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INVITED REVIEW – OPEN ACCESS

Future of Lung Transplantation in Turkey

Muhammet Ali Beyoğlu[1], Hülya Yiğit Özay[2], Sema Turan[2], Erdal Yekeler[1]

ABSTRACT

Lung transplantation significantly improves the quality of life and survival in end-stage lung diseases. Successful lung transplantation has been performed only for 35 years. Despite the increase in the number of lung transplants in recent years, the difference between potential recipient candidates and the number of lung transplants increases further. In Turkey, which has significant experience in other solid-organ transplantations, lung transplantation has only been routinely applied in the last decade. In this review, the history of lung transplantation in Turkey, current situation, and prospects will be discussed.

Keywords: Donors, organ donation, lung transplantation

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[1]Department of General Thoracic Surgery and Lung Transplantation, Ankara City Hospital, University of Health Sciences, Ankara, Turkey
[2]Department of Anesthesiology and Reanimation, Ankara City Hospital, University of Health Sciences, Ankara, Turkey

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Correspondence
Muhammet Ali Beyoğlu, University of Health Sciences, Ankara City Hospital, Department of General Thoracic Surgery and Lung Transplantation, Ankara, Turkey
Phone: +90 530 370 79 03
e-mail: muhammetalibeyoglu@gmail.com

INTRODUCTION

Lung transplantation is a radical surgical treatment option for individuals who are unresponsive to maximum medical therapy and has low predicted survival. It significantly improves the quality of life and survival in end-stage lung diseases. In the last 35 years, there has been a serious increase in the number of lung transplants. According to the International Society of Heart and Lung Transplantation (ISHLT), more than 60,000 lung transplants were performed between 1988 and 2016 (1). Despite the increase in the number of lung transplants, the difference between potential recipient candidates and the number of lung transplants increases further. The mortality rate of candidates in the lung transplant waiting list can reach up to 50% (2). Lung donor shortage is the most critical constraints in Turkey and the rest of the world. In addition to the low number of donations, lung availability in multiorgan donors is insufficient. Donation from living donors, which increases the number of lung transplantations, is not yet implemented in Turkey. In this study, the history of lung transplantation in Turkey, current situation, and future prospects will be reviewed and discussed.

History of Lung Transplantation

The first intrathoracic lung transplant was performed on a dog by Vladimir P. Demikhov in 1946, and the dog survived up to 7 days (3). The first human lung transplant was performed by James D. Hardy in 1963. A left lung from a patient who died of acute myocardial infarction was transplanted to a patient with left hilar lung cancer (4). After the transplant, the patient lived for 18 days and died from acute renal failure (5). Lung transplantation was performed in humans until 1980, but long-term survival could not be achieved. The 10-month survival following a lung transplant performed by Fritz Derom in 1968 was considered the most positive result (6). The right lung transplant performed by the Toronto lung transplant team, led by Joel D. Cooper, in 1983 was considered the first successful human lung transplant (7). In 1985, the same team performed the first bilateral sequential lung transplantation in humans in 1985 (5). Lung transplant from a living donor was first performed in 1990. The right lower lobe of the lung of a 45-year-old mother was transplanted to her 12-year-old daughter with bronchopulmonary dysplasia (8).

Lung transplantation has shown a challenging and slow course. Successful lung transplantation can be performed later than other solid-organ transplantation. The number of lung transplants has increased, thanks to new immunosuppressant agents, advances in organ-protective techniques, and improvements in postoperative care techniques.

Lung Transplantation in Turkey

The first heart–lung transplant in Turkey was performed in Dokuz Eylul University Hospital in 1998. The recipient was discharged 2 months after the surgery and survived for 9 months (9). The first isolated lung transplant in Turkey was performed in Istanbul University Hospital in 2004. The recipient was a 44-year-old man with idiopathic pulmonary fibrosis (IPF), but died from bleeding disorder and multiorgan failure 11 days after surgery.

Lung transplantation was applied to two more patients with IPF in 2004 and 2005 in the same center, but the patients died in the early postoperative period (10).

Turkey's first successful isolated lung transplant was conducted in 2009 in Sureyyapasa Chest Disease and Thoracic Surgery Hospital by the Sureyyapasa Lung Transplantation Group (SLTG) (11). A single lung transplant was performed on a 34-year-old male patient with silicosis. In 2009, Turkey's first successful double lung transplant and the first lung transplant in a pediatric patient were conducted in Ege University Hospital (12). A 14-year-old male patient with bronchiolitis obliterans underwent sequential double lung transplantation, and the patient lived for 2.5 years.

The year 2012 has been a turning point for lung transplantation in Turkey. Many centers have received a lung transplant license from the Ministry of Health. In 2012, SLTG moved to Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital (TRH), a successful heart transplant center. A lung transplantation team started operations at Yedikule Chest Diseases and Thoracic Surgery TRH. In 2012, 25 lung transplants took place in Turkey: 14 in Kartal Koşuyolu Yüksek İhtisas TRH, 10 in Yedikule Chest Diseases and Thoracic Surgery TRH, and one in Gulhane Military Medical Academy Hospital. Another lung transplant team started operations in 2013 in Ankara Yüksek İhtisas TRH and performed bilateral sequential lung transplant on a 57-year-old patient with chronic obstructive pulmonary disease (COPD). In 2019, this lung transplantation team moved to the newly built City Hospital in Ankara. The numbers of lung transplants performed in Turkey until the end of 2020 are shown in Table 1 and Figure 1 according to the lung transplant centers and years (Fig. 1).

As of January 2021, Turkey has four centers granted a license to perform lung transplantation. To date, lung transplantation licenses of six centers have been terminated (Table 2). Kartal Koşuyolu Yüksek İhtisas TRH and Ankara City Hospital lung transplant clinics actively continue their activities. Until December 2020, 216 (75.2%) of 287 lung transplants were conducted in these two centers.

Donor shortage ranks first in the list of reasons of the low number of lung transplants in Turkey, as in the whole world, followed by low donor lung availability rate, which is more prominent in Turkey than in other countries. A study conducted by our clinic reported a lung utilization rate from cadaveric multiorgan donors of 15% (13). The low number of organ donations, deficiencies in donor care and management, and absence of living lung donation policies are the main rate-limiting factors in lung transplantation. In addition, the ex vivo lung perfusion (EVLP) system, which increases the availability of organs, is still not covered by the health insurance system. Measures to increase the number of lung transplants in Turkey can be evaluated under six topics.

Increasing Organ Donation

According to the legislation in Turkey, relatives of donor candidates who are brain dead can decide on organ donation. For living-organ donation, up to fourth-degree relatives of recipients on the waiting list can decide on organ donation. In 2018, the number of organ donations from brain-dead donors was 7.54 per million people (pmp) (14) and that from living-organ donors was 52.01

Table 1. Number of transplants to years and lung transplant centers in Turkey

Center/Year	2004	2005	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
Süreyyapaşa Chest Disease and Thoracic Surgery RTH*	-	-	6	3	5	-	-	-	-	-	-	-	-	-	14
Koşuyolu Yüksek İhtisas RTH	-	-	-	-	-	14	18	12	18	4	26	25	16	4	137
Yedikule Chest Disease and Thoracic Surgery RTH	-	-	-	-	-	10	7	11	3	--	-	-	-	-	31
TYIH**/Ankara City Hospital	-	-	-	-	-	-	5	6	5	11	12	18	15	7	79
İstanbul MFH***	2	1	-	-	-	1	-	2	2	4	-	-	-	-	12
Marmara MFH	-	-	-	-	-	-	-	1	2	1	3	-	-	-	7
Ege MFH	-	-	1	-	-	-	-	-	-	2	1	-	2	-	6
Gülhane Askeri Tıp Akademisi	-	-	-	-	-	-	1	-	-	-	-	-	-	-	1
Total	2	1	7	3	5	25	31	32	30	22	42	43	33	11	287

RTH*: Research and Training Hospital, TYIH**: Turkiye Yuksek Ihtisas Hospital; MFH***: Medical Faculty Hospital

Table 2. Lung transplantation centers in Turkey

Certified lung transplantation centers	Ankara City Hospital
	Koşuyolu Yüksek İhtisas RTH*
	Marmara Univercity Medical Faculty Hospital
	Ege Univercity Medical Faculty Hospital
Centers which certificates have been revoked	Süreyyapaşa Chest Disease and Thoracic Surgery Research and Training Hospital
	Yedikule Chest Disease and Thoracic Surgery RTH
	Gülhane Askeri Tip Akademisi Hospital
	İstanbul Univercity Medical Faculty Hospital
	Bakırköy Sadi Konuk RTH
	Ankara Yuksek İhtisas RTH

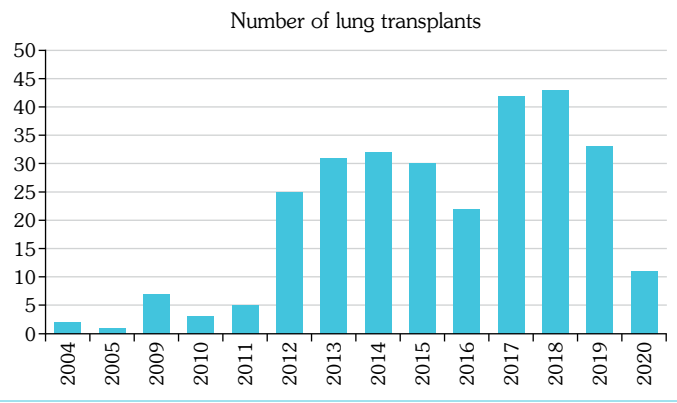

Figure 1. Number of lung transplants in Turkey by year

pmp. While Turkey ranks first in the rate of living-organ donations in Europe, it ranks last in the rate of brain-dead donation. In 2014, with the regulations for diagnosing brain death in Turkey, judgment of two, instead of four, physicians has become sufficient. In this way, while 700 brain death notifications were made in 2012, more than 2000 brain death notifications were made annually in accordance with the new regulation. No increase at the same rate was achieved in the number of donations.

Several studies have evaluated the perception of the Turkish population on organ donation. Aykas et al. (15) reported that 82% of the 2154 participants stated that Islam allows organ donation, and 56% of them do not have enough knowledge regarding organ donation. Tantus noted that 91.1% of 4000 survey participants support organ donation, 84% are not against organ donation, and 75.3% can donate their organs (16). These results indicate that most of the Turkish citizens are aware of organ donation and think that organ donation is religiously appropriate.

The increase in the number of organ donations in the last 10 years is related to the advertising activities of the Ministry of Health, which encourage organ donation, and the encouraging statements of the Directorate of Religious Affairs. Nevertheless, these state institutions mainly use national media and public spaces in their promotion activities. The use of social media in the promotion of organ donation may increase the number of donations. Moreover, participation of well-known people, who can significantly affect the society, in organ donation campaigns may increase the number of donations. Giving priority to organ donors and/or their relatives if they are placed on the waiting list, which has been implemented in Israel since 2008, caused an increase in the number of donors within a short time. Turkey's implementation of this method may cause an increase in the number of donations.

Donor Care and Lung Management

If possible donors are patients who are declared brain dead, treatments involving donor care are applied in the intensive care unit until harvesting of organs (17). After the first successful lung transplant, donor selection criteria were made randomly according to a center's experience. Considering the differences in donor criteria, ISHLT published the "Lung Transplant Donor Criteria" report in 2003 to gather evidence that support the current recommendations or present their deficiencies (18). Among the criteria included in this report and examined in the literature, age, sex, smoking history, bronchoscopic and radiographic findings, organ size, graft ischemia time, blood group (ABO) compatibility, arterial blood gas (oxygenation), and donor's duration of mechanical ventilation and cause of death was considered important. The standard criteria include a history of smoking less than 20 pack-years, absence of a lung disease, absence of systemic or pulmonary infection, regular gas exchange, and clean chest radiography finding (19).

Compared with other organs, lungs from brain-dead donors are easily damaged and more susceptible to traumatic events. Lungs can be damaged shortly before and after brain death because of conditions resulting from direct trauma, resuscitation maneuvers, neurogenic edema, aspiration of gastric contents, ventilator-associated trauma, and pneumonia (20). Moreover, 15%–25% of lungs from brain-dead multiorgan donors are used in lung transplantation (21). For these reasons, it is crucial to fully define brain death, obtain family consent, and protect and optimize all functions of organs until harvest. In a study conducted by the San Antonio/Texas group and Texas Organ Sharing Network, employees in the organ-sharing network were informed that each organ donor was a potential lung donor. These people were trained for lung donor management strategies. Compared with the rate at the pretraining period, the rate of lung harvest from organ donors increased by 2.2 times after the training. Another study showed that flexible cooperation with the intensive care unit as regards donor care resulted in 60% higher utilization rate of the lungs recommended for transplantation. Therefore, the organ-sharing referral network and early contact with the donor center are thought to help obtain viable lungs from potential donors (20).

General organ donor management focuses on blood pressure regulation, maintenance of acid/base balance, electrolyte monitoring, maintenance of intravascular volume, normothermia, and prevention of infections. Lung-specific approaches should be considered for optimization of lung function. Following brain death, hemodynamic, hormonal, and inflammatory disorders may occur, leading to cardiac arrest in a potential donor or irreversible damage to different organs. Sympathetic discharge results in hypertensive crisis, followed by neurogenic hypotension and systemic inflammatory response, leading to alveolar membrane disruption. Subsequent neurogenic pulmonary edema and endothelial dysfunction can lead to acute lung injury, which is similar to acute respiratory distress syndrome (ARDS) (19, 22). The availability of lungs can be increased by minimizing edema while providing adequate fluid to the kidneys (diuresis 0.5–2.5 ml/kg/h) (22). To prevent aspiration, the head of the bed should be raised 30°, and the endotracheal cuff pressure should be adjusted to avoid leakage. Airway clearance should be ensured with bronchoscopy and revision of respiratory physiotherapy, and antibiotic treatment should be initiated. Keeping the ratio of the arterial oxygen partial pressure to fractional inspired oxygen >300 mmHg is considered ideal.

Accurate findings are needed when initiating continuous monitoring of hemodynamics, arterial and central venous routes, and pulmonary artery monitoring of candidate donors. Hemodynamic instability (neurogenic shock) following brain death causes fluid overload in the lungs. If such condition is not managed well, pulmonary edema and impaired oxygenation may occur. A study reported that neurogenic edema negatively affects the post-transplant process (20). Initially, evaluation of cardiac functions through transesophageal echography and fluid (crystalloid) resuscitation to ensure euvolemia is recommended. If the target hemodynamic values (mean arterial pressure >60 mmHg, central venous pressure 6–10 cmH_2O) cannot be achieved, vasopressin (0.6–2.4 U/h) or inotropic agents (dopamine <10 mcg/kg) can be administered (22).

In addition, brain death causes a sudden decrease in the levels of hormones, such as cortisol, antidiuretic hormone, and thyroid hormone. A study presented that organ utilization can be increased if deficient hormones are replaced. Negative events associated with brain death can be alleviated especially with the administration of thyroid hormone, methylprednisolone (15 mg/kg), and vasopressin (22).

Ventilation Strategies

In the intensive care unit, lung-protective strategies that are employed in ARDS cases are included in the follow-up of candidate donors on mechanical ventilation (23). Compared with ventilation with standard tidal volumes, low tidal volumes provide protection against acute lung injury and ARDS (24). In the largest prospective randomized controlled study on this topic, 118 potential lung donors received conventional ventilation therapy (with tidal volume of 10–12 mL/kg and 3–5 cmH_2O positive end-expiratory pressure [PEEP] and ventilation with a clear tracheal aspiration circuit, and apnea test was performed by disconnecting the patient from the ventilator while applying high-flow oxygen] and protective ventilation (tidal volume of 6–8 mL/kg and 8–10 cmH_2O PEEP according to body weight, using a closed circuit for tracheal aspiration, continuous positive airway pressure control mode on ventilator, and apnea tests). After a 6-hour observation period, the number of donors who meet the lung donor eligibility criteria (54% versus 95%) and the number of donors whose lungs were transplanted (54% versus 27%) were higher in the protective group (25). At the final consensus, ISHLT in lung-protective ventilation presented the following updated values: tidal volume of 6–8 ml/kg, PEEP of 8–10 cmH_2O, peak airway pressure <35 mmHg, pH of 7.35–7.45, pCO_2 of 35–45 mmHg, pO_2 of 80–100 mmHg, and oxygen saturation >95% (22). However, controversy still exists regarding the best ventilation strategy in patients declared brain dead.

Many single-center studies have shown that donor management protocols increase donor lung utilization rates. Compared with previous protocols, these protocols have been found to increase donor lung recovery from 20% to 40%–50%, without an increase in primary graft dysfunction (PGD) rates (26). The implementation of a lung-focused protocol does not affect the heart, liver, kidney, or pancreas procurement rates or long-term kidney graft survival (27). Evidence showed that any factor that makes a donor more acceptable than ideal will have no significant negative effect on the recipient's prognosis. However, PGD and stay in the intensive care unit by recipients whose donors have met two or more extended criteria increased (28).

Bridge to Lung Transplantation

Extracorporeal membrane oxygenation (ECMO) is used in lung transplantation to provide mechanical respiratory and circulatory support in the preoperative, intraoperative, and postoperative periods (Fig. 2). Providing hemodynamic stability in the intraoperative period, which is associated with less incidence of heparinization and PGD than cardiopulmonary bypass, gained widespread application (29). As in other solid-organ transplants, shortage of lung donors, long waiting times of those in the transplant lists, and infection exacerbations increase the mortality rates of those in the waiting list. In cases with resistant hypoxemia and hypercapnia despite medical treatment, specialized centers may use ECMO in selected patients as a bridge to lung transplantation. Following rigorous daily clinical evaluation, ECMO can be used to successfully bridge patients with critically illness to lung transplantation (30).

Split Lung Transplantation

One of the methods of increasing the donor pool is split lung transplantation. Split lung transplantation is a single lung transplantation into two recipients of a lung taken from a donor or single lung transplantation in one recipient and two-sided lobar transplantation in the other recipient. Given the survival advantage, the number of double lung transplants is higher than that of single lung transplants (1). Although transplant centers tend to perform double lung transplantation, among other methods, single lung transplantation can be performed to increase the number of transplants despite organ shortage and high lung waiting-list mortality rate. Current publications claimed successful long-term results of single lung transplantation in patients with COPD and IPF, which constitute a significant portion of patients on the waiting list (31–33).

Lobar Lung Transplantation from Living Donors

Living donor-lobar lung transplantation (LDLLT) was first introduced in 1990 in the United States to solve severe organ scarcity (8). Lung transplantation was performed to patients with high mortality risk and rapidly progressing condition because of the long

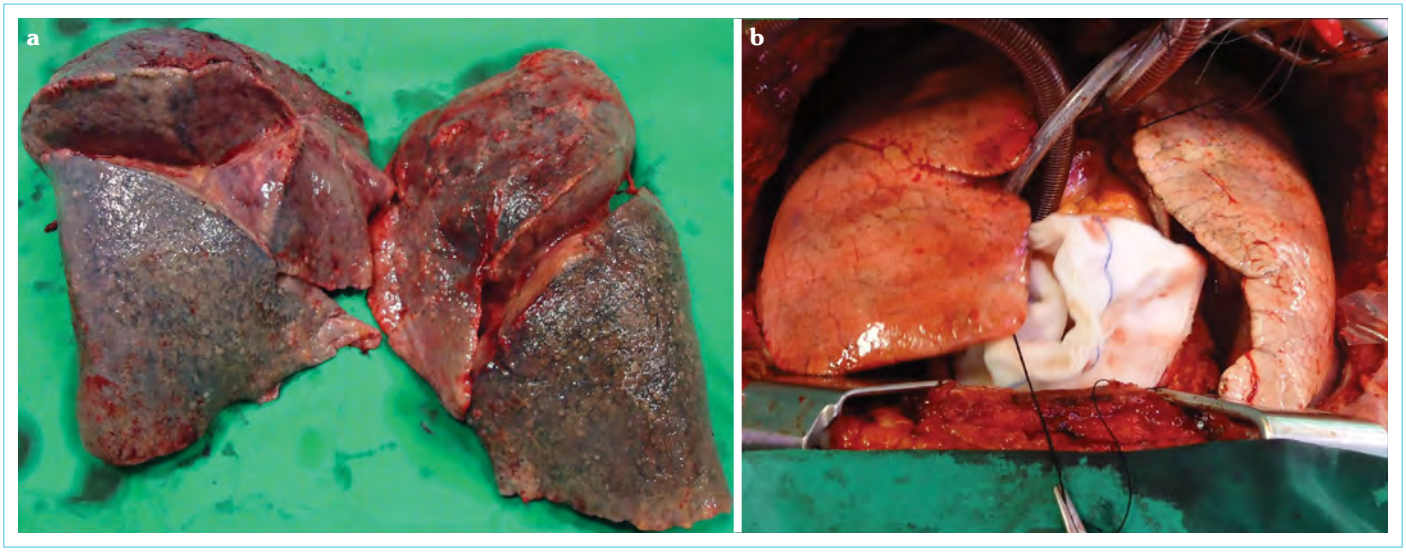

Figure 2. Lung transplant procedure. (a) Explant lung of a patient with idiopathic pulmonary fibrosis. (b) Double-lung transplantation in the same patient under central extracorporeal membrane oxygenation

waiting time. Pediatric patients and adult patients with small body frame were mostly selected for LDLLT. With the application of the lung allocation score in the United States, lung recipient selection was made based on the mortality risk rather than on the waiting list times, thereby reducing the number of LDLLTs. At present, LDLLT is routinely applied in Japan, where the waiting period for lung transplantation exceeds 800 days and lung transplantation from donation after circulatory death (DCD) is prohibited (2).

Two donors are needed for each patient indicated for LDLLT. Generally, the right lower lobe from one donor and the left lower lobe from the other are taken and transplanted. By removing the right lower lobe of both donors, one of the right lobes can be transplanted to the left hemithorax by turning it 180° along the vertical line. Initially, LDLLT can be applied only to pediatric patients and adult patients with small frames. LDLLT can be also successfully applied to adults with normal body frames, thanks to lobar transplantation while preserving the recipient's upper lobes. Since the right lower lobe is 25% larger than the left lower lobe, more lung tissues can be transplanted by performing right lower lobe transplantation to both sides of the hemithorax (34).

While one recipient can benefit from LDLLT, two donors can incur injury. In LDLLT, donor selection and provision of detailed information about the donor operation are crucial. The complication rate observed after donor lobectomy is higher than normal lobectomy. Heparin administration to the donor and inclined cutting of the lower lobe bronchus are the reasons for the high complication rate. Organ waiting time and ischemia time are shorter in LDLLT than in cadaveric lung transplantation. Transplant surgery can be elective, and chronic rejection occurs unilaterally, and the PGD ratio is lower. Two lungs consisting of 19 segments are involved in cadaveric lung transplantation, whereas 9 or 10 segments are involved in LDLLT.

At present, although the utilization rate of cadaveric donor is 60%, LDLLT is often employed in Japan, where the mortality rate of patients on the waiting list for lung transplant is 50% (2). Between 1998 and 2015, 283 (60.9%) of 464 lung transplants performed in Japan were cadaveric lung transplants and 181 (39.1%) were LLDLTs. The 5-year survival rates were comparable (72.3% vs 71.6%) (2).

Among other methods, LDLLT can be employed to expand the donor pool. At present, lung transplantation can be performed in adult patients with normal body frames, in addition to pediatric patients and adult patients with small body size. Lobe-sparing LDLLT performed by preserving the recipient's upper lobes is more effective in maximizing respiratory function than standard LDLLT (35).

EVLP

The EVLP system is a complex closed system in which the lung removed from the donor is ventilated and perfused in a normothermic sterile chamber with negative pressure. In the EVLP system, it is possible to measure physiological parameters and administer treatment when necessary. In 2001, Steen et al. (36) successfully transplanted lungs removed from a DCD donor following evaluation by EVLP.

EVLP allows external, bronchoscopic, radiologic, and physiological evaluation of the donor lungs that were found unsuitable for transplantation at the first evaluation, before transplantation to the recipient. Two EVLP systems are widely used and commercially available: XVIVO Perfusion System (XPS Perfusion, Goteborg, Sweden) and Organ Care System (Transmedics, Andover, MA). The two systems have fundamental differences, such as the quality of the perfusate used, use of continuous versus pulsatile perfusate flow, and use of open versus closed atrial cuff.

Unlike solid organs such as the liver and kidney, the utilization rate of lungs from circulatory death donors is low. In a study performed in Turkey, the rate of donor lung utilization was 15% (13). With the introduction of EVLP systems in lung transplantation, the rate of donor lung utilization has increased to 15%–20% (37). The introduction of the EVLP system, among other methods, can increase the rate of donor availability in countries without cadaveric donors, such as Turkey. At present, Turkey has not use an EVLP system in lung transplant centers.

DCD

Unsuccessful results in the early period of lung transplantation have excluded organ transplantation from DCD donors for many years. Failure to meet the increase in the number of patients on the lung transplant waiting list by DBD donors has led to a rise in DCD donor interest over time. Experimental lung transplantation studies have been performed after circulatory death, and successful results have been published (38). The first successful human lung transplantation of a DCD lung was performed by Love et al. (39) in 1995. DCD refers to organ harvesting from a donor with irreversible unresponsiveness, apnea, and circulation shutdown. It was previously called non-heart-beating organ donation after cessation of cardiac activity.

Lung transplantation from DCD donors has been viewed with suspicion because of concerns regarding prolongation of warm ischemia time, high PGD rate, and low surveillance. DCD lung transplantation became a routine only a decade after the first successful DCD lung transplantation. Mason et al. (40) reported that the development of PGD and early and long-term survival outcomes in 31 lung transplants from DCD donors between 2004 and 2011 were similar to those from DBD donors.

In Turkey, lung transplantation from only DBD donors is one of the obstacles to increasing lung transplants. No legislation has been established on organ donation following circulatory death. Thus, legal arrangements should be made on this topic. Promotion and incentive activities related to DCD are necessary to gain public support. Training on DCD donor selection and management should be planned for emergency room physicians, intensive care physicians, and organ transplant coordinators. Moreover, the provision of an EVLP system, which is not yet available in Turkey, is essential for utilization of DCD organs. The use of these organs, which have a long warm ischemia time, following evaluation by the EVLP system and subjected to reconditioning, as appropriate, is necessary for successful DCD lung transplantation.

CONCLUSION

While Turkey gain ranks in the list for solid-organ transplants, such as liver and kidney, in Europe, lung transplantation has only recently been routinely performed. Worldwide, the increase in the number of patients on the waiting list for lung transplant is not approximate to the number of transplants that can be performed. Thus, there is a need to develop policies to encourage organ donation and raise awareness regarding lung transplantation. Living-donor lung transplantation, DCD lung transplantation, and split lung transplantation should be performed to increase the number of lung transplants in the short term. Healthcare professionals should be trained, and the EVLP system should be used to increase donor availability.

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