Initial Experience with Cadaveric Lobar Lung Transplantation in Turkey

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ABSTRACT

Introduction: Lung transplantation is the final treatment option for end-stage lung diseases. A scarce donor pool is the primary cause of waiting list mortality. Lobar lung transplantation has been proposed to overcome the donor pool shortage. Herein we present our initial experience with patients who underwent lobar lung transplantation.

Patients and Methods: This single-center retrospective study included patients who underwent cadaveric lobar lung transplantation between December 2016 and December 2018 at our Lung Transplant Center. The procedure was performed only in patients with an emergency status.

Results: Of the 55 lung transplants during the study period, six [10.9%; four female, two male; median age, 35.3 years (range, 22-42 years)] were lobar lung transplants. The indications were bronchiectasis (three patients), chronic obstructive pulmonary disease (one patient), cystic lung disease (one patient), and lepidic type adenocarcinoma (one patient). The transplantations included bilateral lobar lung in two patients, the right single lung and the left lower lobe in two patients, and the left single lung and the right lower lobe in two patients. One-year mortality was 16.6% (1/6). Two patients died 23 and 24 months after lung transplantation. Three patients were alive at the last follow-up (at 24, 25, 47 months).

Conclusion: Lobar lung transplantation can be a life-saving treatment option in critically ill patients with small thoracic cavities to overcome donor shortage. Furthermore, it is a feasible operative technique in recipients with a reduced unilateral thoracic cavity.

Key Words: Cadaveric donor; donor-recipient size matching; lobar lung transplantation.

Kadavradan Lober Akciğer Nakli: Türkiye'de İlk Deneyimler

ÖZ

Giriş: Akciğer nakli, son dönem akciğer hastalıkları için son tedavi seçeneğidir. Donör havuzunun azlığı, bekleme listesi ölümlerinin başlıca nedenidir. Donör havuzu azlığının üstesinden gelmek için lober akciğer nakli önerilmiştir. Bu çalışmada, lober akciğer nakli yapılan hastalar ile ilgili ilk deneyimimiz sunulmuştur.

Hastalar ve Yöntem: Bu tek merkezli retrospektif çalışma, akciğer nakli merkezimizde Aralık 2016-Aralık 2018 tarihleri arasında kadavra lober akciğer nakli yapılan hastaları içermektedir. Bu prosedür sadece acil durumu olan hastalarda uygulanmıştır.

Bulgular: Çalışma dönemindeki 55 akciğer naklinden altısı [%10.9; dördü kadın, ikisi erkek; medyan yaş 35.3 yıl (aralık, 22-42 yaş)] lober akciğer nakli idi. Endikasyonlar bronşektazi (üç hasta), kronik obstrüktif akciğer hastalığı (bir hasta), kistik akciğer hastalığı (bir hasta) ve lepidik tip adenokarsinom (bir hasta) idi. İki hastada bilateral lober akciğer, iki hastada sağ tek akciğer ve sol alt lob, iki hastada sol tek akciğer ve sağ alt lob akciğer nakli idi. Bir yıllık mortalite %16.6 (1/6) idi. Akciğer naklinden sonra 23. ve 24. ayda iki hasta ölmüştür. Üç hasta halen hayattadır (24, 25 ve 47. aylarda).

Sonuç: Lober akciğer nakli, donör eksikliğinin üstesinden gelmek için küçük göğüs boşlukları olan kritik hastalarda hayat kurtarıcı bir tedavi seçeneği olabilir. Aynı zamanda, tek taraflı göğüs boşluğu azalmış alıcılarda uygulanabilir bir ameliyat tekniğidir.

Anahtar Kelimeler: Kadavra donör; donör-alıcı boyutu eşleştirme; lober akciğer nakli.

INTRODUCTION

Lung transplantation has emerged as a life-saving treatment option for end-stage lung diseases with accumulating surgical experience and improved immunosuppressive therapy, donor care and protection, infection treatment, postoperative follow-up, and medical

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technology. Survival outcomes have also improved with increasing lung transplants in the recent years. Because of the disproportionate increase in the number of transplant candidates vs. cadaver donor lungs, availability of feasible donors is a challenge. In particular, patients with a small thoracic cavity and end-stage lung disease, such as pulmonary fibrosis and cystic fibrosis, experience long waiting times for appropriately sized donor lungs. Cadaveric lobar lung transplantation can be a life-saving option for such patients with worsening or critical conditions.

In 1994, Bisson et al. reported the first cadaveric bilateral lobar lung transplantation in two recipients with a diagnosis of cystic fibrosis[1]. Subsequently, several centers have published their outcomes with cadaveric lobar lung transplantation[2-4]. Lobar lung transplantation is not performed routinely; owing to the difficulty of donor and recipient lung size matching, only a few experienced centers perform this procedure. Small grafts cause lung hyperextension and limit exercise tolerance because of hemodynamic deterioration, whereas oversized grafts cause atelectasis, diaphragm dysfunction, high pulmonary vascular resistance, and poor gas exchange.

Further challenges with lobar lung transplantation include unexpectedly large donor organs, pathology localized in a single lobe, and the small size of the unilateral thoracic cavity. We aimed to present the outcomes of cadaveric lobar lung transplantation at our institution.

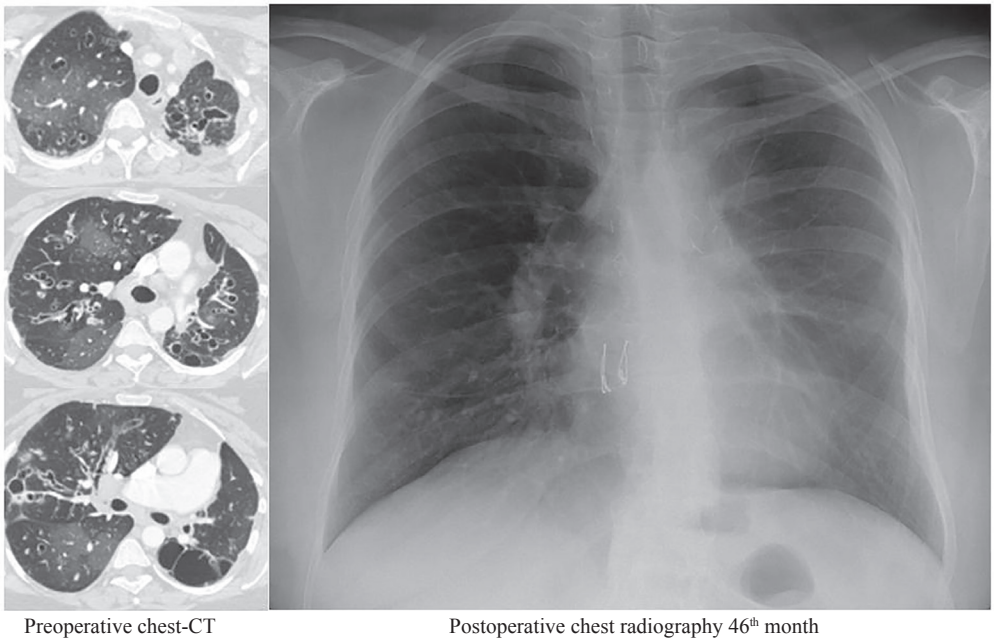
PATIENTS and METHODS

This single-center retrospective study included cadaveric lobar lung transplants performed between December 2016 and December 2018 at Kartal Kosuyolu High Specialization Training and Research Hospital, Istanbul, Turkey. Lobar lung transplantation was performed in patients with a small chest wall cavity with a deteriorating condition that precluded waiting for an appropriately sized donor lung. Furthermore, it was performed unilaterally owing to a decreased thoracic cavity volume because of underlying disease or previous lobectomy (Figure 1).

Patients with end-stage lung disease were listed for lung transplantation according to the consensus document for the selection of lung transplant candidates of the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation[5]. Demographic characteristics, preoperative patient data, intraoperative data, length of intensive care unit stay, and primary graft dysfunction (PGD) and survival data of the patients were recorded. All data were recorded prospectively and retrospectively analyzed. PGD was defined according to the 2016 report of the International Society for Heart and Lung Transplantation Working Group on PGD[6].

Donor Selection

The predicted total lung capacities (pTLC) of the donor and the recipient were calculated using a formula considering donor



Preoperative chest-CT examination

Postoperative chest radiography 46th month

Figure 1. Right lung and left lower lobe lung transplantation.

height and sex[7]. The pTLC of the donors ranged between 75% and 125% of the pTLC of the recipients. The final decision was made by visual examination in the operating room.

The estimated donor total lung capacity (L) was calculated as follows:

pTLC (male)= 7.99 x height in meters - 7.08

pTLC (female)= 6.6 x height in meters - 5.79.

The total lung capacity (sr-TLC) of the transplanted lung was calculated as follows:

sr-TLC = donor TLC x (1 - S x 0.0526)

Where, S is the number of resected segments.

Surgery Procedure

Donor lobectomy was performed on the back table. On the right, an upper lobectomy was performed to transplant the middle and lower lobes. The oblique fissure was dissected, and the interlobar pulmonary artery was prepared. The upper lobe vein was cut to preserve the atrial cuff covering both the right upper and lower veins. The upper part of the oblique fissure between the upper and lower lobes and the horizontal fissure between the upper and middle lobes were separated using a stapler. The branches of the upper lobe of the pulmonary artery were dissected and cut. Bronchial transection was performed on only one ring of the middle lobe and the apical segment bronchus of the lower lobe in the distal part of the intermediary bronchus. Care was taken to protect the peribronchial connective tissue. An aortic graft obtained from the donor was used when atrial anastomosis was required to expand and preserve venous flow from the middle lobe in the donor. A sufficient length of the proximal donor pulmonary artery was maintained sufficiently to allow anastomosis without any tension.

An upper lobectomy was performed to transplant the left lower lobe. The fissure was prepared, and the bridge between the upper and lower lobes was cut with a stapler. The interlobar pulmonary artery was dissected. The lingula artery and the branches of the upper lobe were dissected and cut. The upper pulmonary vein was ligated and cut. The atrial cuff was preserved. The left lower lobe bronchus was cut at the bronchial bifurcation level, and the apical segment bronchus of the lower lobe was preserved to allow anastomosis.

In our clinic, indications for the use of intraoperative central venoarterial extracorporeal membrane oxygenation (C-VA-ECMO) were hypercapnia ($PaCO_2$ > 55 mmHg), arterial saturation < 85%, cardiac index < 2 L/min/m^2, and mPAP > 40 mmHg. C-VA-ECMO was used for intraoperative cardiopulmonary support by cannulating the right atrial auricle and the ascending aorta. A 15-19 French (Fr) arterial cannula was used for the aorta, and a 2-stage venous cannula or a 36 Fr curved-tip cannula was used for the right atrium. C-VA-ECMO was performed after unilateral pneumonectomy, without considering the aforementioned criteria, during bilateral lower lobe transplantation. Whole-lung and unilateral lobar transplantation were performed in cases with a unilateral small thoracic cavity. In the case of unbalanced lung perfusion, pneumonectomy of the less-perfused lung was first performed. After strict bleeding control, C-VA-ECMO support was initiated. C-VA-ECMO was gradually weaned and terminated after the implantation of both lungs. C-VA-ECMO support was discontinued in patients who were hemodynamically stable and had the following arterial blood measures: PaO_2 > 70 mmHg, $PaCO_2$ of 35-50 mmHg, tidal volume of 6-10 mL/kg, positive end-expiratory pressure within acceptable limits (10 cmH_2O), and low pulmonary artery pressure without right ventricular failure.

The study was approved by the Kartal Kosuyolu High Specialization Training and Research Hospital Local Ethics Committee (ID: 2020/8/355).

RESULTS

Between December 2016 and December 2019, 55 patients underwent lung transplantation, of which 6 (10.9%) underwent lobar transplantation from deceased donors. Of the six patients, four were female and two were male; their median age was 35.3 years (range, 22-42 years). The primary diagnoses among the patients were bronchiectasis (three patients), chronic obstructive pulmonary disease (one patient), cystic lung disease (one patient), and lepidic type adenocarcinoma (one patient). ECMO was used a bridge to lung transplantation in one patient. The mean resting O_2 flow rate was 5.6 L/min (range, 4-10 L/min) during the pre-transplant examination for lung transplantation feasibility. Hypoxemia (PaO_2 < 60 mmHg) and hypercarbia ($PaCO_2$ > 45 mmHg) were observed in all and four patients, respectively, on blood arterial gas analyses. Pulmonary function tests could not be performed in four patients. Four patients did not achieve maximal exercise capacity during the 6-minute walk test (6MWT). Right ventricular dilatation was seen in three patients; the mean tricuspid annular plane systolic excursion value was 20 mm (range, 15-26 mm) on echocardiographic examination. Pulmonary hypertension was observed in three patients, as measured using right heart catheterization with the patient supine and at rest (Table 1).

The cause of donor brain death was intracranial hemorrhage in two patients and head trauma in four patients. The mean oxygenation index [partial pressure of oxygen (PaO_2) at a

Table 1. Clinical characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	42	35	58	27	28	22
Gender	Male	Female	Female	Female	Female	Male
Height	175	157	157	158	159	180
Diagnosis	Adenocarcinoma lepidic type	Bronchiectasis	COPD	Cystic lung disease	Bronchiectasis	Bronchiectasis
Waiting list time days	4	36	54	181	363	194
BMI (kg/m^2)	29.3	25.6	24.1	16.2	16.1	28
O_2-therapy (L/min)	ECMO (bridge to lung transplantaion)	5	4	5	10	4
Arterial blood gas						
pH	None	7.34	7.4	7.42	7.4	7.33
PaO_2		42.5	50.6	42.6	52.4	46.7
$PaCO_2$		60.9	52.5	56.7	38	66.1
Sat %		79.9	86	89.8	69.2	78.5
Pulmonary function test						
FVC (% of predicted)	Unperformed	23	91	24	34	35
FEV_1 (% of predicted)		18	28	22	27	23
DLCO (% of predicted)		Unperformed	Unperformed	Unperformed	24	38
6MWT						
Distance m	Unperformed	Unperformed	66	290	Unperformed	266
Final SpO_2 (%)			75	83		85
Echocardiogram						
RV dilation	+	-	-	-	+	+
TAPSE mm	18	16	26	26	15	21
Right heart catheterization						
PABs (mmHg)	None	41	28	25	70	44
PABm (mmHg)		26	17	13	49	30
CO (mL/min)		5.54	3.4	5	4.4	6.5
PAWP (mmHg)		-	-	6	8	12

COPD: Chronic obstructive pulmonary disease, BMI: Body mass index, ECMO: Extracorporeal membrane oxygenation, FVC: Forced vital capacity, FEV_1: Expiratory volume in one second, DLCO: Diffusing capacity for carbon monoxide, 6-MWT: 6 minute walk test, RV: Right ventricle, RHC: Right heart catheterization, PAPs: Systolic pulmonary arterial pressure, PAPm: Mean pulmonary arterial pressure, CO: Cardiac output, PAWP: Pulmonary artery wedge pressure.

positive end-expiratory pressure (PEEP) of 5 mmHg and fraction of inspired oxygen (FiO_2) of 1.0] at the time of organ offer was 384 (range, 269-480). The mean mechanical ventilation time was 4.16 days (range, 2-9 days). Three donors had a history of smoking (> 20 packs/year; Table 2). The pTLC of the donor was between 76% and 114% of the pTLC of the recipient. The donor-recipient sex match was male to female in three patients, female to female in one patient, female to male in one patient, and male to male in one patient (Table 3).

The mean waiting time was 139 days (range, 4-363 days). The lobar lung transplantations performed were bilateral in two patients, whereas two patients received the right single lung and left lower lobe and two patients received the left single lung and right lower lobe transplant. All transplantation was performed with C-VA-ECMO support. ECMO as a bridge to lung transplantation was used in one patient. The mean mechanical ventilation duration and intensive care unit stay were 4.5 days (range, 1-4 days) and 7.8 days (range, 4-20 days), respectively. The mean red blood cell, fresh frozen plasma, and pooled platelet units transfused peri- and post-operatively were 11.3 units (range, 6-21 units), 9.5 units (6-11 units), and 1.3 units (0-3 units), respectively (Table 4).

One-year mortality was 16.6% (1/6). The causes of death included multiorgan failure on postoperative day 85, relapse of lepidic type adenocarcinoma on postoperative month 23, and chronic lung allograft dysfunction on postoperative month 24. The second patient and two patients who underwent bilateral lower lobe transplantation are alive without any complaints on follow-up at postoperative months 24, 25, and 47 (Figure 2).

Table 2. Donor characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Cause of death	Intracranial hemorrhage	Head trauma	Intracranial hemorrhage	Head trauma	Head trauma	Head trauma
Gender	Female	Male	Female	Male	Male	Male
Age	21	19	51	39	52	37
Height (cm)	170	172	160	182	180	181
Heavy smoker (> 20 pack/year)	-	-	+	+	+	-
PaO_2 mmHg on FiO_2 of 1.0	351	394	473	480	341	269
Intubation time (day)	2	2	4	3	5	9

FiO_2: Fraction of inspired oxygen, pTLC: Predicted total lung capacity.

Table 3. Gender and pTLC mismatch

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Donor to recipent	F/M	M/F	F/F	M/F	M/F	M/M
Recipent pTLC (Liter)	5.08	4.57	4.57	4.63	4.70	7.30
Donor pTLC (Liter)	5.79	6.66	4.77	7.46	7.30	7.38
Sr-TLC	4.26	5.25	3.51	4.71	3.84	5.84
Calculated range in D/R TLC ratio	-0.83	+1.14	-0.76	+1.01	-0.81	-0.8

pTLC: Predicted total lung capacity, M: Male, F: Female, Sr-TLC: Total lung capacity in the transplanted lung, D/R: Donor/recipent.

DISCUSSION

Despite the recommendations of the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation, in our experience, patients with end-stage lung disease were not referred at the optimal time and were listed for lung transplantation despite significant deterioration in respiratory function. Most patients were already on long-term oxygen therapy, had pulmonary hypertension, and were unable to perform pulmonary function tests and the 6MWT[5]. Owing to the deteriorating condition, insufficient time to identify a suitable donor was available in all patients, leaving the use of an oversized lung graft by lobectomy as the only option to prevent waiting list mortality. The Toronto Lung Transplant Group, one of the most experienced teams, has performed lobar lung transplantation in 4.5% of all standard lung transplantations[8]. In our study, the ratio of lobar lung transplantation was 10.9%. This high ratio could be attributed to a high number of critically ill patients and the small number of waitlisted patients. Another reason could be that most patients had underlying diseases, such as bronchiectasis, that caused unilateral lung volume loss.

Selecting between wedge resection or anatomic lobectomy in case of unexpected size mismatch during the procedure is challenging. Loizzi et al. compared patients who underwent standard lung transplant with those who underwent lobar lung transplant. They concluded that the upper limit for the donor to recipient pTLC ratio should be 1.15-1.20, with a definite preference for lobar transplantation when the ratio is > 1.20[9]. Lobectomy can be performed on the back-table or after implantation to reduce size. Using back-table lobectomy can help reduce ischemia time as it can be performed by a separate surgeon concurrently with recipient preparation and prevents impaired visibility of the hilum because of the large lung thoracic cavity, this preventing mismatch. Another benefit of back-table lobectomy over post-implant lobectomy

Table 4. Intraoperative data and outcomes

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Transplantation type	Left lung Right lower lob	Right lung Left lower lob	Left lung Right lower lob	Right middle + lower lob left lower lob	Bilateral lower lob	Right lung Left lower lob
Intraoperative ECMO	+	+	+	+	+	+
Number of transfusions on first postoperative day, units						
RBC	21	6	15	10	6	10
FFP	11	6	11	9	11	9
Pooled platelet	1	2	3	3	1	1
Severe PGD	+	-	+	-	+	-
Mechanical ventilation (days)	14	1	3	2	3	4
ICU stay (days)	20	4	10	4	5	4
Hospital stay (day)	52	22	44	17	34	39
Mortality	Died	Alive	Died	Alive	Alive	Died
Survival (month)	23	47	3	25	24	23
Cause of death	Relapse		Multi-organ failure progression			CLAD

ECMO: Extracorporeal membrane oxygenation, FFP: Fresh frozen plasma, RBC: Red blood cells, PGD: Primary graft dysfunction, ICU: Intensive care unit.

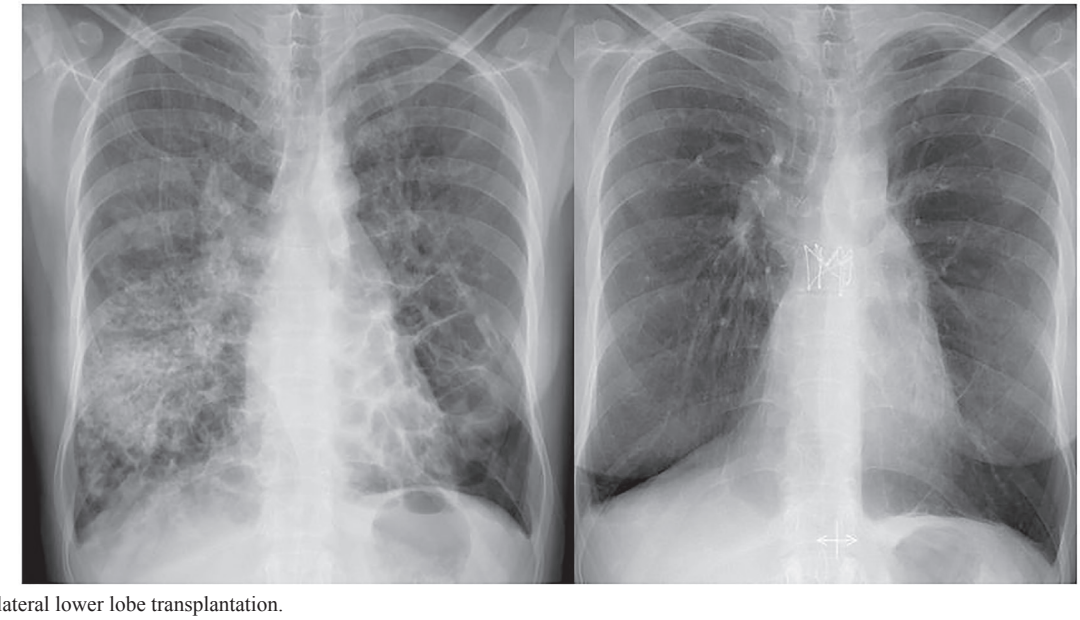


Figure 2. Bilateral lower lobe transplantation.

is that a bronchial stump is not required. However, performing back-table lobectomy poses technical challenges as dissection becomes difficult owing to the lack of blood circulation in the vessels, whereas post-transplant lobectomy may be challenging because of the large size of the lung within a small chest cavity. Another disadvantage of post-implantation lobectomy is that the manipulation of the recently perfused lung may cause reperfusion injury, which may cause further damage to the transplanted lung.

Lobar lung transplantation candidates are at higher risk owing to hemodynamic instability because of their poor general condition during the perioperative reperfusion phase.

Perioperative management for lobar lung transplant recipients differs from that for standard lung transplant recipients. After implantation, the implanted lobe receives almost all the cardiac output during the remnant native lung pneumonectomy. This excessive increase in pulmonary circulation causes increased pulmonary pressure and extravascular fluid leakage and eventually, pulmonary edema. Cardiopulmonary bypass or ECMO support is recommended during the procedure to prevent overloading of the pulmonary vascular bed[10]. Peripheral or central venoarterial ECMO, which requires less heparin and provides thoracic epidural analgesia, has replaced CPB[11].

Cadaveric lobar lung transplantation is increasingly being performed to expand the donor pool for critically ill patients and patients with a deteriorating condition while waiting. However, although lobectomy is a standard and simple technique, lobar lung transplantation is not performed routinely. Only a few centers have reported their short- and long-term results with lobar lung transplantation in the last decade[2,3,8,12]. In a report published by the Toronto Lung Transplant Team that included 75 patients, the 1-, 3-, and 5-year survival rates did not differ significantly between lobar lung transplantation and standard lung transplantation recipients (73.2% vs. 84.4%, 56.9% vs. 68.4%, and 50.4% vs. 55.8%, respectively)[8]. We experienced only one in-hospital mortality; while two patients died at 23 and 24 months postoperatively, these deaths directly related to the lobar transplantation.

Early postoperative mortality among transplant recipients ranges from 0% to 28%[2,3,13,14]. Reportedly, mortality is higher among lobar lung transplants than among standard lung transplants[4]. However, most studies have reported no significant differences in long-term survival among both groups[15]. Lobar lung transplantations are performed mostly urgently owing to patient condition deterioration[16]. In our study, two patients who underwent lower lobar transplantation had an urgent status and both survived. No complications were seen within two years postoperatively. Whether to perform lobar lung transplantation instead of standard lung transplantation in case of an available appropriately sized recipient remains unclear. Although the two urgent patients survived with acceptable outcomes, lobar lung transplantation is not routinely performed at our clinic. However, given the increase in the number of transplant candidates with small thoracic cavities, such as those with cystic fibrosis, it is poised to become routine practice owing to donor unavailability. Future case series evidence would better our understanding of technical feasibility and outcomes.

This study has several limitations. This was a retrospective, single-center study. A control group was absent. Owing to our limited experience with patients undergoing lobar lung transplantation in Turkey, our sample size was limited. Regardless of the limitations, in our experience, lobar lung transplantation is a life-saving treatment option for critically ill recipients with small thoracic cavities, particularly those with cystic fibrosis and pulmonary fibrosis. Furthermore, it is a feasible surgical technique in recipients with a reduced unilateral thoracic cavity.

Ethics Committee Approval: The study was approved by Kartal Kosuyolu High Specialization Training and Research Hospital Local Ethics Committee (ID: 2020/8/355).

Informed Consent: Informed consent was obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept/Design - MV; Analysis/Interpretation - AE; Data Collection - MV; Writing - AE, MV; Critical Revision - AE; Final Approval - MV; Statistical Analysis - AE; Obtainel Funding - MV; Overall Responsibility - MV.

Conflict of Interest: The authors have no conflicts of interest to declare

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