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Current Status and Future of Lung Donation in Korea

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Lung transplantation is the only effective treatment option for patients with end-stage lung disease. However, donor organ shortage makes timely transplant not possible for all patients, especially in Korea. We investigated the number and utilization of donor lungs by retrospectively reviewing all donor organs registered in the Korea Network for Organ Sharing database from March 2012 to March 2016. The donors were stratified into 4 groups by donor acceptability criteria. A total of 1,304 donors were included. Of those, 295 brain-dead donors (22.6%) consented to lung donation. Among these consented donors, 168 donors (12.9%) were retrieved for lung transplant. Retrieval rate was very low compared with that of the kidney (93.9%), liver (86.3%), and heart (27.3%). The characteristics of utilized donor lungs were: mean age, 40.5 years (range: 18 to 63 years); mean partial pressure of oxygen, 356.5 mmHg; mean smoking history, 5.9 pack-years; and mean body mass index, 22.6 kg/m^2. The proportion of donors with acceptable condition of the transplanted lungs was only 39.3% (ideal 19, standard 47, marginal 70, unusable 32). Among brain-dead patients who denied to donate lungs (n = 1,009), 82 were potentially acceptable donors (ideal 19, standard 63), which was equal to half of actually transplanted lung donations. Many potential donor lungs, which are currently excluded, may be successfully used in lung transplantation in Korea. The available lung donors must be actively selected and managed to maximize the utilization of this precious resource.

Keywords: Lung Transplantation; Donor; End Stage Lung Disease; Korea

INTRODUCTION

Lung transplantation is the only effective treatment option for patients with end stage lung disease. However, donor organ shortage makes timely transplant not possible for all patients. In 2014, a total of 154 patients were listed for lung transplantation in Korea, but only 55 lungs were used for transplantation (1). This gap between supply and demand has increased and it remains a major problem. Furthermore, not all donor referrals materialize to successful organ retrievals as assessment of the donor in the operating theatre does not allow adequate time for donor optimization, which may in turn lead to poor retrieval rate. This leads to a long period on a waiting list with a high mortality rate of patients awaiting transplantation (2). Globally, lung transplantation suffers from a very low rate of lung procurement that is nearly 15%–20% (3,4). Recently, lung transplantation is getting popular in Korea and time on a waiting list is expected to further increase in the near future (5-7). Grasping the present condition of lung donor shortage is very meaningful at this time. In this study, we present the current status of lung donation in Korea and also explore various factors that could help improve the country's low procurement rate.

MATERIALS AND METHODS

We retrospectively reviewed the Korea Network for Organ Sharing (KONOS) database to identify all adult lung donors between March 2012 and March 2016 in Korea. Collected variables consisted of age, sex, ABO blood group, mean partial pressure of oxygen in arterial blood (PaO_2) fraction of inspired oxygen (FIO_2) ratio (PF ratio), smoking history, mean body mass index (BMI), causes of death, chest X-ray and bronchoscopy findings, results of sputum culture, lung ischemic time, and a reason for not using a donor. In total, 1,481 patients were identified. We excluded 84 donors who were aged < 18 years and 93 donors who did not have records of PF ratio results. The remaining 1,304 donors were stratified into 4 groups by donor acceptability criteria (8). The ideal donor group was defined as donors with the following: age from 20 to 45 years, PF ratio > 350 mmHg, no smoking history, clear chest radiograph, absence of organisms in sputum cultures, and clear bronchoscopy findings. The standard donor group was defined as follows: 45 < age < 55 years, 300 < PF ratio ≤ 350 mmHg, smoking history < 20 pack-years, clear chest radiograph, absence of organisms in sputum, and no purulent secretions on bronchoscopy. The marginal donor criteria was defined as follows: 55 ≤ age ≤ 65 years, 200 ≤ PF ratio ≤ 300

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mmHg, smoking history ≥ 20 pack-years, consolidation or collapse in the chest radiograph, organisms in sputum cultures, and purulent secretion or inflammation on bronchoscopy. A donor was defined as unusable if any of the following was found: age > 65 years, PF ratio < 200 mmHg, current smoking status, dense consolidation or persistent collapse in the chest radiograph, pan-resistant organisms or mycobacteria in sputum cultures, and visualized tumor in bronchoscopy findings.

Statistical analysis

Data are expressed as mean standard deviation of the mean or number (%), unless otherwise specified. The student's t-test was used to test continuous variables with normal distributions, and the Mann-Whitney U test was used for non-normal continuous variables. Categoric variables were analyzed using the χ^2 test or Fisher's exact test. Analysis of variance (ANOVA) was used for multi-group comparisons along with post hoc pairwise comparisons. All of the statistical analyses were performed using the R software, version 3.0.1 (R Foundation, Vienna, Austria; http://www.R-project.org). All of the tests were two sided, and *P* values less than 0.05 were considered statistically significant.

Ethics statement

This study was approved by the Institutional Review Board of Pusan National University Yangsan Hospital (approval number: 05-2016-132). The requirement of informed consent from the patients was waived due to the retrospective nature of this study.

RESULTS

During the study period, 1,397 brain-dead donors registered in the KONOS (≥ 18 years). However, the results of PF ratio were missing in 93 patients. A total of 1,304 donors (41 ideal donors, 128 standard donors, 468 marginal donors, and 667 unusable donors) were included in this study (Fig. 1; Table 1). Donors consisted of 888 males (68.1%) and 416 females (31.9%) of age ranging from 18 to 83 years (mean age: 47.9 years). The cause of brain death was: cerebrovascular system/stroke in 686 (52.6%), traumatic head injury in 266 (20.4%), hypoxic brain damage in 343 (26.3%), central nervous system tumor in 8 (0.6%), and other miscellaneous causes in 1 (0.1%). The most common mechanism of brain injury was intracerebral hemorrhage/stroke in 955 (73.2%); hanging in 213 (16.3%), cardiovascular disease in 98 (7.5%), drowning in 9 (0.7%), seizure in 4 (0.3%), drug intoxication in 6 (0.5%), and other miscellaneous causes in 19 (1.5%). The characteristics of donors according to the acceptability criteria are shown in Table 1.

Of those, 295 brain-dead donors (22.6%) were consented to lung donation. Among these consented lung donors, 168 (12.9%) were finally transplanted to allocated recipients (ideal 19, standard 47, marginal 70, and unusable 32; Fig. 2A). Otherwise, 127 (9.7%) lungs of consented donors were disused due to no final recipient (n = 105), medical ineligibility (n = 20), and unknown

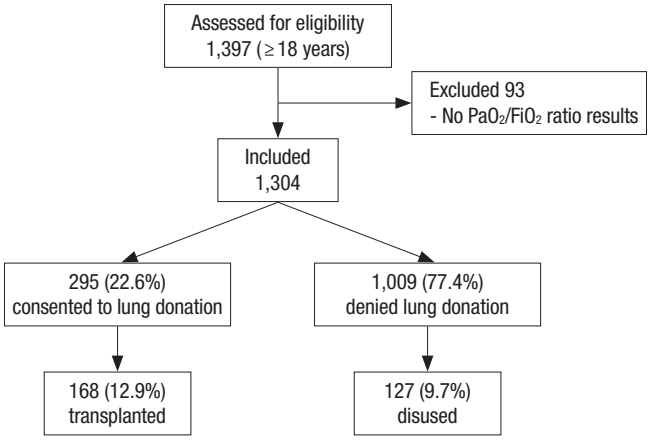

Fig. 1. Flowchart of donor lung utilization. During the study period, 1,397 brain-dead donors registered in the KONOS (≥ 18 years). A total of 1,304 donors were included except for 93 who had no PF ratio results. Of those, 295 brain-dead donors (22.6%) were consented to lung donation. Among these consented lung donors, 168 (12.9%) were finally transplanted to allocated recipients.
KONOS = Korea Network for Organ Sharing, PaO_2 = partial pressure of oxygen in arterial blood, FIO_2 = fraction of inspired oxygen, PF ratio = PaO_2/FIO_2 ratio.

Table 1. Comparison of the potential donors according to the acceptability criteria

Variables	Ideal (n = 41)	Standard (n = 128)	Marginal (n = 468)	Unusable (n = 667)
Age, yr	34.4 ± 7.6	42.0 ± 10.2	47.4 ± 11.6	50.3 ± 14.7
Male	17 (41.5)	86 (67.2)	326 (69.7)	459 (68.8)
Height, m	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1	1.7 ± 0.1
Body weight, kg	63.9 ± 13.5	63.0 ± 11.2	65.8 ± 11.1	67.1 ± 12.6
PF ratio	542.6 ± 390.2	425.6 ± 111.9	374.9 ± 512.7	217.0 ± 130.6
PO_2, mmHg	349.2 ± 214.8	285.3 ± 159.9	208.7 ± 153.7	140.2 ± 95.6
PCO_2, mmHg	36.1 ± 8.6	35.9 ± 8.2	36.2 ± 7.1	41.4 ± 25.8
Pack-years	0	5.6 ± 7.0	9.6 ± 13.5	7.4 ± 12.0
X-ray abnormalities	0	0	165 (35.3)	348 (52.2)
Purulent secretions on bronchoscopy	0	0	119 (25.4)	282 (42.3)

Data are presented as number (%) or mean ± standard deviation.
PO_2 = partial pressure of oxygen, PCO_2 = partial pressure of carbon dioxide, PaO_2 = partial pressure of oxygen in arterial blood, FIO_2 = fraction of inspired oxygen, PF ratio = PaO_2/FIO_2 ratio.

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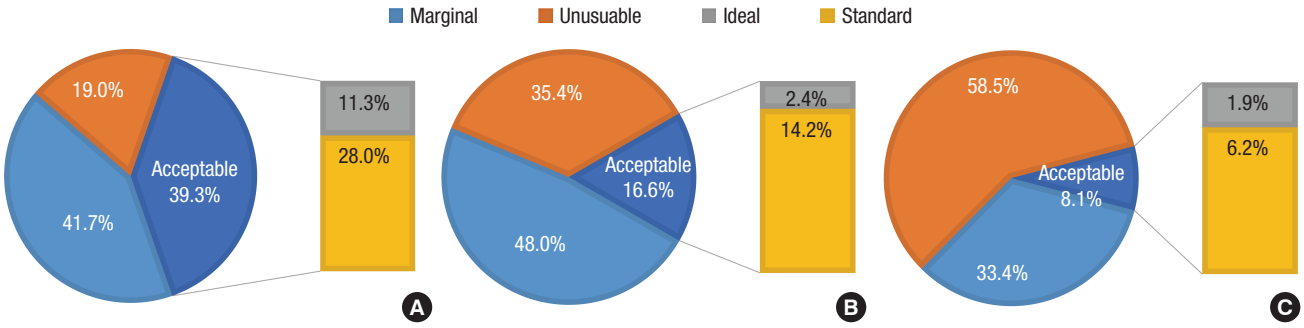

Fig. 2. Classification of utilized lung donors, disused lung donors and lungs that were refused to be donated according to the donor acceptability criteria. (**A**) Utilized donor lungs. (**B**) Disused donor lungs. (**C**) Denied lung donation. The percent of donors with acceptable condition of the transplanted lungs was only 39.3%. Among brain-dead patients who denied to donate lungs (n = 1,009), 82 were potentially acceptable donors, which was equal to half of actually transplanted lung donations.

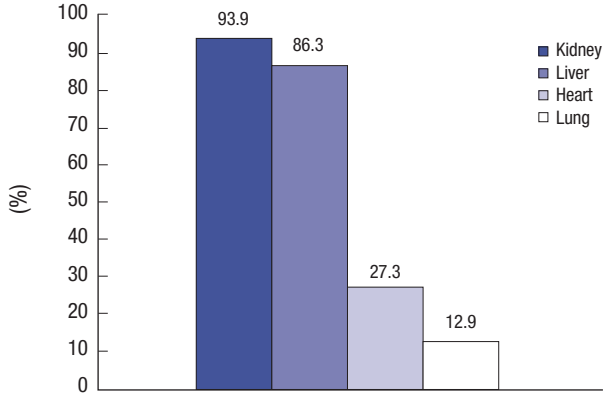

Fig. 3. Utilization rates of donor organs. Overall, 12.9% of organ donors were accepted and retrieved for lung transplant. Retrieval rate was very low compared with the kidney (93.9%), liver (86.3%), and heart (27.3%) use.

Table 2. Comparison of transplanted vs. non-transplanted donor lungs

Variables	Transplanted (n = 168)	Non-transplanted (n = 1,136)	*P*
Age, yr	40.5 ± 11.6	49.0 ± 13.4	< 0.001
BMI, kg/m^2	22.6 ± 3.5	23.7 ± 3.6	< 0.001
Male	102 (60.7)	786 (69.2)	0.028
PO_2, mmHg	356.5 ± 167.5	160.3 ± 118.3	< 0.001
PCO_2, mmHg	39.0 ± 34.4	38.8 ± 15.9	0.924
PF ratio	440.8 ± 137.5	284.2 ± 359.5	< 0.001
Pack-years	5.9 ± 9.2	8.0 ± 12.5	0.007
X-ray abnormalities	60 (35.7)	453 (39.9)	0.303
Purulent secretions on bronchoscopy	40 (23.8)	361 (31.8)	0.037

Data are presented as number (%) or mean ± standard deviation.
BMI = body mass index, PO_2 = partial pressure of oxygen, PCO_2 = partial pressure of carbon dioxide, PaO_2 = partial pressure of oxygen in arterial blood, FIO_2 = fraction of inspired oxygen, PF ratio = PaO_2/FIO_2 ratio.

reasons (n = 2). Disused donor lungs consisted of 3 ideal, 18 standard, 61 marginal, and 45 unusable lungs according to the acceptability criteria (Fig. 2B).

Among brain-dead patients who denied to donate lungs (n = 1,009), 82 were potentially acceptable donors (ideal 19, standard 63), 337 were marginal donors, and 590 were unusable donors (Fig. 2C). The reasons of refusal in patients who were potentially acceptable donors were withdrawn consent (n = 14) and unknown (n = 68).

Overall, 12.9% of organ donors were accepted and retrieved for lung transplant. Retrieval rate was very low compared with kidney (93.9%), liver (86.3%), and heart (27.3%) use (Fig. 3). The mean age of donors of transplanted lungs was 40.5 years (range: 18 to 63 years) compared with 49.0 years for other organs (P < 0.001, Table 2). The characteristics of utilized donor lungs were: mean PaO_2, 356.5 mmHg; mean smoking history, 5.9 pack-years; and mean BMI, 22.6 kg/m^2. It consisted of 19 ideal, 47 standard, 70 marginal, and 32 unusable donors according to the acceptability criteria (Fig. 2A). The percent of donors with acceptable condition of the transplanted lungs was only 39.3% (n = 66). The causes included marginal donor criteria with abnormal X-ray (n = 31), smoking history (n = 11), abnormal sputum (n = 10), low PF ratio (n = 10), and aging (n = 8). Additionally, the causes included unusable donor criteria with abnormal X-ray (n = 28) and low PF ratio (n = 4).

Donor composition and conditions were compared between patients who consented to lung donation and patients who did not consent to lung donation (Table 3). There were significant differences of acceptable donor rate, age, BMI, PF ratio, and amount of smoking exposure between the three groups (transplanted vs. disused vs. denied).

Retrieval rates were compared according to the location of donors. The location was divided into three regions (region 1: Seoul, Incheon, Gyeonggi, Gangwon, Jeju; region 2: Daejeon, Gwangju, Chungbuk, Chungnam, Jeonbuk, Jeonnam; and region 3: Daegu, Gyeongbuk, Busan, Ulsan, Gyeongnam). The retrieval rate was highest in region 1 among the 3 regions (region 1: 16.1%, region 2: 12.7%, region 3: 5.1%; P < 0.001). The rate of acceptable donor including ideal and standard criteria was highest in the region 2 (region 1: 11.1%, region 2: 20.8%, region 3: 12.3%; P = 0.008).

Table 3. Comparison of consented vs. non-consented donor lungs

Variables	Consented to lung donation (n = 295)		Denied lung donation (n = 1,009)	*P*
	Transplanted (n = 168)	Disused (n = 127)		
Ideal	19 (11.3)	3 (2.4)	19 (1.9)	< 0.001
Standard	47 (28.0)	18 (14.2)	63 (6.2)	< 0.001
Marginal	70 (41.7)	61 (48.0)	337 (33.4)	< 0.001
Unusable	32 (19.0)	45 (35.4)	590 (58.5)	< 0.001
Acceptable	66 (39.3)	21 (16.5)	82 (8.1)	< 0.001
Age, yr	40.5 ± 11.6	42.6 ± 12.2	49.8 ± 13.4	< 0.001
BMI, kg/m^2	22.6 ± 3.5	23.0 ± 3.0	23.8 ± 3.6	0.001
Male	102 (60.7)	93 (73.2)	693 (68.7)	0.052
PO_2, mmHg	356.5 ± 167.5	273.1 ± 218.2	146.1 ± 89.4	< 0.001
PCO_2, mmHg	39.0 ± 34.4	40.9 ± 24.5	38.6 ± 14.5	0.453
PF ratio	440.8 ± 137.5	364.8 ± 196.0	274.0 ± 373.9	< 0.001
Pack-years	5.9 ± 9.2	9.9 ± 12.2	7.8 ± 12.6	0.019
X-ray abnormalities	60 (35.7)	55 (43.3)	398 (39.4)	0.413
Purulent secretions on bronchoscopy	40 (23.8)	38 (29.9)	323 (32.0)	0.100

Data are presented as number (%) or mean ± standard deviation.
BMI = body mass index, PO_2 = partial pressure of oxygen, PCO_2 = partial pressure of carbon dioxide, PaO_2 = partial pressure of oxygen in arterial blood, FIO_2 = fraction of inspired oxygen, PF ratio = PaO_2/FIO_2 ratio.

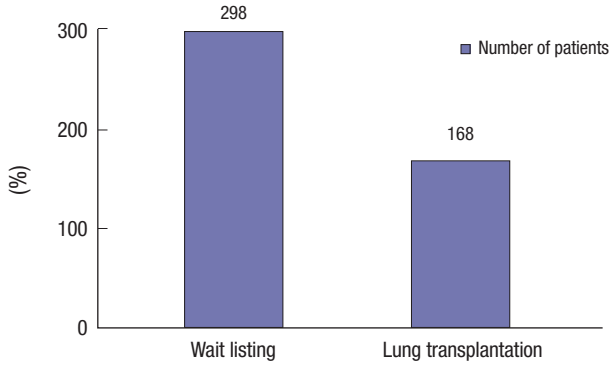

Fig. 4. Lung transplantation and wait-listing rates during the study duration. During the study period, there were 298 patients on the waiting list for lung transplantation, only 56% (n = 168) received lung transplants.

DISCUSSION

In Korea, the lack of donor lungs still remains a major limitation with increasing number of patients awaiting lung transplantation (1). In this study, only 12.9% of donor lungs were used, which was much lower than in other countries (3,9-12). During the study period, there were 298 patients on the waiting list for lung transplantation; only 56% (n = 168, Fig. 4) received the lung transplants. To lessen this discrepancy, the understanding of current status of lung donation in Korea is firstly required. This study showed that the majority of brain-dead donors (74%) were not evaluated for lung donation. Among these, 82 were potentially acceptable donors, which was equal to half of actually transplanted lung donations. Additionally, over half (60.7%) of transplanted lungs were categorized as coming from unacceptable donors. Therefore, current inefficient donor utilization requires to be further analyzed and corrected.

As shown in this study, the retrieval rate of lungs is generally lower than those of other organs. It is associated with the occurrence of major pulmonary complications such as acute respiratory distress syndrome, ventilator associated pneumonia, and neurogenic pulmonary edema after brain injury (13). Although the pathophysiology of brain death induced lung injury remain incompletely understood, excessive release of catecholamines, and systemic inflammatory responses play an integral role in the development of pulmonary dysfunction after brain injuries (14). Catecholamine causes pulmonary edema due to increased pulmonary vascular hydrostatic pressure and increased lung capillary permeability. A systemic inflammatory reaction as a result of the primary brain injury induces an alteration in blood-brain barrier permeability, migration of neutrophils and activated macrophages in alveolar spaces, and ultrastructural damage of type II pneumocytes. This preclinical injury makes the lungs more susceptible to the mechanical stress such as mechanical ventilator or transfusion.

In this study, a substantial proportion of marginal or unusable donors was used. One main cause is that there are many potential lung donors who did not consent to lung donation. Although overall donation rates have increased in recent years, Korea still has relatively low rates of lung donation compared with other countries (1). A decrease in the available donor pool results in the use of unusable or marginal donors. By the KONOS data, the rate of lung transplantation of status 0 was about 50% for the last 3 years (1). There are several potential reasons to explain this observation. First, the timing of registration or referral for transplantation was late. It is clear that late referral or enrollment has detrimental effects on post-transplant outcomes as these are affected by pre-transplant disease severity. Second, the waiting time has become longer after registration due to shortage of donors. Long waiting time may adversely affect the recipient's condition due to disease aggravation. Addi-

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tionally, worsening recipient's status inevitably leads to transplantation of unusable or marginal donors. For these reasons, shortage of donors may adversely affect the final outcome after transplantation.

To solve these problems, firstly, all initiatives to increase lung donation rates should be encouraged, such as public education, campaigns, and professional training programs. In this analysis, a significant number of potentially acceptable donors was not used due to obscure reasons (n = 60). Currently, the majority of organs come from patients who are certified as brain-dead and whose legal representatives agree to organ donation. All clinicians have to encourage lung donation to legal representatives of potential multi-organ donors.

Additionally, systematic donor management strategies to improve the condition of marginal donors are required in Korea. In this study, approximately 60% used donor lungs were categorized into marginal or unusable donor groups. Many donor lungs have become unsuitable for transplantation at the time of offer due to catecholamine and inflammatory responses causing detrimental damage to the donor lungs (14). During the period between confirmation of brain death and organ retrieval, attention to detail and optimization may improve organ function, thereby increasing the utilization rate (15-19). Early donor management can reduce post brain stem death hormonal and inflammatory changes and therefore improve donor organ function and increase the number of available lungs for transplantation. The general principles of intensive care medicine should be applied to the management of the organ donor, and this active donor management can improve the retrieval rate (9,17). Particularly, optimal medical management of donors with a lung protective ventilation strategy has been demonstrated to be effective in increasing eligibility and availability of lungs for transplantation (20). Clear protocol providing general and organ specific goals of therapy along with advice on how to achieve them should be required for all organ procurement organization service centers. Furthermore, cooperation of specialist teams dedicated to donor management provided by transplant centers at government national level is required.

In conclusion, many potential donor lungs, which are currently excluded, may be successfully used in lung transplantation in Korea. During management of donors, lung donation prospect should be always taken into account, being aware that satisfactory results can be achieved even with marginal donors (21,22). All clinicians involved in the hard field of transplantation should carefully manage lungs. One of the many efforts to improve lung transplantation prognosis and to reduce the mortality on current waiting lists is introduction of the efficient donor utilization system. To allow an appropriate maximal use of this insufficient resource, a clear and organized donor management protocol and a liberal approach on extended donor criteria are required. Available lung donors must be actively selected and managed judiciously to maximize utilization of this precious resource. We believe that many patients will benefit from these different approaches; the introduction of an organized donor management strategy along with new approaches of donation will increase lung transplantation activity. Further studies are required to identify the most optimal donor management system on the basis of a national registry for increasing successful lung transplantation.

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DISCLOSURE

The authors have no potential conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Conceptualization: Yeo HJ, Cho WH. Data curation: Yeo HJ, Yoon SH, Lee SE. Investigation: Yeo HJ, Cho WH, Kim DH. Writing - original draft: Yeo HJ, Cho WH. Writing - review & editing: Jeon D, Kim YS, Cho WH.

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