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# Donor selection for lung transplant in Turkey: Is it necessary to wait for an ideal donor?

*Türkiye´de akciğer nakli için donör seçimi: İdeal bir donör beklemek gerekir mi?*

**Mustafa Vayvada, Ahmet Erdal Taşçı**

Department of Thoracic Surgery, Kartal Koşuyolu High Specialization Training and Research Hospital, Istanbul, Türkiye

## ABSTRACT

***Background:*** The aim of this study was to evaluate the donor criteria used in lung transplantation in our clinic.

***Methods:*** A total of 55 cadaveric donors who were accepted for lung transplantation in our clinic between December 2016 and January 2019 were retrospectively analyzed according to ideal donor criteria. The donors were divided into two groups as ideal and non-ideal ones according to their age, partial pressure of oxygen in arterial blood, history of smoking, and ventilation day. Donor data, recipient characteristics and survival outcomes were evaluated.

***Results:*** Of 55 donors accepted for lung transplantation, 24 (43.7%) were ideal and 31 (56.3%) were non-ideal donors. The 90-day mortality and one-year survival rates were not significantly different between the two groups. The 90-day mortality was 25% in the ideal group and 22.6% in the non-ideal group (p=0.834). The one-year survival rates after lung transplantation were 64.5% versus 70.6% in the ideal and non-ideal groups, respectively (p=0.444).

***Conclusion:*** The whole clinical picture should be evaluated before accepting or rejecting donors for lung transplantation. The use of lung donors that do not meet the ideal criteria does not impair short- and mid-term results, compared to ideal lung donors. Strict implementation of donor criteria may prevent using suitable donors for lung transplantation. Use of non-ideal donors can reduce waiting list mortality.

***Keywords:*** Donor lung, ideal donor, lung transplantation.

## ÖZ

***Amaç:*** Bu çalışmada kliniğimizde akciğer naklinde kullanılan donör kriterleri değerlendirildi.

***Çalışma planı:*** Aralık 2016 - Ocak 2019 tarihleri arasında kliniğimizde akciğer nakli için kabul edilen toplam 55 kadaverik donör ideal donör kriterlerine göre geriye dönük olarak değerlendirildi. Donörler yaşlarına, arteriyel kandaki kısmi oksijen basıncına, sigara öyküsüne ve ventilasyon gününe göre ideal ve ideal olmayanlar olmak üzere iki gruba ayrıldı. Donör verileri, alıcı özellikleri ve sağkalım sonuçları değerlendirildi.

***Bulgular:*** Akciğer nakli için kabul edilen 55 donörün 24'ü (%43.7) ideal ve 31'i (%56.3) ideal olmayan dönörler idi. Doksan günlük mortalite ve bir yıllık sağkalım oranları açısından iki grup arasında anlamlı bir fark yoktu. Doksan günlük mortalite ideal grupta %25 iken, ideal olmayan grupta %22.6 idi (p=0.834). Akciğer naklinden sonraki bir yıllık sağkalım oranı, ideal ve ideal olmayan gruplarda sırasıyla %64.5 ve %70.6 idi (p=0.444).

***Sonuç:*** Akciğer nakli için donörleri kabul etmeden veya reddetmeden önce tüm klinik tablo değerlendirilmelidir. İdeal kriterleri karşılamayan akciğer donörlerinin kullanılması, ideal akciğer donörleri ile karşılaştırıldığında, kısa ve orta vadeli sonuçları bozmaz. Donör kriterlerinin sıkı uygulanması, akciğer nakli için uygun donörlerin kullanılmasını engelleyebilir. İdeal olmayan donörlerin kullanılması bekleme listesi mortalitesini azaltabilir.

***Anahtar sözcükler:*** Donör akciğer, ideal donör, akciğer nakli.

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**Correspondence:** Mustafa Vayvada, MD. Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Göğüs Cerrahisi, 34865 Kartal, İstanbul, Türkiye.
Tel: +90 216 - 500 15 00 e-mail: mustafavayvada@gmail.com

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Lung transplantation (LTx) has become a treatment modality in advanced lung diseases. Short and long-term outcomes have improved with the development of surgical techniques, postoperative care, and immunosuppressive treatment strategies. The number of lung transplants has increased over the years due to the success rates. However, there is a difference between the number of patients waiting for transplantation and the presence of lung donors. The shortage of suitable donors increases waiting list mortality. Data from a 2017 report in the United States showed that waiting list mortality was 19.7%.[1] Mortality varies according to the diagnosis of diseases and waiting list mortality is up to 44%, particularly in idiopathic pulmonary diagnoses.[2] In particular for poor recipients, ideal lung donor criteria can be ignored, as there may not be enough time to find the ideal donor. Many donors are evaluated according to criteria that have been developed, which are too strict for most centers.[3,4] These criteria include age between 20 and 45 years, partial pressure of oxygen ($PaO_2$) in arterial blood higher than 350 mmHg on fraction of inspired oxygen ($FiO_2$) of 1.0, and positive end-expiratory pressure (PEEP) of 5 $cmH_2O$, ventilation days less than five days, clear chest radiography, clear bronchoscopy, and minimal ischemic time.[5,6]

According to the United Network for Organ Sharing (UNOS) database, 29.3% of donors were accepted for LTx.[7] In Turkey, the rate of donor lung use was 7.5% in 2017 and 7.1% in 2018.[8,9] In the present study, we aimed to evaluate donor lungs accepted by our lung transplant center and investigate the possible ways of increasing the donor use rates.

## PATIENTS AND METHODS

This single-center, retrospective study was conducted at Kartal Koşuyolu High Specialization Training and Research Hospital, Department of Thoracic Surgery between December 2016 and January 2019. A total of 55 cadaveric donors who were accepted for LTx in our transplant program were included. The donors were divided into two groups as ideal (n=24) and non-ideal donors (n=31). We chose four inclusion criteria for donor evaluation for the ideal group: age between 20 and 45 years, $PaO_2$ in arterial blood higher than 350 mmHg ($FiO_2$ of 1.0 and PEEP of 5 $cmH_2O$), history of smoking less than 20 pack-year, and less than five ventilation days. These four criteria were chosen on the basis of objectivity. The criteria excluded from our study were bronchoscopy findings and chest X-ray interpretation, as exclusion criteria could be significantly influenced by individual assessment. Patients with purulent bronchoscopy and infiltration findings on chest X-ray were not considered as suitable donors. A written informed consent was obtained from each participant. The study protocol was approved by the Kartal Koşuyolu High Specialization Training and Research Hospital Ethics Committee (No: 2021/61492). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Donor age, sex, cause of death, history of smoking, $PaO_2/FiO_2$, duration of mechanical ventilation, pulmonary graft dysfunction (PGD) within 72 h after transplantation, 30-day and one-year mortality were analyzed. Minimum follow-up was one year.

### Donor evaluation and retrieval technique

When offered a potential donor, the clinician should have the patient's chart available and should be evaluated the following information: patient's name, age, date of birth, sex, height, weight, patient's admitting diagnosis, ventilator status, brain death testing, current vital signs, laboratory values, medications used, and past medical history. A flow chart of the donor evaluation is given in Figure 1.

In this study, all bronchial structures were examined in detail using bronchoscopy. Secretions and crusts were removed and samples were taken for microbiology. The presence of significant purulent discharge after aspiration was considered in favor of active infection and was not appropriate for acceptance.

A standard median sternotomy was performed. We palpated the donor lungs after opening the pleural cavity on both sides by incising the mediastinal pleura. The presence of mass or nodules was checked. A collapse test was performed. If the lungs collapsed instantly or symmetrically after disconnection from mechanical ventilator, it was accepted as donor. Following mediastinal dissection, an intravenous 250 to 300 U/kg bolus of heparin was administered. A large pulmoplegia cannula was inserted just below the main pulmonary artery bifurcation. Prostaglandin (500 µg) was injected. The vena cava superior was ligated, the vena cava inferior was cut, the left atrium was cut to allow it to drain, and the aorta was clamped. Simultaneously, perfusion fluids were flushed through both lungs using gravity (40 to 60 $cmH_2O$) and no pressure was applied for rapid flow. Ventilation was continued during flushing. In our clinic, we use cold Perfadex® preservation fluid (XVIVO AB, Gothenburg, Sweden) as a perfusate. This results in a total flush volume of 40 to 70 mL/kg. Perfadex® was supplemented with

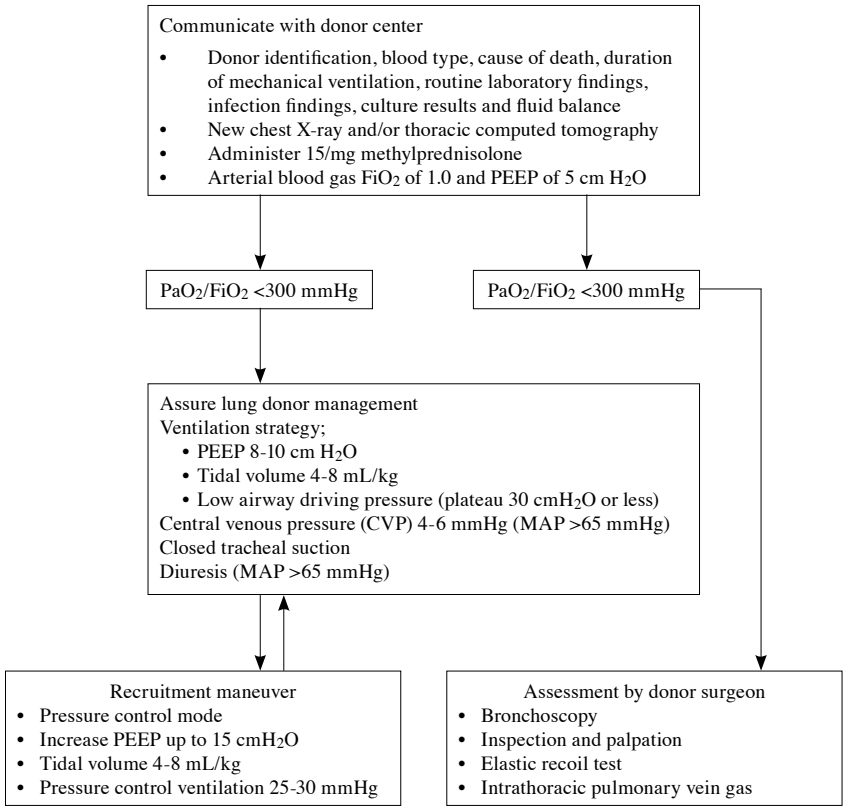


**Figure 1.** Flow chart of the donor evaluation.

PEEP: Positive end-expiratory pressure; $FiO_2$: Fraction of inspired oxygen; $PaO_2$: Partial pressure of oxygen; MAP: Mean arterial pressure.

tromethamine 3.3 mL/L, $Ca^{++}$ chloride 0.6 mL/L, and epoprostenol sodium 2.5 mL/L. Retrograde flushing was performed with 1 L of Perfadex®. After pneumonectomy and a back table inspection, the lungs were preserved in an organ bag filled with 3 L of Perfadex®.

### Statistical analysis

Statistical analysis was performed using the IBM SPSS for Windows version 22.0 software (IBM Corp., Armonk, NY, USA). Distribution of quantitative data was analyzed using the Kolmogorov-Smirnov test. Normally distributed data were presented in mean ± standard deviation, while non-normally distributed variables were presented in median (min-max). Qualitative data were presented in number and frequency. To compare characteristics between donor lungs with ideal versus non-ideal, the Student t-test and Mann-Whitney U test were used, when appropriate. Qualitative data were compared using the Fisher's exact test and chi-square test. The Kaplan-Maier method was used for survival analysis, while differences between recipients who received donor lungs that ideal and non-ideal were analyzed using the log-rank test. A $p$ value of $<0.05$ was considered statistically significant.

## RESULTS

Throughout the study period, 55 LTx procedures were performed of which 24 (43.7%) were ideal and 31 (56.3%) were non-ideal. Table 1 shows the non-ideal donor distribution. Of the 31 non-ideal donors, 16 had one criterion. Four had ≥20 pack-years smoking, three were aged >45 years, two had an intubation time >5 days, and seven had a $PaO_2/FiO_2$ ratio <350 mm Hg.

The median waiting time was 66 (range, 3 to 396) days in the ideal group and 97 (range, 3 to 427) in the non-ideal group (p=0.114). Single-LTx was performed in three of 55 transplantations, all of which were ideal donors. Indications for transplantation were idiopathic interstitial pneumonia in 26 patients (ideal n=12 *vs*. non-ideal n=14), chronic obstructive pulmonary disease in 10 patients (ideal n=6 *vs*. non-ideal n=4), bronchiectasis in eight patients

**Table 1. Distribution of non-ideal donors**

| | ≥20 pack-year smoking | $PaO_2/FiO_2$ ratio <350 mmHg | Age >45 years | Intubation time >5 days |
|---|---|---|---|---|
| | n | n | n | n |
| ≥20 pack-year smoking | 12 | 6 | 6 | 0 |
| $PaO_2/FiO_2$ ratio <350 mmHg | | 19 | 8 | 3 |
| Age >45 years | | | 14 | 2 |
| Intubation time >5 days | | | | 5 |

$PaO_2$: Partial pressure of oxygen; $FiO_2$: Fraction of inspired oxygen.

**Table 2. Recipient characteristics**

| | Ideal group (n=24) | | | | Non-ideal group (n=31) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | Median | Min-Max | n | % | Median | Min-Max | *p* |
| Age (year) | | | 50 | 19-64 | | | 48 | 22-64 | 0.592 |
| Sex | | | | | | | | | 0.789 |
| Male | 16 | 75 | | | 22 | 70.9 | | | |
| Female | 8 | 25 | | | 9 | 29.1 | | | |
| Waiting time (day) | | | 66 | 3-391 | | | 97 | 5-427 | 0.114 |
| Diagnosis | | | | | | | | | |
| IIP | 12 | | | | 14 | | | | |
| Bronchiectasis | 3 | | | | 5 | | | | |
| CF | 1 | | | | 2 | | | | |
| COPD | 6 | | | | 4 | | | | |
| Adenocarcinoma | 1 | | | | 1 | | | | |
| IPAH | - | | | | 1 | | | | |
| Sarcoidosis | - | | | | 2 | | | | |
| Re-transplantation | 1 | | | | - | | | | |
| Silicosis | - | | | | 2 | | | | |
| Blood group | | | | | | | | | |
| O | 7 | | | | 9 | | | | |
| A | 14 | | | | 18 | | | | |
| B | 2 | | | | 2 | | | | |
| AB | 1 | | | | 1 | | | | |
| BMI ($kg/m^2$) | | | 24.9 | 13-32 | | | 25 | 16-31.7 | 0.622 |
| 6MWT (meter) | | | 172 | 0-398 | | | 105 | 0-440 | 0.402 |
| >180 | 11 | | | | 18 | | | | 0.773 |
| <180 | 13 | | | | 13 | | | | |
| RV dilation | 13 | 54.2 | | | 18 | 58 | | | 0.422 |
| RHC | | | | | | | | | |
| PAPs | | | 51 | 21-95 | | | 42.2 | 21-73 | 0.144 |
| PAPm | | | 33.2 | 15-78 | | | 24.6 | 11-41 | 0.041 |
| PHT (PAPm >25 mmHg) | 17 | 70.8 | | | 15 | 48.3 | | | 0.112 |

IIP: Idiopathic interstitial pneumonias; CF: Cystic fibrosis; COPD: Chronic obstructive pulmonary disease; IPAH: Idiopathic pulmonary arterial hypertension; BMI: Body mass index; 6MWT: Six minute walk test; RV: Right ventricle; RHC: Right heart catheterization; PAPs: Systolic pulmonary arterial pressure, PAPm: Mean pulmonary arterial pressure, PHT: Pulmonary arterial hypertension.

**Table 3. Donor variables**

| | Ideal group (n=24) | | | | Non-ideal group (n=31) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | n | % | Median | Min-Max | n | % | Median | Min-Max | *p* |
| Age (year) | | | 26.5 | 17-45 | | | 42 | 16-55 | <0.001 |
| <16 | | | | | 2 | | | | |
| >45 | | | | | 14 | | | | |
| Sex | | | | | | | | | 0.868 |
| Male | 16 | 75 | | | 20 | 64.5 | | | |
| Female | 8 | 25 | | | 11 | 35.5 | | | |
| Blood group | | | | | | | | | |
| O | 8 | | | | 16 | | | | |
| A | 14 | | | | 13 | | | | |
| B | 3 | | | | 2 | | | | |
| AB | 0 | | | | 0 | | | | |
| Cause of death | | | | | | | | | |
| Head trauma | 12 | | | | 10 | | | | |
| Intracranial hemorrhage | 8 | | | | 18 | | | | |
| Heart unknown cause | 2 | | | | 1 | | | | |
| Alcohol intoxication | 1 | | | | 1 | | | | |
| Suicide (Hanging) | 1 | | | | 1 | | | | |
| $PaO_2$-$FiO_2$ of 1.0 | | | 420 | 352-588 | | | 341 | 220-660 | <0.001 |
| $PaO_2$ <300 mmHg | | | | | 9 | | | | |
| $PaO_2$ <350 mmHg | | | | | 19 | | | | |
| ≥20 pack-year smoking | | | | | 12 | | | | 0.001 |
| Intubation time (day) | | | 3 | 1-5 | | | 3 | 1-9 | 0.586 |
| >5 | | | | | 5 | | | | |
| PGD | 8 | 33.3 | | | 10 | 32.3 | | | 0.939 |
| 90-day mortality | 6 | 25 | | | 7 | 22.6 | | | 0.834 |
| One-year survival (%) | | 64.5 | | | | 70.6 | | | 0.444 |

$PaO_2$: Partial pressure of oxygen; $FiO_2$: Fraction of inspired oxygen; PGD: Primary graft dysfunction.

(ideal n=3 *vs*. non-ideal n=5), cystic fibrosis in three patients (ideal n=1 *vs*. non-ideal n=2), adenocarcinoma in two patients (ideal n=1 *vs*. non-ideal n=1), idiopathic pulmonary arterial hypertension in one patient (ideal n=1), sarcoidosis in two patients (non-ideal n=2), and re-transplantation in one patient (ideal n=1). There was no statistically significant difference between the two groups in terms of age, sex, 6-Minute Walking Test, and waiting time. In the ideal group, the incidence of pulmonary artery hypertension was higher with right heart catheterization (70.8% *vs*. 48.3%, respectively); however, it was not statistically significant. The mean pulmonary artery pressure measured in the right heart catheterization was statistically higher in the ideal group (p=0.041) (Table 2).

Donor characteristics are given in Table 3. In both groups, there was no use of donors with an AB blood group; the O blood group was used in two patients due to the urgency of the patient's condition. The use of O blood group was higher in the non-ideal group. The ABO incompatibility was 2/24 (8.3%) in the ideal group, 8/31 (25.8%) in the non-ideal group. There was no Grade 3 PGD within 72 h in either group.

**Survival**

There were no significant differences in 90-day mortality and one-year survival. The 90-day mortality was 25% in the ideal group and 22.6% in the non-ideal group (p=0.834). Survival at one year after LTx was in 64.5% and 70.6% in the ideal and non-ideal groups (p=0.444) (Figure 2).

Nineteen of donors were under the $PaO_2/FiO_2$ ratio of 350 mmHg. The 90-day mortality was 25% and 20% in ideal and non-ideal group, respectively

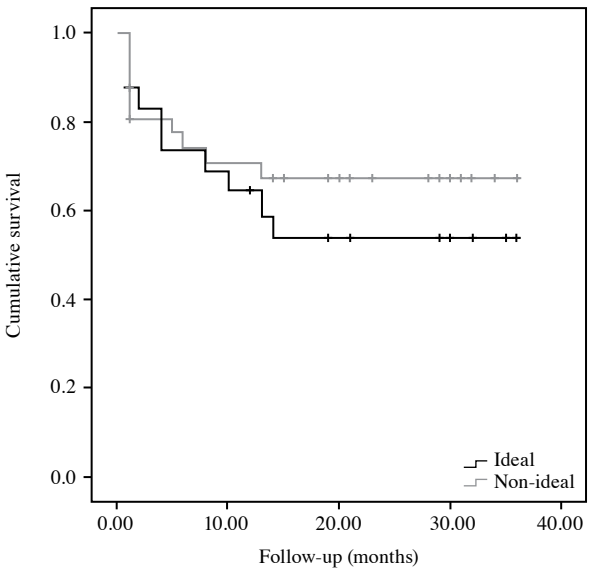


**Figure 2.** Cumulative survival for recipients of ideal versus nonideal donor lungs.

(p=0.749). The one-year survival rate was higher in the non-ideal group, but it was not statistically significant (61.4% *vs*. 79.7%, respectively; p=0.749). Interestingly, the one-year survival was 87.5% with donors whose $PaO_2/FiO_2$ ratio was under 300 mmHg.

There were 12 donors in the heavy smoker group. The 90-day mortality was 16.7% for smokers and 25% for non-smokers (p=0.709). There was no significant difference in one-year survival rates (smokers 75% *vs*. non-smokers 66%, respectively; p=0.33).

In 14 donors, age was over 45 years. The median age was 52 (range, 46 to 55) years. The 90-day mortality was 23.1% in the >45-year age group, and 25% in the <45-year age group. The one-year survival rate was 70.3% *vs*. 62.5%, respectively (p=0.975). There was no significant difference in the 90-day mortality (20% *vs*. 24%, respectively; p=0.999) and one-year survival (60% *vs*. 68.9%, respectively; p=0.999) in donors with intubation duration longer than five days.

## DISCUSSION

Lung transplantation is the most appropriate treatment method for patients with end-stage respiratory failure. The increase in the number of patients waiting for organs in spite of the increased number of transplantations has led to transplant teams using marginal donors. Criteria for donor lung evaluation such as age, ABO compatibility, chest radiography, $PaO_2$ in arterial blood, absence of chest trauma, no evidence of aspiration sepsis, no prior cardiopulmonary surgery, chest X-ray, bronchoscopy, and microbiological culture. The evaluation of these criteria varies according to the experience of the clinics. Singh et al.[7] showed that one donated lung who was accepted even after rejection from more than three clinics had no deleterious effect on survival of recipients; therefore, donor quality should not be judged by a single person or a single team.

According to the results of a large study of UNOS, use of donors aged <18 and ≥65 years had increased rates of one-year graft failure.[10] In donors aged over 65 years, the one- or three- year mortality rates increased; however, there was no significant difference in one-year mortality in donor subgroups aged under 65 years. Furthermore, donors aged over 70 years have not been shown to be associated with poorer outcomes than younger donors and the short intubation time and the absence of a history of smoking are remarkable features.[11] In our study, 14 donors aged over 45 years were used. The one-year survival rate was 64%. This rate was lower than the world literature. Smoking was present in six of 14 donors and, interestingly, the one-year survival rate was 83.3% in these patients. We attributed this difference to the small number of transplantation procedures. A study by Taghevi et al.,[12] evaluated 5,134 non-smoking donors and 766 donors who were heavy smokers. Although the duration of intubation and length of stay in the intensive care unit (ICU) were longer in the heavy smoker group than the other group, the three-year survival was equal in both groups. Although successful results are obtained in heavy smoker donors, caution must be taken in the case of donors aged over 55 years.[13]

The donor $PaO_2/FiO_2$ ratio has been discussed since 1999 and continues to the present day.[14-16] The common opinion is that $PaO_2/FiO_2$ ratio is associated with donor care. Donor criteria should be included, but donors with low blood gas values should be seen at the donor center and should not be rejected without evaluation. In our study, patients with low $PaO_2/FiO_2$ ratios were not statistically significantly different and, interestingly these patients had a better survival rate. If the oxygenation of the donor is low, we definitely communicate with the donor center. We evaluate optimal mechanical ventilation parameters and diuresis. The recruitment maneuver is performed as long as the patient's condition allows. In the event of improvement in oxygenation, we evaluate the donor at the operation site.

Ideally, chest radiography must be normal. There is no study investigating the relationship between infiltration and infection. The assessment varies among

individuals. The presence of atelectasis or infiltration does not preclude further evaluation, since gas exchange and lung condition can be corrected by manipulation of fluid balance, PEEP application, and removal of secretions. Bronchoscopy should be performed to rule out aspiration in the donor or to collect samples from purulent secretions, if present. The presence of significant purulence that continues after aspiration is a finding in favor of active infection and constitutes a contraindication for ingestion. Positive Gram staining in donor endobronchial secretions does not predict the risk of developing pneumonia in the recipient after transplantation.[17]

The duration of donor mechanical ventilation does not affect lung transplant results. If the donor meets the criteria, they should be accepted. Donor lungs should be protected against ventilator-associated lung damage. Pulmonary protective ventilation should be applied. Pulmonary protective ventilation, low tidal volume ventilation (tidal volume 6 to 8 mL/kg per ideal body weight, plateau pressure 30 $cmH_2O$) in patients at risk of developing acute respiratory distress syndrome have been shown to be associated with a significant reduction in the risk of disease development and a reduced risk of lung infection. Low tidal volume can be also used for donor lungs.[18,19] Donor lungs, similar to all lungs, are at risk of developing atelectasis. Optimal use of PEEP (8 to 10 $cmH_2O$) is identified at this point; however, special care should be exercised to avoid excessive pressures and volumes.[19]

Although usable donor rate was 25% according to classic information, there are publications currently that report an acceptance rate of 43%.[20] The acceptance rate of offered donors was 25.7% (26/101) in 2017 and 17.2% (25/148) in 2018 in our clinic. Since the date we started the lung transplant program, it was 21.9% (55/259). However, in Turkey, 554 donors were reported in 2017, and 598 in 2018.[8] We believe that the difference is related to the organ donation system. Each organ is donated separately. Lungs are donated less than other organs, particularly than liver and kidney.

Our study has some limitations. It has a retrospective design and, therefore, some data may have been missed. The short follow-up period and presence of recipients with different diagnoses were the other limitations. Also, a significant relationship between diseases and donors could not be established, probably due to the small sample size. On the other hand, this study is valuable as it is the first report in Turkey. Although the waiting time for transplantation was short, waiting list mortality was high. This was related to the general condition of the patients and the low number of patients on the waiting list. Therefore, a relationship was unable to be identified between non-ideal recipients +/- ideal recipients and ideal +/- non-ideal donors.

In conclusion, implementation of a lung donor treatment protocol increases lung acceptance rates, allowing for more lung transplants without compromising survival. Non-ideal donors should be treated with care, particularly those with a partial pressure of oxygen/fraction of inspired oxygen ratio of <300 mmHg, and the entire clinical picture should be considered while accepting or rejecting donors for lung transplantation.

**Declaration of conflicting interests**

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