

The outcomes of 80 lung transplants in a single center from Saudi Arabia

Saeed Akram,^a Imran Yaqoob Nizami,^a Mohamed Hussein,^{a,b} Waleed Saleh,^{a,b} Mohammed Said Ismail,^c Khaled AlKattan,^b Muhammad Shaheryar Ahmed Rajput^d

From the ^aOrgan Transplant Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; ^bDepartment of Surgery, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia; ^cDepartment of Chest Medicine, Cairo University, Cairo, Egypt; ^dDepartment of Otolaryngology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Correspondence: Dr. Saeed Akram · MBC 46 Department of Medicine, King Faisal Specialist Hospital and Research Centre, PO Box 3354 Riyadh 11211, Saudi Arabia · SaAkram@kfshrc.edu.sa · ORCID: <https://orcid.org/0000-0002-5124-4254>

Citation: Akram S, Nizami IY, Hussein M, Saleh W, Ismail MS, Kattan KM, Rajput MS. The outcomes of 80 lung transplants in a single center from Saudi Arabia. *Ann Saudi Med* 2019; 39 (4): 221-228. DOI: 10.5144/0256-4947.2019.221

Received: November 7, 2018

Accepted: April 13, 2019

Published: August 5, 2019

Copyright: Copyright © 2019, Annals of Saudi Medicine, Saudi Arabia. This is an open access article under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License (CC BY-NC-ND). The details of which can be accessed at <http://creativecommons.org/licenses/by-nc-nd/4.0/>

Funding: None.

BACKGROUND: Lung transplantation has become a standard of care for a select group of patients with advanced lung diseases. Lung transplantation has undergone rapid growth in the last few years in Saudi Arabia.

OBJECTIVE: Describe five years of experience with lung transplantation.

DESIGN: Retrospective, descriptive.

SETTINGS: Major tertiary care hospital.

PATIENTS: All patients who underwent lung transplant surgery between 2010 to 2015.

MAIN OUTCOME MEASURES: Indications for lung transplant demographics, body mass index, blood group, type of transplant surgery, morbidity rate using the Clavien-Dindo classification, rate of early- and late-onset bronchiolitis obliterans syndrome (BOS), bronchiolitis obliterans-free survival, 30- and 90-day mortality rate, and survival (30 days, 90 days, 1-year, 3-years and 5- years) for lung transplant recipients. The duration of mechanical ventilation, colonization by bacteria and need for lung volume reduction surgery for lung donors.

SAMPLE SIZE: 80, 45% women and 55% men.

RESULTS: The most common indication for lung transplant in Saudi Arabia is pulmonary fibrosis (45%), followed by non-cystic fibrosis bronchiectasis (25%) and cystic fibrosis-related bronchiectasis (20%). Only 45% of our lung transplant recipients had a normal BMI (18-28 kg/m²). The most frequent blood group was A (40%), followed by blood group O (32.5%). Most (85%) lung transplants were bilateral while 15% were single lung transplants. Postoperative complications developed in 64 patients, 34 (42.5%) had minor grade 1 complications, while 13 (16.5%) had severe complications leading to death (grade V). Early onset BOS developed in 6 (7.5%) patients while 16 (20%) had late onset BOS. The BOS-free survival rate was 72.5%. The mean duration of mechanical ventilation in lung donors was 9 days and most were infected by bacteria. The majority of recipients required lung volume reduction. The 30-day mortality rate was 12.5% and the 90-day mortality rate was 17.5%. Survival rates at our center were 87.5% at 30 days, 82.5% at 90 days, 81.2% at 1 year, 67.9% at 2 years and 62.1% at 5 years.

CONCLUSIONS: Lung transplantation has become an invaluable approach for the treatment of end-stage respiratory disease. Our 5-year experience has shown exciting promises for lung transplantation in Saudi Arabia.

LIMITATIONS: Retrospective design, single center experience.

CONFLICT OF INTEREST: None.

Hardy and colleagues performed the first human lung transplantation in 1963, in which the recipient survived for 18 days but ultimately died of renal failure.¹ Although this event demonstrated the technical feasibility of lung transplantation surgery, it took 20 years before meaningful survival was achieved.² In 1981, the first successful heart-lung transplantation was performed in a patient with idiopathic pulmonary arterial hypertension.³ This was followed in 1983 by the first successful single lung transplantation for idiopathic pulmonary fibrosis⁴ and in 1986 by the first double lung transplantation for emphysema.⁵ These successes were attributed to improved surgical techniques and the advent of immunosuppression drugs such as cyclosporine. Since then, >50 000 lung transplantation surgeries have been performed.⁶ Lung transplantation is now considered the standard of care for a select group of patients with advanced, medically untreatable lung conditions.

The International Society for Heart and Lung Transplantation (ISHLT) registry reported around 1900 lung transplantation procedures annually between the years 1993 to 2000, although the transplantation activity showed steady growth later with 4122 adult lung transplantations reported in 2015. The median survival for all adult lung transplant recipients is 6.0 years, according to the 2017 ISHLT registry.⁷

The first lung transplantation in Saudi Arabia was performed in 1998. In the last 6 years, the program has witnessed rapid growth. Lungs are recovered from deceased donors after carefully reviewing all donor data offered by Saudi Center for Organ Transplantation. A total of 80 lung transplantation surgeries were performed between 2010 and 2015. Our program presents unique differences from the characteristics reported in the ISHLT registry,^{8,9} and these differences have brought unique challenges. The present study surveyed these challenges and the steps taken by our lung transplantation team to overcome them. The goal of this study was to present the history of lung transplantation in Saudi Arabia and to familiarize the reader with the different aspects of lung transplantation. We reviewed the different outcomes of lung transplantation, including indications, demographics, body mass index (BMI), type of transplantation surgery, complications, and survival.

PATIENTS AND METHODS

Using our institutional electronic database, we performed a retrospective analysis and identified patients who underwent lung transplantation surgery between January 2010 and December 2015. We included all

80 lung transplant recipients operated on during the study period. Ethical approval was obtained from our institutional ethical board.

The data were collected by a trained research assistant and counterchecked by a lung transplantation consultant. All patient charts and hospital electronic database records were reviewed. The outcome variables, including indications for lung transplantation surgery, demographics, body mass index (BMI), blood group, and type of transplantation surgery, were recorded. We used the Clavien-Dindo classification for grading the postoperative morbidities. Grades I and II consisted of minor complications, whereas grades III and IV consisted of complications that required surgical, endoscopic, or radiologic intervention. Grade V included severe complications that resulted in death (**Table 1**).¹⁰

In all recipients, we used standard immunosuppression protocols with steroids, tacrolimus, and mycophenolate mofetil as triple maintenance immunosuppressive medicines after lung transplantation. The prophylactic management included 3 months of antifungal therapy (itraconazole and amphotericin B nebulization), 1 year of antiviral therapy (valganciclovir), and lifelong antibacterial medication (sulfamethoxazole-trimethoprim) after lung transplantation.

All patients underwent surveillance bronchoscopy at 2 weeks, 4 weeks, 3 months, 6 months, and 1 year after lung transplantation, as part of our transplantation protocol to rule out silent lung rejection. Bronchoscopies were also performed whenever clinically indicated to rule out infections or lung rejection.

Bronchiolitis obliterans syndrome (BOS) was defined as persistent airflow limitation without an alternative cause, consistent with accepted international definitions.¹¹ Airflow limitation was defined as a decrease in the forced expiratory volume in 1 second (FEV1) and the FEV1/forced vital capacity (FVC) ratio, as determined using a pulmonary function test. The baseline value was ascertained after lung transplantation, by taking the average of the two highest values of FEV1 obtained at least 3 weeks apart and without preceding bronchodilator inhalation. A 20% change in FEV1 from the baseline value was defined as significant. Pulmonary function tests are routinely done in all post-lung transplantation patients at each clinic visit. BOS was divided into early onset (<2 years) and late onset (>2 years). The BOS-free survival and survival rates (30 days, 90 days, 1 month, 3 months, and 5 years) for lung transplant recipients were calculated. The duration of mechanical ventilation, incidence of bacterial infection, and need for lung volume reduction surgery for lung donors were noted. The statistical analysis was carried

out using IBM SPSS version 22 (IBM Corp., Armonk, NY, USA). Frequency and percentages were calculated for categorical variables, and means were calculated for continuous variables.

RESULTS

A total of 80 lung transplants were performed from January 2010 to December 2015. The most common indication was pulmonary fibrosis (45%), followed by noncystic fibrosis bronchiectasis (25%) and cystic fibrosis-related bronchiectasis (20%). The indications in other patients included sarcoidosis (5%) and, in small numbers of patients, chronic obstructive airways disease, pulmonary capillary hemangiomas, lymphangioleiomyomatosis, and BOS (Figure 1).

Of the 80 lung transplant recipients, 45% were women and 55% were men. Most lung transplant recipients were young and only 17% were older than 50 years (range 12–65 years). The most common age group was 18–29 years (34%), followed by 40–49 years (18%, Figure 2). Only 45% of our lung transplant recipients had a normal BMI of 18–28 kg/m², whereas 37% were underweight (BMI <18 kg/m²) and 18% were overweight (BMI >28 kg/m²).

The most frequent blood group of the lung transplant recipients was A (40%), followed by O (32.5%), B (23.75%), and AB (3.75%). Most (85%) of the lung transplantations were bilateral procedures, whereas 15% were single lung transplantations. Of the 80 lung recipients, 64 had postoperative complications based on the Clavien-Dindo classification. Most of the patients (42.5%) had grade I complications, whereas 6.3% had grade II, 10% had grade III, 5% had grade IV, and 16.3% had grade V complications. Among the 80 transplant recipients, 22 (27.5%) developed BOS, of whom 6 patients (7.5%) had early onset BOS and 16 patients (20%) had late onset BOS. The BOS-free survival among our lung transplant recipients was 72.5% (58 patients). The mortality rate was 12.5% (10 patients) at 30 days and 17.5% (14 patients) at 90 days after lung transplantation. Survival rates at our center were 87.5% at 30 days, 82.5% at 90 days, 81.2% at 1 year, 67.9% at 2 years and 62.1% at 5 years. (Figure 3).

The mean duration of mechanical ventilation in our lung donors was 9 days. Most of the lung donors (70%) were infected by bacteria, including multidrug-resistant bacteria such as *Acinetobacter* (26%), *Klebsiella* (20%), methicillin-sensitive *Staphylococcus aureus* (15%), and *Pseudomonas* (12%) (Figure 4). The organisms were identified using surgical cultures (bronchoalveolar lavage fluid) obtained using bronchoscopy during the transplantation.

Table 1. The Clavien-Dindo classification of surgical complications.

Grade	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimes are: drugs as antiemetic, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade III ^a	Intervention not under general anesthesia
Grade III ^b	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IV ^a	Single organ dysfunction (including dialysis)
Grade IV ^b	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d"	If the patient suffers from a complication at the time of the discharge (see examples in Table 2), the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow up to fully evacuate complication.

*Brain hemorrhage, ischemic stroke, subarachnoid bleeding, but excluding transient ischemic attacks

CNS: central nervous system, IC: intermediate care, ICU: intensive care unit

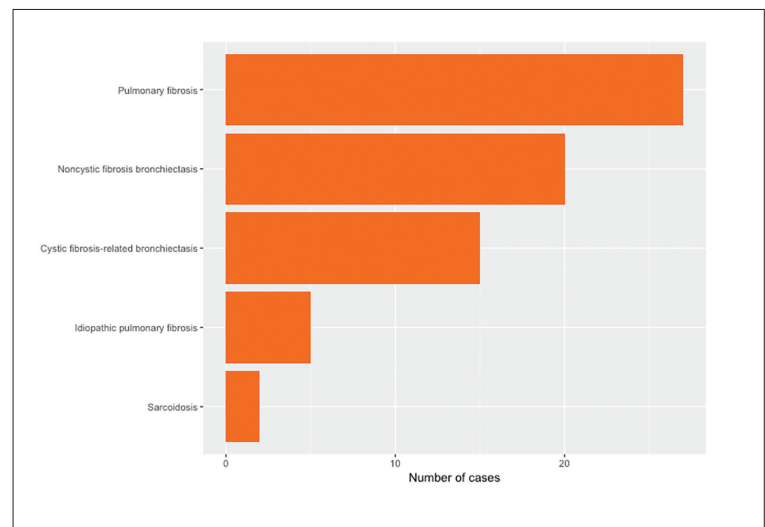


Figure 1. Indications for lung transplant in Saudi Arabia 2010-2015. One each: Bronchiolitis obliterans, chronic obstructive pulmonary disease, fibrocystic lung disease, interstitial lung disease, Interstitial lung disease + pulmonary hypertension, lymphangioleiomyomatosis, lung fibrosis, pulmonary Langerhans cell histiocytosis, pulmonary vascular disease, sarcoidosis + pulmonary hypertension.

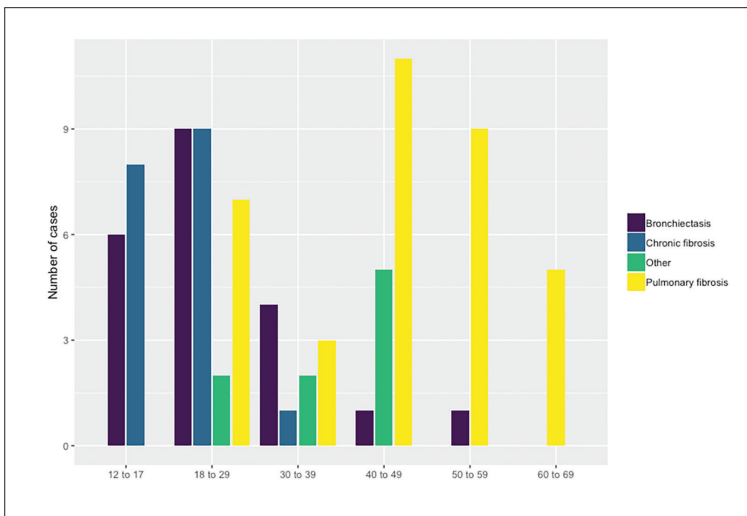


Figure 2. Age distribution of lung transplant recipients and major disease indications in Saudi Arabia, 2010-2015.

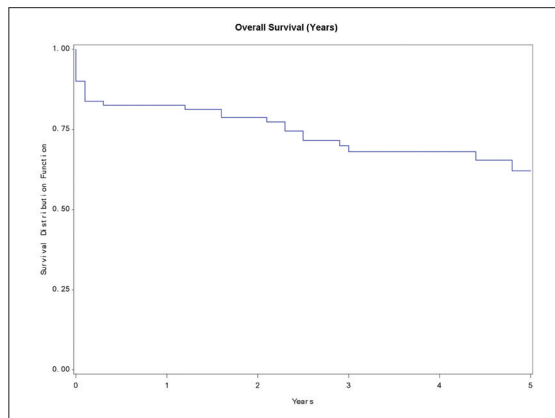


Figure 3. Kaplan-Meier survival curve for lung transplant patients, 2010-2015.

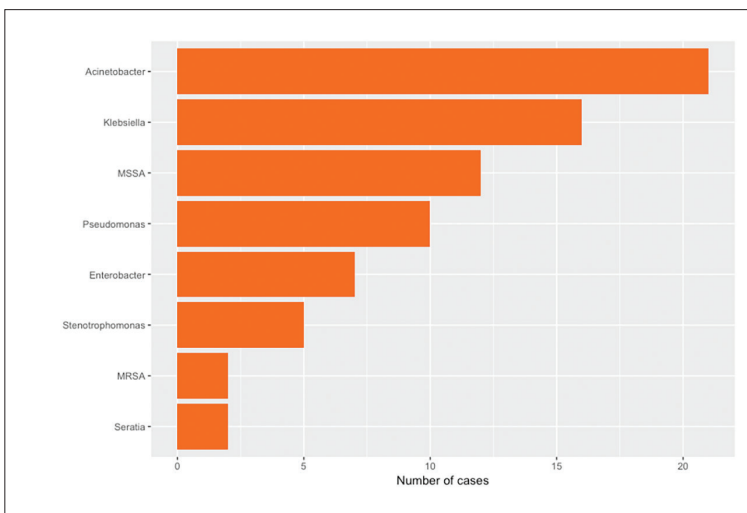


Figure 4. Bacteria identified in lung transplant donors, 2010-2015. MSSA: Methicillin-sensitive *Staphylococcus aureus*, MRSA: Methicillin-resistant *Staphylococcus aureus*. One each: *Burkholderia cepacia*, *Enterococcus*, *Salmonella*, *Citrobacter*, *Mycobacterium tuberculosis*.

Lung volume reduction surgery was required in 70% of the recipients. In two cases of extreme donor-recipient size mismatch, bilateral lower lobar transplantations were performed. In 3 other patients, unilateral upper lobe transplantation with contralateral volume reduction was performed.

DISCUSSION

Our lung transplantation program presents some unique differences from the data published in the ISHLT registry and from the published reports in the worldwide medical literature. We highlight these differences in our report. The most common worldwide indications for lung transplantation include chronic obstructive pulmonary disease (COPD) (>40%), pulmonary fibrosis (25%), and cystic fibrosis (16%).^{8,9} However, for lung transplantations performed in Saudi Arabia, pulmonary fibrosis is the most common indication (45%), followed by noncystic fibrosis bronchiectasis (25%) and cystic fibrosis-related bronchiectasis (20%). These pulmonary fibrosis cases were idiopathic with negative results in tests for connective tissue and genetic disorders, and the pathology of the explanted lung showed advance fibrosis with honeycombing and, in some cases, fibrotic nonspecific interstitial pneumonitis and hypersensitivity pneumonitis. Surprisingly, COPD is a rare indication for lung transplantation in Saudi Arabia as compared with other countries, as mentioned above. Smoking is the main risk factor for the development and progression of COPD. Overall, the prevalence of smoking in the adult Saudi population is 21.6% (35% of Saudi men and 4.7% of Saudi women).¹² The prevalence of COPD among the general population in Saudi Arabia is 4.2%, comparable with the reported prevalence rate of 3.6% in the entire Middle East.¹³ Interestingly, in patients in Saudi Arabia, COPD does not progress to end-stage lung disease requiring lung transplantation, which is contrary to worldwide reports in which COPD is the most common cause for lung transplantation. More research is needed to investigate whether some genetic or environmental factors are responsible for such a marked difference.

Another unique difference in the lung transplant population at our center is reflected in the patients' age. While most (>50%) of the patients who received a lung transplant in other countries were older than 50 years,⁹ lung transplant recipients in Saudi Arabia are much younger, with only 17% being older than 50 years. This is because of the nature of end-stage lung disease in Saudi Arabia. Most of our patients were young and had pulmonary fibrosis and bronchiectasis (either secondary to cystic fibrosis or idiopathic).

Nutritional status and BMI represent other challeng-

es. The nutritional status of lung transplant candidates can adversely affect their posttransplantation survival. Multiple studies have identified pretransplantation obesity as a significant risk factor for mortality after transplantation, independent of other risk factors.^{14,15} Low BMI has not been considered a risk factor for mortality after transplantation in the ISHLT registry, although a previous study found higher mortality among recipients with a BMI of <18.5 kg/m² and another study found a trend of higher 90-day mortality among recipients with a BMI of <17 kg/m².^{16,17} Only 45% of our lung transplant recipients had a normal BMI of 18–28 kg/m², whereas 55% were either underweight with a BMI of <18 kg/m² (37%) or overweight with a BMI of >28 kg/m² (18%). In Saudi Arabia, a country that has experienced marked nutritional changes and rapid urbanization in recent decades, there is an increasing trend in the prevalence of obesity and overweight both in adults and children.^{18,19} Patients with chronic end-stage lung diseases generally have low BMI because of the nature of lung disease and respiratory failure. Patients with cystic fibrosis and bronchiectasis have a chronic catabolic state attributable to multiple factors, including enhanced proteolysis due to recurrent infection and inflammation, increased energy requirements, defects in insulin secretion and sensitivity, and, in some cases, intestinal malabsorption. In our data, the high prevalence of abnormal BMI is a cause for concern, as both high or low BMI are associated with several complications that increase both morbidity and mortality.²⁰ The consensus guidelines for recipient selection state that class I obesity (BMI 30–34.9 kg/m²) is a relative contraindication for lung transplantation, whereas class II or III obesity (BMI ≥ 35 kg/m²) is an absolute contraindication.²¹ Unless the BMI is very low (<14 kg/m²), low BMI alone generally does not preclude transplantation or being included in the waiting list. When patients are considered for lung transplantation referral, the primary physician needs to address their nutritional status, refer the patient to a dietitian, and prescribe nutritional supplements (in some cases, gastrostomy tube insertion may be warranted).

Organs are allocated based on blood group compatibility and the Lung Allocation Score (LAS).²² Our lung transplant recipients most frequently belonged to blood group A (40%), followed by blood group O (32.5%), blood group B (23.75%), and blood group AB (3.75%). On receiving donor data, patients are selected from the waiting list based on their blood group, human leukocyte antigen type, size matching, and disease severity according to the LAS score. Our waiting time was variable, ranging from a few days to up to 1–2 years depending on the availability of suitable donors, and the

rate of mortality while on the waiting list was 18%. The waitlist mortality rate varies among different transplantation centers depending on donor availability and an increasingly sick candidate pool.²³

We used the Clavien-Dindo classification to assess postoperative morbidities.²⁴ To our knowledge, this is the first study to describe postoperative complications in lung transplant recipients based on this grading system, which is an objective and simple way of reporting postoperative complications. In this classification system, grades I and II include only a minor deviation from the normal postoperative course, and these cases can be treated with drugs, blood transfusion, physiotherapy, and nutritional support. Meanwhile, grades III and IV include cases that require surgical, endoscopic, or radiologic intervention. Because lung transplantation is a major surgery, 64 patients had 1 or more postoperative complications. A substantial proportion of the complications were minor (grade I, 42.5%; grade II, 6.25%), and all these patients recovered without any long-term complications. Eight patients (10%) had grade III complications requiring surgical or radiological intervention, such as bleeding, fluid collection, and hematoma. Four patients (5%) had single-organ or multiorgan dysfunction, such as renal failure with or without a need for dialysis, pulmonary embolism, and critical illness neuromyopathy requiring prolonged stay in the intensive care unit. Thirteen patients (16.25%) with severe grade V complications, including massive hemorrhage, severe graft dysfunction, septic shock, and heart failure, died in the intraoperative or perioperative period. This grading system seems to be useful in recognizing a normal postoperative course from a complicated one; unfortunately, there are no published studies in lung transplantation patients for comparison with our data. This grading system has been used in other surgical operations, as it has clinical impact on the length of hospital stay.²⁵ During the last 5 years, we observed a decreasing trend in these complications, which is possibly related to a better understanding of the lung transplantation protocols, immunosuppression combinations, and aggressive treatment of infections. Acute allograft rejection is a significant problem in lung transplantation that usually occurs in the first year after the transplantation. Of our patients, 30% developed acute lung rejection. Several factors have been implicated as contributing to the development of acute rejection.^{26,27} Despite advances in induction and maintenance immunosuppression, more than one-third of lung transplant recipients are treated for acute cellular rejection in the first year after the transplantation. Treatment is usually initiated with high-dose parenteral glucocorticoids for 3 days and then switched

to oral steroids tapered over several weeks.²⁸ Acute cellular lung rejection is a major risk factor of the development of chronic lung rejection manifesting as BOS.

BOS is the predominant feature of chronic lung transplant rejection and manifests clinically as obstructive lung disease detected as decreases in FEV1 and the FEV1/FVC ratio.²⁹ The degree of decrease in FEV1 determines the stage of BOS, and the rate of progression varies among different patients. Although a variety of therapies have been tried for BOS, there is still no well-established protocol among different transplantation centers. BOS remains a major cause of morbidity and mortality after lung transplantation. The rate of mortality associated with BOS ranges from 25% to 55%.³⁰ The risk of death increases by approximately 3-fold with each increase in the BOS grade. The exact prevalence of BOS is uncertain, in part because of inconsistent definitions used among the various reports and the different lengths of follow-up. Among our lung transplant recipients, 22 patients (27.5%) developed BOS, of whom 6 patients had early-onset BOS (<2 years) and 16 had BOS after 2 years. The BOS-free survival rate was 72.5%; however, the longest survival in our series was still relatively short. Because the occurrence of BOS increases over time, centers with a long experience and large transplantation volume report higher prevalence rates. The largest experience, from the ISHLT registry, reports that 48% of recipients developed BOS by 5 years after lung transplantation and 76% developed BOS after 10 years.¹⁴

A standard deceased lung donor is defined as having an age of 55 years or less, no history of significant lung disease, a non-asthma-related cause of death, a limited cumulative cigarette smoking history (e.g., <20 packs year), a clear lung field on chest radiographs (small atelectasis is acceptable), adequate oxygenation (arterial PaO₂>300 mmHg at FiO₂=1.0, 120 mmHg at FiO₂=0.4, or 150 mmHg at FiO₂=0.5), no purulent secretions on suction, and a satisfactory gross appearance of the airways on bronchoscopic inspection.^{31,32} Most (>90%) of the lungs provided by deceased donors in Saudi Arabia do not meet the standard donor criteria. The lungs of brain-dead organ donors are susceptible to a variety of injuries, including volume overload, acute lung injury, atelectasis, aspiration- and ventilator-associated pneumonia, contusions, and injuries from prior smoking. The situation with respect to deceased donors appears to be more serious in Saudi Arabia than in other parts of the world. Logistic considerations cause a significant delay in obtaining consent for organ donation and retrieval after the declaration of brain death. The mean duration of mechanical ventilation in our lung donors before or-

gan recovery is 9 days. A longer stay in the mechanical ventilator is likely associated with further compromise of the lungs resulting from the above-mentioned disease processes. In addition, most of the critical care personnel working in remote areas of Saudi Arabia are unfamiliar with the management protocol for deceased donors. Prolonged mechanical ventilation and suboptimal infection prevention and control lead to bacterial infection in lung donors. Our data revealed that 70% of the lung donors had positive respiratory cultures for pathogenic bacteria, including multidrug-resistant bacteria such as *Acinetobacter* (26%), *Klebsiella* (20%), and *Pseudomonas* (12%). As intrapulmonary infection has been a major cause of early morbidity and mortality in lung transplant recipients, utilization of lungs from such donors is generally avoided. However, with the use of aggressive antibiotic treatment in both donors and recipients, the incidence of recipient pneumonia has recently decreased substantially.³³ We accept the lungs if there are no infiltrates (consolidation) on chest radiographs or purulent secretions on donor bronchoscopy, and if there is acceptable oxygenation. As most of our donors have bacterial infections, we are now using broad-spectrum antibiotics for recipients. Then, upon obtaining the final culture and sensitivity patterns, we tend to narrow down the antibiotic coverage.

As most of our donors are infected, it is difficult to know the exact incidence of reperfusion injury or primary graft dysfunction, which represents a diagnosis of exclusion.³⁴ During the last 5 years, veno-venous or veno-arterial extracorporeal membrane oxygenation (ECMO) was used in 24% of our lung transplantation patients for primary graft dysfunction (reperfusion injury), with a 30-day survival rate of 92% and a 1-year survival rate of 89%. Intraoperatively, 38% of the patients needed cardiopulmonary bypass and 30% required ECMO, either during single lung ventilation to support oxygenation or to stabilize hemodynamics, which was successfully removed at the end of surgery.

The demand for donor lungs by far exceeds the number of available organs, causing substantial waiting list mortality. Donor lungs are particularly susceptible to damage not only from direct external contact but also from the development of neurogenic edema and proinflammatory changes caused by brain death. The worldwide rate of lung retrieval from multiorgan deceased donors is only 15% to 20%.³⁵ One way to overcome the scarcity of donor organs is to use lungs that do not meet the standard lung donor criteria, often referred to as "marginal donor lungs."^{35,36}

Ex vivo lung perfusion (EVLP) is the most recent approach for expanding the available pool of donor

lungs.³⁷ It has been used to recondition and reevaluate marginal lungs in which the PaO₂ remained <300 mm Hg at an FiO₂ of 1 and a positive end-expiratory pressure of 5 cm H₂O with no other exclusion criteria being met upon assessment by our lung recovery team at the donor hospital. Lungs were accepted for EVLP if inspection revealed no obvious contraindications; otherwise, the lungs were discarded. EVLP was performed following the technique described by Lund's group.^{37,38} The first successful lung transplantation using an EVLP machine was performed at our center in December 2013. This novel technology is expected to expand our deceased donor pool. Thus far, only two patients had received ex vivo conditioned lungs. Although this number is small, we did not notice any difference from the other recipients in terms of graft function, postoperative recovery, and length of hospital stay.

The choice of the surgical procedure (single or bilateral) depends on the underlying lung condition and the availability of suitable lungs. Patients with COPD and fibrotic lung disease can be offered single lung transplantation, whereas those with suppurative lung diseases need bilateral lung transplantation. Recent data have suggested that bilateral lung transplantation offers a long-term survival advantage to younger patients with pulmonary fibrosis.³⁹ Similar to other studies in the literature, most (85%) of the lung transplantations performed at our center have been bilateral procedures.

Donor-recipient size matching is another important consideration at the time of transplantation.^{40,41} Most of our lung transplant recipients had pulmonary fibrosis with constricted thoracic cages, and a young age. Therefore, the size of their chest cavity was usually smaller than that of full-sized mature donors. At the same time, we encountered a severe shortage of donor lungs. Therefore, it was often not possible to find a suitable size match for many recipients. To prevent a prolonged waiting time and the associated risk factors of mortality while on the waiting list, surgeons often choose to perform lung volume reduction in donor lungs. Volume reduction surgery was required in 70% of our cases. In two cases of extreme donor-recipient size mismatch, bilateral lower lobar transplantations were performed with excellent posttransplantation outcomes. In addition, unilateral upper lobe transplantation with contralateral volume reduction was performed in three patients.

Although the survival rate after lung transplantation has improved worldwide, it remains inferior to that observed after the transplantation of other solid organs.^{6,9} To improve survival after lung transplantation, an in-depth knowledge of the various factors that may

affect outcome in this distinct patient group is necessary. Previous reports have documented a significant influence of pretransplantation patient characteristics, surgical risk factors, and posttransplantation course.^{42,43} Postoperative factors such as primary graft dysfunction, BOS, acute lung rejection, and development of infections may significantly affect the overall survival. Our mortality rate after transplantation was 12.5% (10 patients) at 30 days and 17.5% (14 patients) at 90 days. Among these, a few died of massive intraoperative bleeding and others developed severe graft dysfunction and infections. According to the 2016 report of the ISHLT registry,⁹ adult patients who underwent lung transplantation between January 1990 and June 2014 had a median survival of 5.8 years, with unadjusted survival rates of 89% at 3 months, 80% at 1 year, 65% at 3 years, 54% at 5 years, and 32% at 10 years. Our 1-month, 3-month, 1-year, 3-year, and 5-year survival rates after lung transplantation were 87.5%, 82.5%, 81.2%, 67.9%, and 62.1%, respectively. Our data are comparable to internationally reported survival rates, although our 5-year survival rate seems to be higher, which might be related to the fact that most of our recipients were relatively young with less risk of comorbidities.

A successful outcome after a transplantation procedure requires full commitment from the patient, the patient's family, and the dedicated multidisciplinary lung transplantation team. Timely referral and careful selection of candidates for lung transplantation can maximize the outcomes of the procedure, including providing a longer lifespan with improved physical health. On the basis of our experience, we recommend educating general physicians, pulmonologists, and intensive care personnel around Saudi Arabia about the key elements of a standard donor protocol, as well as teaching the general population about the good outcomes of lung transplantation such that families may be inclined to make positive decisions with respect to organ donation.

This study has the limitations of having a single-center retrospective design and a small patient volume. As our center is the only lung transplantation center in the region, more studies are needed to better understand the differences and characteristics we highlighted in our study. The increasing experience of our surgeons, transplant pulmonologists, and intensivists with these patient challenges has resulted in excellent outcomes. In conclusion, lung transplantation has become an invaluable approach for the treatment of end-stage respiratory disease in selected patients, and our 5-year experience demonstrates some exciting possibilities in the field of lung transplantation in Saudi Arabia.

REFERENCES

1. Hardy JD, Webb WR, Dalton ML Jr, Walker GR Jr. Lung homotransplantations in man. *JAMA*. 1963;186:1065-74.
2. Kotloff RM, Thabut G. Lung transplantation. *Am J Respir Crit Care Med*. 2011; 184:159-71.
3. Reitz BA, Wallwork JL, Hunt SA, Pennock JL, Billingham ME, Oyer PE, et al. Heart-lung transplantation: successful therapy for patients with pulmonary vascular disease. *N Engl J Med*. 1982; 306:557.
4. Toronto Lung Transplant Group. Unilateral lung transplantation for pulmonary fibrosis. *N Engl J Med*. 1986; 314:1140.
5. Cooper JD, Patterson GA, Grossman R, Maurer J. Double-lung transplant for advanced chronic obstructive lung disease. *Am Rev Respir Dis*. 1989; 139:303.
6. Roger DY, Jason DC, Leah BE, Anna YK, Christian B, Anne ID, et al. ISHLT adult lung and heart-lung transplant report. *J Heart and Lung Transplantation*. 2015;34(10):1264-77.
7. Chambers DC, Yusen RD, Cherikh WS, Goldfarb SB, Kucheryavaya AY, Kusch K, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirtyfourth Adult Lung And Heart-Lung Transplantation Report-2017; Focus Theme: Allograft ischemic time. *J Heart Lung Transplant*. 2017;36:1047-1059.
8. Yusen RD, Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report—2013; focus theme: age. *J Heart Lung Transplant*. 2013;32(10):965-78.
9. Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Lewvey BJ, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart-Lung Transplant Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transplant*. 2016;35:1170-84.
10. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009; 250:187-96.
11. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. *J Heart Lung Transplant*. 2014;33:127.
12. Al-Bedah A. Studies and research about smoking in Saudi Arabia. Riyadh: King Fahd national library; 2007.
13. Alsubaie ME, Frith PA, Cafarella PA, Quinn S, Al Moamary MS, McEvoy RD, et al. COPD care in Saudi Arabia: physicians' awareness and knowledge of guidelines and barriers to implementation. *Int J Tuberc Lung Dis*. 2017;21(5):592-595.
14. Christie JD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Dobbels F, et al. The Registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. *J Heart Lung Transplant*. 2012; 31:1073.
15. Madill J, Gutierrez C, Grossman J, Allard J, Chan C, Hutcheon M, et al. Nutritional assessment of the lung transplant patient: body mass index as a predictor of 90-day mortality following transplantation. *J Heart Lung Transplant*. 2001; 20:288.
16. Benden C, Ridout DA, Edwards LB, Boehler A, Christie JD, Sweet SC. Body mass index and its effect on outcome in children after lung transplantation. *J Heart Lung Transplant*. 2013; 32:196.
17. Singer JP, Peterson ER, Snyder ME, Katz PP, Golden JA, D'Ovidio F, et al. Body composition and mortality after adult lung transplantation in the United States. *Am J Respir Crit Care Med*. 2014; 190:1012.
18. Al-Hazzaa HM. Rising trends in BMI of Saudi adolescents: evidence from three national cross sectional studies. *Asia Pac J Clin Nutr*. 2007;16:462-466.
19. Al-Hazzaa HM. Prevalence and trends in obesity among school boys in Central Saudi Arabia between 1988 and 2005. *Saudi Medical J*. 2007;28:1569-1574.
20. Lederer DJ, Wilt JS, D'Ovidio F, Bacchetta MD, Shah L, Ravichandran S, et al. Obesity and underweight are associated with an increased risk of death after lung transplantation. *Am J Respir Crit Care Med*. 2009; 180:887.
21. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2015; 34(1):1-15.
22. Gottlieb J. Lung allocation. *J Thorac Dis*. 2017; 9:2670.
23. Valapour M, Skeans MA, Smith JM, Edwards LB, Cherikh WS, Uccellini K, et al. OPTN/SRTR 2015 Annual Data Report: Lung. *Am J Transplant*. 2017;17(1):357-424.
24. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*. 2009; 250:187-96.
25. Dindo D, Demartines N, Clavien PA. Classification of surgical complications. A new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004; 240:205-13.
26. Martinu T, Pavlisko EN, Chen DF, Palmer SM. Acute allograft rejection: cellular and humoral processes. *Clin Chest Med*. 2011; 32:295.
27. Girnita DM, Webber SA, Zeevi A. Clinical impact of cytokine and growth factor genetic polymorphisms in thoracic organ transplantation. *Clin Lab Med*. 2008; 28:423.
28. Levine SM, Transplant/Immunology Network of the American College of Chest Physicians. A survey of clinical practice of lung transplantation in North America. *Chest*. 2004; 125:1224.
29. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. *J Heart Lung Transplant*. 2014;33:127.
30. Burton CM, Carlsen J, Mortensen J, Andersen CB, Milman N, Iversen M. Long-term survival after lung transplantation depends on development and severity of bronchiolitis obliterans syndrome. *J Heart Lung Transplant*. 2007; 26:681.
31. Chaney J, Suzuki Y, Cantu E, III, van Berkel V. Lung donor selection criteria. *J Thorac Dis*. 2014;6(8):1032-38.
32. Munshi L, Keshavjee S, Cypel M. Donor management and lung preservation for lung transplantation. *Lancet Respir Med*. 2013;1(4):318-28.
33. Avlonitis VS, Krause A, Luzzi L, Powell H, Phillips JA, Corris PA, et al. Bacterial colonization of the donor lower airways is a predictor of poor outcome in lung transplantation. *Eur J Cardiothorac Surg*. 2003;24(4):601-7.
34. Snell GI, Yusen RD, Weill D, Strueber M, Garrity E, Reed A, et al. Report of the ISHLT Working Group on Primary Lung Graft Dysfunction, part I: Definition and grading—A 2016 Consensus Group statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2017; 36:1097.
35. Whiting D, Banerji A, Ross D, Levine M, Shpiner R, Lackey S, et al. Liberalization of donor criteria in lung transplantation. *Am Surg*. 2003;69:909.
36. Sommer W, Kühn C, Tudorache I, Avsar M, Gottlieb J, Boethig D, et al. Extended criteria donor lungs and clinical outcome: results of an alternative allocation algorithm. *J Heart Lung Transplant*. 2013; 32:1065.
37. Lindstedt S, Eyjolfsson A, Koul B, Wierup P, Pierre L, Gustafsson R, et al. How to recondition ex vivo initially rejected donor lungs for clinical transplantation; clinical experience from Lund University Hospital. *J Transplant*. 2011;754:383.
38. Steen S, Sjoberg T, Pierre L, Liao Q, Eriksson L, Algotsson L. Transplantation of lungs from a non-heart-beating donor. *Lancet*. 2001;357:825-29.
39. Seth D Force, Pat Kilgo, David C Neujahr, Andres Pelaez, Allan Pickens, Felix G Fernandez, et al. Bilateral lung transplantation offers better long-term survival, compared with single-lung transplantation, for younger patients with idiopathic pulmonary fibrosis. *Ann Thorac Surg*. 2011;91(1):244-49.
40. Mason DP, Batizy LH, Wu J, Nowicki ER, Murthy SC, McNeill AM, et al. Matching donor to recipient in lung transplantation: How much does size matter? *J Thorac Cardiovasc Surg*. 2009; 137:1234.
41. Eberlein M, Reed RM, Permutt S, Chahla MF, Bolukbas S, Nathan Sd, et al. Parameters of donor-recipient size mismatch and survival after bilateral lung transplantation. *J Heart Lung Transplant*. 2012; 31:1207.
42. Thabut G. Estimating the Survival Benefit of Lung Transplantation: Considering the Disease Course during the Wait. *Ann Am Thorac Soc*. 2017;14:163-4.
43. Titman A, Rogers CA, Bonser RS, Banner NR, Sharples LD. Disease-specific survival benefit of lung transplantation in adults: a national cohort study. *Am J Transplant*. 2009; 9:1640.