechanical ventilation or extracorporeal membrane oxygenation (ECMO), length of intensive care unit and hospital stay, occurrence of primary graft dysfunction, and prevalence of acute rejection. The 1-year survival rate for recipients in the standard group and marginal group was 71.7% and 54.2% (P<0.001), respectively. There was a worse survival rate in the subgroups of age >55 years, smoking ≥20 pack-years, and abnormal chest radiographs; however, the 1-year survival rate in the subgroup analysis of donors with ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg and purulent secretions on bronchoscopy was not significantly different.

Conclusions: Our findings suggest that marginal donor recipients can expect to have a lower survival rate than standard donor recipients. However, marginal lung transplant recipients could also gain benefit equivalent to that provided by standard donor LTs in both the short- and long-term when proper assessment and management strategies are implemented.

Keywords: Lung transplantation (LT); marginal donors; end-stage lung disease; survival

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Introduction

Lung transplantation (LT) is widely known as the final treatment for patients with end-stage lung diseases (1-4). With the development of LT, the shortage of eligible donor lungs has posed considerable challenges to medical centers. The prolonged waiting time and the increased waiting list mortality rates among transplant candidates suggest an urgent need to expand the donor pool (5).

Several strategies such as optimal intensive-care donor management and donation after cardiac death have demonstrated effectiveness in augmenting the donor pool of lung donors (6-8). Additionally, there has been growing interest in utilizing marginal donors—donors with characteristics such as older age, significant smoking history, lower ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO_2/FiO_2), and abnormal chest radiography and bronchoscopy findings—as a potential solution (9-11). Although the adoption of marginal donors holds promise for alleviating the donor shortage, concerns regarding the application of marginal donors to LT remain. The related literature offers limited insight into the comparative effectiveness of LT from marginal donors versus that from standard donors.

In 1993, Kron *et al.* first reported that the clinical use of marginal donors for LT did not increase the risk of death (12). A retrospective study conducted by Sundaresan *et al.* revealed no differences in the early outcomes of recipients from marginal and standard donors (10). Similarly, Aigner *et al.* found that the use of marginal donors did not impair the short- or midterm outcomes compared to standard lung donors (13). Several studies also reported no significant difference in the posttransplant outcomes, such as intensive care unit (ICU) stay, pulmonary function, early mortality, and long-term survival, between the two donor groups (14,15). However, a number of studies have reported negative influences of marginal donors on a variety of early posttransplant outcomes. Pierre *et al.* performed a retrospective study of 128 consecutive lung or heart-lung transplants and reported higher 30-day mortality for the marginal donor group compared with standard donor group (9). Luckraz *et al.* found that recipients receiving marginal donor lungs had a higher 30-day mortality but lower rejection rates in the long term (16). A previous retrospective cohort study indicated that recipients from the marginal donor group experienced longer ICU and hospital stay and lower pulmonary function at 1 year despite demonstrating a similar survival status (17). Thus, whether the utilization of marginal donors influences the short- and long-term outcomes of patients undergoing LT remains controversial.

Therefore, we conducted this study to further investigate the short- and long-term outcomes of LT from marginal donors and to identify the characteristics that significantly affect recipient outcomes. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1699/rc).

Highlight box

Key findings

- Marginal donor lung transplantation yielded worse overall short-term and long-term outcomes. However, in the subgroup of donors with a ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg and purulent secretions on bronchoscopy, these outcomes were not significantly different.

What is known and what is new?

- The application of marginal donor lung is an effective means of expanding the donor pool, but the application of marginal donors remains controversial.
- Patients in subgroups age >55 years, smoking ≥20 pack-years, or abnormal chest radiographs exhibited a worse survival rate. However, in the subgroups with PaO_2/FiO_2 <300 mmHg or purulent secretions on bronchoscopy, the short- and long-term survival rates were not significantly different when compared with the standard donor group.

What is the implication, and what should change now?

- The utilization of marginal donors could provide equivalent benefit as that from standard donors. However, proper assessment and management strategies should be carried out before marginal donor transplantation is applied.

Methods

Study population

We retrospectively reviewed a cohort of patients who underwent LT in The Affiliated Wuxi People's Hospital of Nanjing Medical University, Jiangsu Province, China, between 2018 and 2022. The primary clinical information of the donors and recipients was collected. Donors younger than 15 years old at the time of transplant were excluded. In total, 553 LTs performed during the study period were included in the analysis.

Donors were divided into two groups: a standard group and a marginal group. Donors meeting any one of the following criteria were defined as marginal donors: (I)

donor age older than 55 years old; (II) PaO_2/FiO_2 less than 300 mmHg; (III) smoking history more than or equal to 20 pack-years; (IV) abnormal chest radiograph findings; and (V) purulent secretions on bronchoscopy (9-11).

Collected variables and study outcomes

Donor-related variables including age, gender, weight, height, body mass index (BMI), cause of death, PaO_2/FiO_2 ratio, smoking history, and chest X-ray and bronchoscopy findings were compared between the standard donor and marginal donor groups. Preoperative recipient-related variables included age, gender, weight, height, BMI, and underlying disease. We also collected the hospitalization status, requirement of oxygen therapy, preoperative extracorporeal membrane oxygenation (ECMO) support rate, surgical approach, or postoperative ECMO support rate of recipients. The PaO_2/FiO_2 ratio referred to the latest recorded value from arterial blood gas analysis after donor lung maintenance. The chest X-ray and bronchoscopy findings were evaluated based on assessments from the donor lung procurement team and LT specialists. Abnormalities such as pulmonary infiltrates, lung infection, atelectasis and pulmonary contusion were defined as abnormal chest radiograph findings. Purulent secretions were defined as the presence of thick, yellow or green mucus observed under bronchoscopy. Postoperative outcomes included duration of mechanical ventilation and extracorporeal membrane oxygenation (ECMO), length of ICU and hospital stay, the occurrence of primary graft dysfunction (PGD), prevalence of acute rejection, postoperative complications (infection, anastomotic issues, arrhythmia, heart failure, thrombosis, posttransplant lymphoproliferative disorders, psychological issues, and liver and kidney injury), perioperative mortality, cause of perioperative death and 1-year survival. All the clinical information was summarized based on the medical records and was checked by three different clinical doctors to avoid possible deviations and biases. The cases with missing records were excluded from the study. The diagnostic criteria for heart failure included the presence of typical symptoms and physical signs of heart failure, the observation of structural and/or functional cardiac abnormalities on echocardiography, and an N-terminal pro B-type natriuretic peptide (NT-proBNP) level of ≥300 pg/mL. Liver injury was typically defined as an alanine aminotransferase (ALT) level ≥2 times the upper limit of normal (ULN). Kidney injury was defined as meeting one of the following: an increase in serum creatinine (Cr) ≥0.3 mg/dL (≥26.5 mol/L) within 48 h; an increase in serum Cr ≥1.5 times baseline within 7 days; urine volume ≤0.5 mL/kg/h for 6 h. The occurrence of PGD was defined as the presence of edema on chest X-rays within 72 h which was assessed by LT specialists and radiologists.

Statistical analysis

Continuous data were reported as medians and interquartile ranges, and categorical data were reported as percentages. Given the non-normal distribution of the continuous data, the Mann-Whitney test was performed for comparison between two groups. The Pearson Chi-squared test and Fisher exact test were conducted to compare the distribution of categorical variables. Kaplan-Meier survival analysis with the log-rank test was performed to compare recipient survival across the two groups. To evaluate the relationship between marginal donor characteristics and survival rates, multivariate Cox proportional hazards regression was applied. All variables that were statistically significant in the univariate analysis were included in Cox regression. For the Cox model, the proportional hazards assumption was confirmed by time-dependent covariates. A two-sided P value less than 0.05 was considered statistically significant. All analyses were performed using SPSS 25 software (IBM Corp., Armonk, NY, USA).

Ethical considerations

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Commission of The Affiliated Wuxi People's Hospital of Nanjing Medical University (No. KY24076). The need for informed consent was waived by the Ethics Commission of The Affiliated Wuxi People's Hospital of Nanjing Medical University due to the retrospective nature of the analysis.

Results

Distribution of marginal donors

A total of 553 lung donors were included in the study. According to the criteria of marginal donors, 334 donors were classified as marginal and 219 as standard. Of the marginal donors, 230 (68.9%) did not meet 1 criterion, 95 (28.4%) did not meet 2 criteria, and 9 (2.7%) failed to meet 3 criteria. The distribution of marginal donors based

on each criterion is presented in *Table 1*. Two hundred and fifty-two marginal donors showed abnormal findings on chest radiographs and 91 marginal donors had purulent bronchial secretions, which were the most frequently observed criteria.

Donor and recipient characteristics

We compared the demographic characteristics between standard donors and marginal donors (*Table 2*). The median age was older in the marginal group than in the standard group (43 *vs.* 41 years; P<0.001). The median PaO_2/FiO_2 ratio in standard group was 440 while that in the marginal group was 416 (P=0.001). Cerebrovascular diseases were the most common cause of death in both groups, followed by brain trauma and hypoxia or cardiac arrest. Smoking history, chest X-ray, and bronchoscopy findings all differed significantly between the two groups, whereas no significant differences were observed in terms of gender, weight, height, BMI, or cause of death.

The recipients' characteristics are summarized in *Table 3*. Sixty-three-point-nine percent of the recipients in standard donor group received bilateral LT and the number was 56.6% in the marginal donor group. Most patients of both groups needed ECMO support after LT (standard donor group: 79.9%, marginal donor group: 81.7%). There were no significant differences in gender, age, weight, height, BMI, primary diagnosis, Hospitalization status, requirement of oxygen therapy, preoperative ECMO support rate, surgical approach, or postoperative ECMO support rate

Table 1 Distribution of patients in the marginal donor subgroups

Variables	Marginal donors (n=334)
Age >55 years	52
PaO_2/FiO_2 <300 mmHg	26
Smoking ≥20 pack-years	26
Abnormal chest radiographs	252
Purulent bronchial secretions	91

Data are expressed as number. PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen.

Table 2 Donor characteristics

Variables	Standard donor (n=219)	Marginal donor (n=334)	P value
Gender (%)			0.20
Male	79.9	84.1	
Female	20.1	15.9	
Age (years)	41 [32–47]	43 [36–52]	<0.001
Weight (kg)	65 [60–75]	67 [60–75]	0.12
Height (cm)	170 [165–174]	170 [165–174]	0.56
BMI (kg/m^2)	23.2 [21.4–25.0]	23.4 [21.3–25.2]	0.30
Cause of death (%)			0.38
Brain trauma	38.6	34.5	
Cerebrovascular diseases	54.4	59.7	
Hypoxia/cardiac arrest	5.1	3.1	
Others	1.9	2.8	
PaO_2/FiO_2 ratio (mmHg)	440 [392–500]	416 [356–483]	0.001
Significant smoking history (≥20 pack-years) (%)	0	7.8	<0.001
Abnormal chest X-ray (%)	0	75.4	<0.001
Abnormal bronchoscopy (%)	0	27.2	<0.001

Data are expressed as median [interquartile range] if not otherwise specified. BMI, body mass index; PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen.

Table 3 Recipient characteristics

Variables	Standard donor (n=219)	Marginal donor (n=334)	P value
Gender (%)			0.87
Male	79.9	79.3	
Female	20.1	20.7	
Age (years)	55 [47–64]	57 [49–64]	0.34
Weight (kg)	58 [49–67]	57 [50–67]	0.92
Height (cm)	168 [162–172]	169 [164–173]	0.20
BMI (kg/m^2)	20.7 [17.6–23.6]	20.6 [17.4–23.6]	0.76
Diagnosis (%)			0.54
COPD	16.0	16.5	
IPF	20.1	26.9	
SPF	22.4	20.7	
Pneumoconiosis	18.7	14.7	
Bronchiectasis	5.0	4.5	
BO	2.7	1.5	
PH	0.5	1.2	
Others	14.6	14.1	
Hospitalization status (%)			0.15
Hospitalized in ward	85.4	85.0	
ICU	5.9	6.3	
Not hospitalized	5.9	3.0	
Oxygen therapy (%)	84.5	88.3	0.32
Preoperative ECMO support (%)	3.2	5.7	0.31
Surgical approach (%)			0.09
Bilateral	63.9	56.6	
Single	36.1	43.4	
Postoperative ECMO support (%)	79.9	81.7	0.84

Data are expressed as median [interquartile range] if not otherwise specified. BMI, body mass index; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; SPF, secondary pulmonary fibrosis; BO, bronchiolitis obliterans; PH, pulmonary hypertension; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation.

between patients receiving donor lungs from standard donors and those receiving donor lungs from marginal donors.

Early transplantation outcomes

Table 4 presents the early postoperative outcomes of recipients from both groups of donors. No statistically significant differences were observed for the duration of postoperative respiratory support including mechanical ventilation and ECMO, lengths of ICU and hospital stays, occurrence of PGD, or prevalence of acute rejection. There were no significant differences in postoperative complications between the two groups. However, the perioperative mortality of recipients who received donor lungs from marginal donors was around 20.8%, while

Table 4 Early postoperative outcomes

Variables	Standard donor (n=219)	Marginal donor (n=334)	RR	P value
Mechanical ventilation (hours)	48 [25–129]	48 [30–144]	–	0.70
Postoperative ECMO (hours)	23 [13–48]	22 [15–60]	–	0.59
ICU stay (hours)	108 [69–216]	120 [68–238]	–	0.51
Hospital stay (days)	37 [21–53]	33 [19–51]	–	0.14
PGD (%)	30	32.8	1.09	0.53
Acute rejection (%)	1.1	0.8	0.74	>0.99
Postoperative complications (%)				
Infection	83.2	81	0.97	0.56
Anastomotic stricture	5.8	7.3	1.23	0.52
Anastomotic leakage	4.7	3.5	0.74	0.67†
Arrhythmia	29.1	27.0	0.93	0.62
Heart failure	16.5	23.0	1.40	0.09
Thrombosis	1.1	2.7	2.56	0.31‡
PTLD	0	0.4	–	>0.99‡
Psychological issues	18.9	16.0	0.84	0.41
Kidney injury	26.8	28.9	1.08	0.63
Liver injury	22.6	25.0	1.10	0.56
Perioperative mortality (%)	13.4	20.8	1.56	0.03*
Cause of death (%)				0.43
MODS	3.7	6.3	1.72	
Pulmonary embolism	0.5	0.3	0.66	
Infection	5.5	9.6	1.75	
Respiratory failure	0	0.6	–	
Bronchial anastomosis complications	0.9	0.6	0.66	
Hypovolemic shock	0.5	1.8	3.93	
Post-cardiac arrest syndrome	0.5	0.3	0.66	
Sudden cardiac death	1.4	0.6	0.44	
PGD	1.4	1.8	1.31	
Others	1.4	1.2	0.87	

Data are expressed as median [interquartile range] if not otherwise specified. †, Yates correction for continuity; ‡, Fisher exact test; *, significant difference. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; PGD, primary graft dysfunction; PTLD, posttransplant lymphoproliferative disorders; MODS, multiple organ dysfunction syndrome; RR, relative risk.

those who received lungs from standard donors had a lower mortality of 13.4% (P=0.03). Multiple organ dysfunction syndrome (MODS) and infection were the most significant reasons of perioperative death in our cohort.

Subgroup analysis

According to the criteria for marginal donors, recipients were further divided into the following five subgroups: subgroup I, recipients receiving lungs from donors aged

Table 5 Subgroup analysis

Variables	Subgroup I (n=52)	Subgroup II (n=26)	Subgroup III (n=26)	Subgroup IV (n=252)	Subgroup V (n=91)	P value[#]
Mechanical ventilation (hours)	48 [25–129]	44 [34–134]	150 [41–486]	48 [27–144]	47 [35–120]	NS
Postoperative ECMO (hours)	22 [17–63]	22 [16–43]	24 [19–133]	23 [15–64]	21 [15–37]	NS
ICU stay (hours)	144 [74–243]	86 [59–197]	159 [92–523]	117 [66–242]	110 [84–190]	NS
Hospital stay (days)	12 [9–32]	34 [21–69]	29 [15–43]	32 [19–51]	35 [20–59]	NS
PGD (%)	39.5	21.7	75.0	30.3	32.3	0.001†* (III)
Acute rejection (%)	0	4.3	0	0.5	0	NS
Postoperative complications (%)						
Infection	86.0	60.9	93.8	83.2	84.8	0.02‡* (II)
Anastomotic stricture	7.0	26.1	0	7.1	11.9	0.005‡* (II)
Anastomotic leakage	2.3	0	6.3	3.6	4.5	NS
Arrhythmia	46.5	17.4	68.8	26.2	27.7	0.03* (I); 0.003†* (III)
Heart failure	23.8	13.0	50.0	22.4	20.0	0.004‡* (III)
Thrombosis	0	13.0	0	3.1	3.1	0.01 (II)
PTLD	0	4.5	0	0.5	1.5	NS
Psychological issues	25.6	17.4	31.3	14.8	20.0	NS
Kidney injury	34.9	34.8	50	29.1	28.1	NS
Liver injury	25.6	13.0	56.3	26.7	27.7	0.008* (III)
Perioperative mortality (%)	34.6	12.0	36.0	20.4	18.7	0.001†* (I); 0.01‡* (III); 0.044* (IV)

Data are expressed as median [interquartile range] if not otherwise specified. Subgroup I: recipients receiving lungs from donors aged more than 55 years; subgroup II: recipients from donors with PaO_2 lower than 300 mmHg; subgroup III: recipients from donors with history of smoking more than or equal to 20 pack-years; subgroup IV: recipients from donors with chest radiograph infiltrations; subgroup V: recipients from donors with purulent secretions on bronchoscopy. [#], P value for comparisons of subgroups I, II, III, IV, and V to "standard donor" in group I; [†], Yates correction for continuity; [‡], Fisher exact test; *, significant difference. NS, not significant; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; PGD, primary graft dysfunction; PTLD, posttransplant lymphoproliferative disorders; PaO_2, arterial partial pressure of oxygen.

over 55 years (n=52); subgroup II, recipients from donors with a PaO_2 lower than 300 mmHg (n=26); subgroup III, recipients from donors with a history of smoking more than or equal to 20 pack-years (n=26); subgroup IV, recipients from donors with infiltrations on chest radiography (n=252); and subgroup V, recipients from donors with purulent secretions on bronchoscopy (n=91). Recipients in these subgroups were compared with recipients from the standard donor group. The median age of the donors in subgroup I was 58 years, which was about 17 years older than the median age of donors in the standard group (P<0.001). The median PaO_2/FiO_2 ratio of donors in subgroup II was 259 mmHg, which was significantly lower than that of donors in the standard group (400 mmHg) (P<0.001).

The early posttransplant outcomes are displayed in *Table 5*. Recipients from subgroup I were significantly more likely to experience arrhythmia after transplantation than were the standard group (46.5% *vs.* 29.1%; P=0.03). Compared to the standard group, subgroup II demonstrated a significantly higher prevalence of postoperative complications, including infection (60.9% *vs.* 83.2%; P=0.02), anastomotic stricture (26.1% *vs.* 5.8%; P=0.005), and thrombosis (13.0% *vs.* 1.1%; P=0.01). For subgroup III, the occurrence of PGD was 75%, while that in the standard group was 30% (P=0.001). Compared with the recipients in the standard group, those from subgroup III were significantly more likely to experience postoperative arrhythmia (68.8% *vs.* 29.1%; P=0.003), heart failure (50.0%

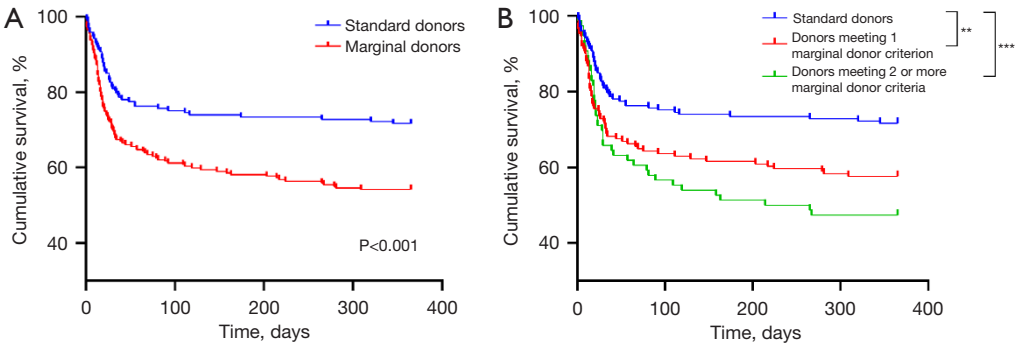

Figure 1 Kaplan-Meier survival analysis between standard donors and marginal donors (A) and further analysis after classification of marginal donors according to the number of criteria they met (B). **, P<0.01; ***, P<0.001.

Table 6 Multivariate Cox proportional hazards regression for patient survival

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Donor age >55 years	2.65 (1.70–4.13)	<0.001	2.51 (1.59–3.96)	<0.001
Donor PaO_2/FiO_2 ratio per 1 mmHg increase	1.000 (0.998–1.002)	0.81	–	–
Donor PaO_2/FiO_2 ratio in two groups				
≥300 mmHg	1.00		–	–
<300 mmHg	0.66 (0.27–1.61)	0.66	–	–
Significant smoking history (≥20 pack-years)	2.02 (1.12–3.64)	0.02	2.30 (1.24–4.29)	0.008
Abnormal chest radiographs	1.60 (1.17–2.20)	0.004	1.67 (1.21–2.31)	0.002
Purulent secretions on bronchoscopy	1.03 (0.69–1.55)	0.88	–	–
Postoperative average PaO_2/FiO_2 ratio per 1 mmHg increase	0.998 (0.996–0.999)	0.003	–	–
Postoperative average PaO_2/FiO_2 ratio in two groups				
≥300 mmHg	1.00		1.00	
<300 mmHg	1.56 (1.11–2.20)	0.01	1.51 (1.07–2.13)	0.02

HR, hazard ratio; CI, confidence interval; PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen.

vs. 16.5%; P=0.004), and liver injury (56.3% *vs.* 22.6%, P=0.008). The perioperative mortality rates of subgroup I, III, and IV was 34.6%, 36.0%, and 20.4%, respectively, all of which were statistically significantly higher compared with that of the standard group (13.4%).

Survival analysis

We evaluated the survival status of the patients who underwent LTs at 1 year after the surgery based on the follow-up record across the different donor groups (*Figure 1*). Survival at 1 year was 71.7% and 54.2% for recipients from the standard group and those from the marginal group, respectively (P<0.001). Based on the number of criteria marginal donors satisfied, they were further divided into two groups (i.e., those meeting one marginal donor criterion and those meeting two or more criteria). The log-rank test showed that the survival rates were statistically significantly different between the standard donor group and two marginal donor subgroups. Recipients receiving from donors that satisfied one marginal donor criterion had a 1-year survival rate of 57.6% after transplantation while the survival at 1 year of those receiving donors that met two or more criteria was 47.4%.

The results of Cox regression are presented in *Table 6*. In the univariate analysis, donor age older than 55 years,

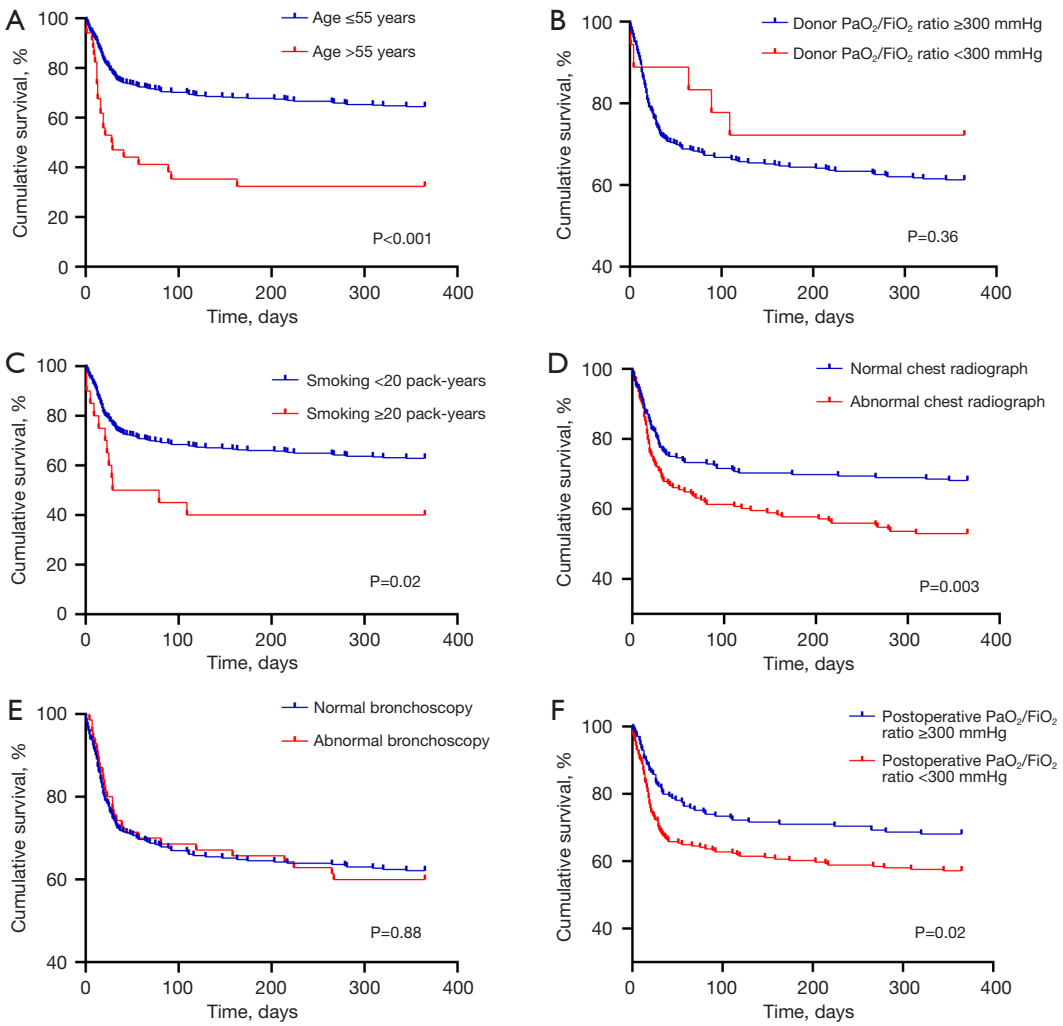

Figure 2 Subgroup results of Kaplan-Meier survival analysis for lung transplant recipients: (A) donor age >55 years compared with donor age ≤55 years; (B) PaO_2/FiO_2 <300 mmHg compared with PaO_2/FiO_2 ≥300 mmHg, (C) smoking history ≥20 pack-years compared with smoking history <20 pack-years; (D) abnormal chest radiograph findings compared with normal chest radiograph findings; (E) purulent secretions on bronchoscopy compared with no purulent secretions on bronchoscopy; (F) patients' postoperative PaO_2/FiO_2 ratio ≥300 mmHg compared with postoperative PaO_2/FiO_2 ratio <300 mmHg. PaO_2, arterial partial pressure of oxygen; FiO_2, fraction of inspired oxygen; postoperative PaO_2/FiO_2 ratio, PaO_2/FiO_2 value of the first arterial blood gas analysis after lung transplantation surgery.

significant smoking history, abnormal chest radiographs, and lower postoperative PaO_2/FiO_2 ratio were associated with a higher risk of poor outcomes. The postoperative PaO_2/FiO_2 ratio referred to the first recorded value from arterial blood gas analysis after LT surgery. For the postoperative PaO_2/FiO_2 ratio, the relationship was maintained whether the variable was continuous variable or a categorical variable based on a cutoff value of 300 [hazard ratio (HR) =1.56, 95% confidence interval (CI): 1.11–2.20; P=0.01]. In the multivariate analysis, statistical significance was reached for the following variables: donor age older than 55 years (HR =2.51, 95% CI: 1.59–3.96; P<0.001), smoking history more than 20 pack-years (HR =2.30, 95% CI: 1.24–4.29; P=0.008), abnormal chest radiographs (HR =1.67, 95% CI: 1.21–2.31; P=0.002), and postoperative PaO_2/FiO_2 ratio <300 mmHg (HR =1.51, 95% CI: 1.07–2.13; P=0.02). *Figure 2* indicates the factors were significantly associated with worse survival.

Discussion

The shortage of suitable donor lungs is being more keenly felt due to the increasing demand of LT. To satisfy the growing requirements and to reduce the mortality of those in the transplantation waitlist, medical centers worldwide have applied extended criteria to donor lungs and defined these donors as "marginal donors", a practice which has emerged as a focal point in the field of LT.

In terms of the definition of marginal donors, the criteria vary across different studies. Considering the subjectivity in interpretating chest X-rays and bronchoscopy findings, Zych *et al.* only considered three criteria: age over 55 years, PaO_2/FiO_2 ratio <300 mmHg, and smoking history ≥20 pack-years (18). In our study, despite the difficulty in quantifying the radiographic and bronchoscopic findings, we qualitatively evaluated the abnormalities of chest X-ray and bronchoscopy to avoid the potential biases of neglecting these two variables, which are believed to still be of significance for assessing the potential of a marginal donor in yielding a successful graft (9). In this study, the criteria we used for recognizing marginal donor lungs were those of Washington University (19).

From our results, we found that there was a significant difference in the overall survival status between the standard and marginal donor group although no short-term transplantation outcomes other than perioperative mortality were observed. The subgroup analysis and survival analysis provide insights into the influence of individual donor factors on postoperative outcomes. It was found that recipients who received donors with a PaO_2/FiO_2 ratio lower than 300 mmHg did not have a significantly higher perioperative mortality or lower overall survival rates. Although a PaO_2/FiO_2 ratio exceeding 300 mmHg is commonly considered to be unequivocal indicator of acceptability, the rationale behind this criterion is constrained, leaving uncertainty regarding the justification for this threshold (20,21). A previous study examined the outcomes of transplants and found there to be no significant differences in 12-month mortality between donor lungs with a PaO_2/FiO_2 ratio more than 300 mmHg and those less than 300 mmHg, making it possible for the donor pool to be expanded by loosening this restriction (22). Our results also showed that purulent bronchial secretions did not lead to either worse short-term transplantation outcomes or lower survival. A few studies have investigated the influence of donor bronchia; secretions on recipient outcomes; however, the influence of positive donor sputum cultures has not been extensively explored. Ahmad *et al.* reported no notable differences in 30-day mortality between recipients with positive cultures and those negative one (23). Similarly, another study conducted by Howell *et al.* also demonstrated no effect of positive sputum culture on the length of ICU and hospital stay and 30-day mortality (24). This suggests that donor lungs with purulent secretions on bronchoscopy could be safely utilized for transplantation and provide satisfactory outcomes.

Our findings might also indicate that—if standard donor lungs are not available—certain marginal donors may be acceptable for recipients with specific background conditions and can avoid poor transplantation outcomes and achieve as good a prognosis as possible. For instance, recipients from subgroup III more often experienced postoperative arrhythmia, heart failure, liver injury, and PGD, which suggests the presence of compromised heart and liver function in recipients after transplantation; thus, it may be advisable to avoid transplanting such donor lungs in those with suboptimal baseline heart and liver function. This finding may be a cause for optimism, as the donor lung pool may be further expanded, with successful transplantations achieved.

Moreover, a greater investment into the preservation and repair technique of donor lungs may be fruitful. *Ex vivo* lung perfusion (EVLP) may be a means to alleviating donor lung scarcity, as it allows for the assessment and restoration of marginal donor lungs and can minimize the risk of prolonged cold-ischemia time (25-28). Researchers have conducted a number of studies on EVLP in order to improve its practicability and utility for clinical practice. Lonati *et al.*'s research indicated that synthetic α-melanocyte-stimulating hormone analogue (Nle4,D-Phe7)-α-MSH (NDP-MSH) which relies upon the melanocortin system during EVLP could enhance the repair of marginal donor lungs before transplantation (29). Additionally, a Toronto team established an artificial intelligence-based machine learning model for assisting clinical physicians in deciding whether to accept donor lungs and combined the model with EVLP to maximize the usage of donor lungs (30). Furthermore, numerous studies have conducted detailed evaluations of donor lungs and examined the further repair of these lungs from various perspectives (31,32). Despite being predominantly in the experimental phase, this research has opened up new avenues and provided a cause for optimism for those patients with end-stage lung disease.

There are several limitations to this study which should be mentioned. First, the sample size was small,

which could restrict the generalizability of the results to some extent. Second, our study employed a single-center, retrospective design, and thus potential biases might have been introduced. Multicenter studies could validate our findings and provide more convincing evidence. Third, the follow-up period was relatively short, due to the relatively recent period of patient inclusion, limiting our capability to assess further long-term outcomes. Fourthly, the complication rate and overall survival condition were not optimistic when compared with the international standard. This might be caused by the absence of EVLP during the whole transplantation procedure as this technique was not widely applied to patients in China. Also due to China's large patient population and shortage of donors, most lung transplant recipients were in poor condition before surgery. In addition, in our center, there was a large number of pneumoconiosis patients, whose surgeries were generally challenging. We believe these factors might partly explain why LT survival rates had not yet reached international leading standards. Fifth, it is worth mentioning that we did not conduct a detailed subgroup analysis for the grades of complications, such as PGD and acute kidney injury. We believe that this is an area that could be improved in future research.

Conclusions

Our findings suggest that marginal lung transplant recipients can survive and benefit in the long-term. Although there remain marked in outcomes between marginal donors and standard donors, the marginal donor subgroups with a lung oxygenation index lower than 300 mmHg and those with purulent secretions under bronchoscopy showed no significant differences in our subgroup survival analysis. We believe that subsequent research could identify those marginal donors eligible for inclusion into the donor pool, which could ultimately benefit more patients with end-stage lung disease.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Commission of The Affiliated Wuxi People's Hospital of Nanjing Medical University (No. KY24076). The need for informed consent was waived by the Ethics Commission of The Affiliated Wuxi People's Hospital of Nanjing Medical University due to the retrospective nature of the analysis.

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