LUNG TRANSPLANTATION AT THE ZAGREB UNIVERSITY HOSPITAL CENTER, ZAGREB, CROATIA

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Objective: Lung transplantation has become a standard of care for patients with a variety of non-malignant end-stage lung diseases. The aim of the study was to report on the safety and feasibility of lung transplantation at the Zagreb University Hospital Center. ***Methods:*** In this single center retrospective observational study, all consecutive patients undergoing lung transplantation at the Zagreb University Hospital Center from April 2021 until December 2022 were included. The only inclusion criterion was surgery for lung transplantation. Patient demographic and operative characteristics were reported, as well as early outcomes, including 30-day mortality, hospital stay, intensive care unit stay, duration of mechanical ventilation, and incidence of primary graft dysfunction. The degree of primary graft dysfunction was graded based on the International Society for Heart and Lung Transplantation criteria at 72 hours after transplantation with grades 0 to 3. ***Results:*** During the 21-month study period, 19 patients were successfully transplanted. There was no 30-day mortality. There was one late death at 18 months after transplantation. Median in-hospital stay was 32 days, ranging from 21 to 62 days. Mean mechanical ventilation duration was 105±58 h and median of intensive care unit stay was 6 days, ranging from 4 to 15 days. Only two (11%) patients had the highest grade 3 primary graft dysfunction. Of the remaining patients, 16 (84%) had none (grade 0) and one (5%) patient had mild primary graft dysfunction (grade 1). ***Conclusion:*** Our results suggest that lung transplantation is safely performed at the Zagreb University Hospital Center. Initial results with no operative mortality are encouraging. Further follow-up and experience are needed to make inferences on long-term outcomes of our lung transplantation patients.

Key words: lung transplantation, end-stage lung disease, extracorporeal membrane oxygenation, primary lung graft dysfunction, survival, operative mortality

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INTRODUCTION

Over the past 35 years, lung transplantation has become a viable option for patients with a variety of non-malignant end-stage lung diseases. Although the first human lung transplantation was performed back in 1963 (1), only a few procedures were performed until the mid-80s, when the operation became a clinical reality. Since the year 2000, a steady growth of lung transplant procedures has been reported with approximately 4500 procedures annually in recent years (2).

Despite favorable results in recent years, lung transplantation remains burdened with the risk of mortality and morbidity, which are related to primary graft dysfunction (PGD) and chronic lung allograft dysfunction (CLAD) (3). Long-term results of lung transplantation are not yet as good as other solid-organ transplants. Early outcomes have been considerably improved by technical advances in graft procurement, preservation, implantation, perioperative care, immunosuppression, and postoperative medical management. However, long-term survival has improved minimally over the last two decades. Various complications with delayed onset, such as CLAD or opportunistic infection, continue to significantly impact recipient quality of life, survival, and long-term outcomes (4).

Primary graft dysfunction is defined as lung injury that occurs within the first 72 hours following lung transplantation as reflected by the appearance of diffuse allograft edema/infiltration on chest radiograph. Severe PGD is the most common cause of early mortality and has also been associated with later dysfunction of the graft (5). Therefore, those surviving this initial insult remain at a risk of long-term morbidity and mortality. It has been reported that the routine application of veno-arterial extracorporeal membrane oxygenation (VA ECMO) during lung transplantation has significantly decreased the rates of severe PGD after lung allograft transplantation (6).

Single lung transplantation used to be more frequent than bilateral, while today the number of bilateral transplants has surpassed the number of single lung transplants (2). First lung transplantation in Croatia was performed in 2003 at the Jordanovac Department of Thoracic Surgery in Zagreb. In the years to follow, lung transplantation was not performed in Croatia until 2021. During this period, patients requiring lung transplantation were transplanted in Vienna (7). Close collaboration with the Department of Thoracic Surgery at Vienna University Hospital was developed, which led to the first bilateral lung transplantation in Croatia on April 17, 2021.

AIM

The aim of this study was to report on the safety and feasibility of lung transplantation at the Zagreb University Hospital Center, and on our initial experience with the procedure.

METHODS

This single center retrospective observational study included all consecutive patients undergoing lung transplantation at the Zagreb University Hospital Center, Zagreb, Croatia, from April 2021 until December 2022. The only inclusion criterion was surgery for lung transplantation. There were no exclusion criteria. Both adult and minor patients were included in the study. The institutional Review Board of the Zagreb University Hospital Center approved the study. It was conducted according to the Declaration of Helsinki. Written informed consent was waived due to the retrospective nature of the study. Individual medical records were reviewed for demographic, clinical, and laboratory data. Patient demographic and operative characteristics were reported, as well as outcomes during the follow-up period, which was completed in January 2023.

Surgery for transplantation

Bilateral thoracosternotomy, also known as clamshell incision, in the fourth intercostal space was performed in all cases. Internal thoracic arteries were ligated and severed. This approach provides the best exposure to both hila and the heart. This was particularly important since central cannulation for VA ECMO support was used (Figure 1).

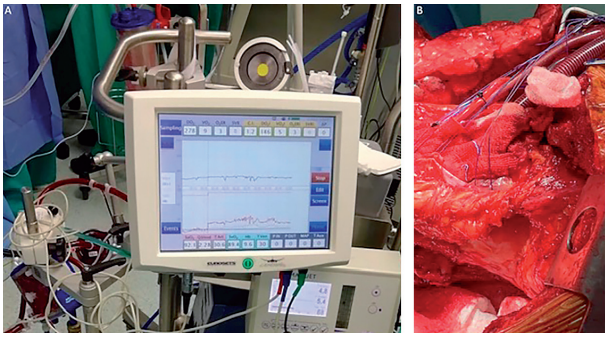

Figure 1. *Intraoperative extracorporeal membrane oxygenation support: (A) intraoperative veno-arterial extracorporeal oxygenation monitoring during lung transplantation; (B) central cannulation of the aorta and the right atrium via clamshell incision for veno-arterial extracorporeal membrane oxygenation.*

Pneumonectomy was performed in a standard manner with stapling of the pulmonary artery and pulmonary veins as peripheral as possible. The bronchus was prepared centrally and divided two rings from the carina. Thereafter, the lung was taken out of the chest cavity. During the entire procedure of pneumonectomy, special attention was always taken to avoid phrenic nerve injury. On the left side, the recurrent laryngeal nerve should also be preserved. In patients with significant adhesions, the lung was mobilized with caution to avoid injuries to the phrenic nerve or vital structures.

The first step in implanting the lung was the formation of bronchial anastomosis. Topical cooling was provided with ice slush. A bacteriologic swab was taken from the donor lung, and the bronchial system was flushed with saline to remove residual mucus. The bronchial anastomosis was performed in a single running suture technique using double-armed 4-0 polydioxanone, starting at one end of the cartilaginous part and going over the membranous portion and then using the same single running suture for the anterior cartilaginous part. After completion of the bronchial anastomosis, the left atrial anastomosis was performed. A Satinsky clamp is placed centrally in the left atrium to ensure a sufficient cuff for the left atrial anastomosis. The anastomosis was performed with a 4-0 running polypropylene suture, at a level where myocardial

muscle tissue is present. Thereafter, the recipient pulmonary artery was centrally clamped and opened. The pulmonary artery anastomosis is again performed in a running technique using a 5-0 polypropylene suture. This anastomosis sequence was used in all our cases (Figure 2).

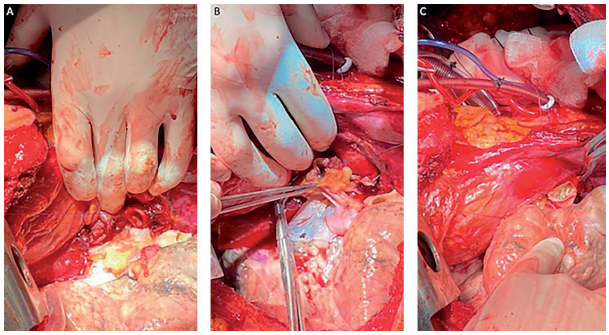

Figure 2. *Anastomosis sequence for lung transplantation: (A)bronchial anastomosis is performed in a single running suture technique. A double-armed 4-0 polydioxanone is used, starting at one end of the cartilaginous part of the bronchus and going over the membranous portion and then using the same single running suture for the anterior cartilaginous part; (B)once a sufficient left atrial cuff of the recipient has been prepared, the left atrial anastomosis is performed with a 4-0 running polypropylene suture, at the level where myocardial muscle tissue is present; (C) pulmonary artery anastomosis is again performed in a running technique using a 5-0 polypropylene suture.*

Before exposing the newly implanted lung to innate circulation, initial immunosuppression with 1 g methylprednisolone was administered. All other immunosuppressants were started upon arrival to the intensive care unit (ICU). Second important step prior to complete releasing the clamps is retrograde and antegrade flushing of the newly implanted lung. Flushing was done to remove the remainder of the preservation solution (Perfadex Plus, Göteborg, Sweden) and to deair the vascular bed in the donor lung. Thereafter, the sutures were knotted and all clamps removed. At this moment of lung transplantation, the ischemic period, started during organ procurement, was completed and lung protective ventilation was started. The same procedure was done for the contralateral lung. We instituted bilateral lung transplantation in all cases.

After implantation of both lungs, meticulous hemostasis was performed with special attention to the donor pulmonary ligament, pericardium, and location of dense adhesions. Fibrin glue and hemostatic gauzes were applied on the vascular suture lines. Chest drainages were placed in the costodiaphragmatic sinus and anterior to the hilus towards the apex on each side. Additionally, a small Jackson-Pratt drain was placed in the posterior aspect of each pleural cavity.

Extracorporeal membrane oxygenation

All patients were transplanted with a preemptive intraoperative central VA ECMO support (Figure 1). Central cannulation sites were the right atrium for inflow cannula and the ascending aorta for outflow cannula. Elongated One-Piece Arterial Cannula (EOPA, Medtronic Inc, Minneapolis, MN, USA) was used for the aorta and a curved-tip cannula also from Medtronic was used for the right atrium. In brief, the circuit consists of the inflow and outflow cannulas, blood pumping device, oxygenator, and integrated heat exchanger. Either Cardiohelp (Getinge AB, Göteborg, Sweden) or Biomedicus (Medtronic) centrifugal pump were used. Hollow fiber membrane oxygenators incorporated in the HLS or PLS Set also from Getinge were applied. Biocompatible surface coating lines were used. All patients received a bolus dose of 50-60 IU/kg unfractionated heparin before cannulation, and the dose was modified based on the coagulation status of the patient and surgeons' preference. Activated clotting time was not monitored routinely.

During pneumonectomy, theVA ECMO flow was set to 50% of predicted cardiac output and adapted according to hemodynamic and gas exchange demands. After implantation of the second lung, flow was gradually reduced, and the patient weaned from ECMO. Function of the lungs was evaluated 10 minutes after decannulation and immediately after chest closure. If lung function did not meet the predefined quality criteria, or if there was clear worsening between measurements, a peripheral VA ECMO system was inserted in a femoro-femoral configuration (Figure 3) and patients were transferred to the ICU support.

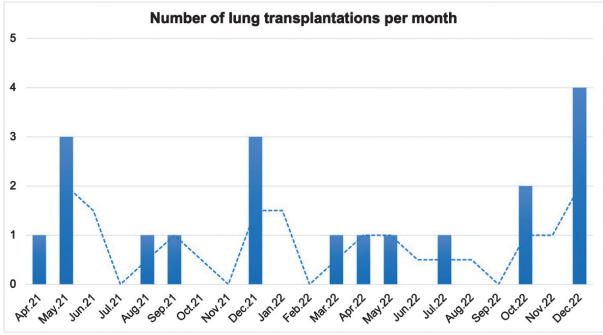

Figure 3. *Number of lung transplantations with trendline performed at the Zagreb University Hospital Center each month from April 2021 until December 2022.*

Immunosuppression, infection prophylaxis and rejection management

After intraoperative administration of methylprednisolone, all patients received induction therapy with alemtuzumab (Campath, Sanofi, MA, USA) upon

arrival to the ICU. Alemtuzumab is a recombinant monoclonal antibody directed against cell surface glycoprotein CD52, which is expressed on several immune cells and its activation induces immune cell depletion (8). Maintenance immunosuppression protocol is provided in Table 1 and is based on the low-dose immunosuppression protocol from the Vienna Lung Transplantation Group (9). Perioperative infectious prophylaxis was based on broad-spectrum antibiotics or adapted to resistance testing. All patients received continuous pneumocystis prophylaxis with trimethoprim-sulfamethoxazole. Prophylactic inhalation therapy with amphotericin B and gentamicin was provided during the initial one-month period after transplantation. Cytomegalovirus (CMV) prophylaxis included CMV-specific human hyperimmune globulins together with valganciclovir for a minimum of 3 months. Surveillance bronchoscopy with transbronchial biopsy and bronchoalveolar lavage was performed during initial hospitalization and at 2, 3, 6 and 12 months after transplantation or whenever clinically indicated. Likewise, all patients underwent chest computed tomography during initial hospitalization prior to bronchoscopy and on follow-up visits. Additional diagnostic scans were performed in case of lung function deterioration, e.g., in case of suspected acute rejection episode or infections. Biopsies were classified according to the International Society of Heart and Lung Transplantation (ISHLT) criteria (10). In case of marked drop in lung function or suspicion of acute rejection, after exclusion of probable/definitive antibody mediated rejection (11), patients were treated with high-dose corticosteroids, and in case of non-response, reinduction with alemtuzumab or an interleukin-2 receptor antagonist (daclizumab) was administered followed by extracorporeal photopheresis.

Table 1 *Maintenance immunosuppression protocol.*

Time after LuTx	Tacrolimus (ng/mL)	Prednisolone (mg)	MMF (mg)*
0-3 months	8-10	25	–
3-6 months	6-8	20	–
6-9 months	6-8	15	–
9-12 months	6-8	10	–
12-24 months	5-7	5	500 twice a day
>24 months	4-6	5	500 twice a day

*LuTx, lung transplantation; MMF, mycophenolate mofetil; *in case of obstructive chronic lung allograft dysfunction, 750-1000 mg twice a day after 12 months.*

Outcome measures

Primary outcome of interest was operative mortality. Operative mortality was defined as death within 30 days after surgery or in-hospital death. Patients were followed-up monthly in the outpatient clinic. Follow-up was terminated in January 2023 for the purpose of this study. There were no patients lost to follow-up. Secondary outcomes of interest were in-hospital stay, ICU stay, duration of mechanical ventilation, and rates of PGD at 72 hours following transplantation. A grading system for PGD incorporating arterial oxygen partial pressure to ractional inspired oxygen (PaO_2/FiO_2) ratio and chest radiograph findings was used. Based on this system, each patient was graded with PGD grade 0-3 as described in the 2017 consensus group statement of the ISHLT (12).

Statistical analysis

Continuous variables were expressed as mean±standard deviation (SD) or median with range, whereas categorical variables were described with frequencies and proportions. To assess distribution, the Shapiro-Wilk test for normality was applied. It was used to determine which variables were normally distributed (mean, SD) and which were non-normally distributed (median, range). Independent (unpaired) Student's t-test was used for normally distributed continuous variables. Fisher exact test was chosen for analysis of categorical variables. All analyses were performed in Microsoft Excel for Mac and R version 4.2.2 for Mac (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In April 2021, after being discussed by the multidisciplinary team, first patients suffering from end-stage chronic obstructive pulmonary disease/emphysema were placed on the transplant waiting list and reported to the Eurotransplant. During the study period, 27 patients were listed overall. Of the patients that were listed, 19 (70%) were transplanted. One patient died due to sepsis while being on the waiting list. This was a patient with end-stage lung disease on VV ECMO after being infected with severe acute respiratory syndrome coronavirus 2 (SARSCoV2) and having contracted coronavirus disease 2019 (COVID-19). A history of COVID-19 was present in 5 (26%) transplanted patients, not related to the indication for lung transplantation. The number of lung transplantations that were performed monthly during the study period was, as expected, highly unpredictable and it ranged from 0 to 4 procedures *per* month (Figure 4). There were 15 (79%) male and 4 (21%) female patients that were transplanted. Median age of these patients was 56, ranging from 12 to 68 years. Underlying diagnoses for transplantation were diverse and are reported in Table 2 alongside with patient comorbidities.

There was one pediatric case. The pediatric patient was transplanted under the indication of graft *versus* host disease (GvHD). After a matched sibling donor hematopoietic stem cell transplantation for acute lymphocytic leukemia, the patient developed GvHD of the lungs. Once the risk of disease recurrence was significantly reduced, he was put on the waiting list and successfully transplanted.

Table 2 *Baseline lung transplant patient characteristics, matching factors, and surgical data.*

		N=19
Demographics and comorbidities		
Age (years)		56 (12-68)
Female		4 (21%)
Height (m)		1.69±0.11
Weight (kg)		67±13
BMI (kg/m^2)		23±3
Arterial hypertension		2 (11%)
Hyperlipidemia		2 (11%)
Diabetes		2 (11%)
GERD		3 (16%)
History of COVID-19		5 (26%)
Secondary PH		8 (42%)
Matching		
ABO matching	Identical	15 (79%)
	Compatible	4 (21%)
High risk CMV mismatch		3 (16%)
Gender mismatch		9 (47%)
Underlying diagnosis		
COPD		6 (32%)
ILD		6 (32%)
AATD		3 (16%)
PH		1 (5%)
CF		1 (5%)
Other		2 (11 %)
Type of transplantation		
Double lung		19 (100%)
Size reduction		5 (26%)
Ischemia right lung (min)		351±59
Ischemia left lung (min)		464±66
Prolonged postoperative ECMO		
VA ECMO		1 (5%)
VV ECMO		1 (5%)

AATD, alpha-1 antitrypsin deficiency; BMI, body mass index; CF, cystic fibrosis; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; GERD, gastroesophageal reflux disease; HFNC, high flow nasal cannula; ILP, interstitial lung disease; LuTx, lung transplantation; PH, pulmonary hypertension; VA, veno-arterial; VV, veno-venous.

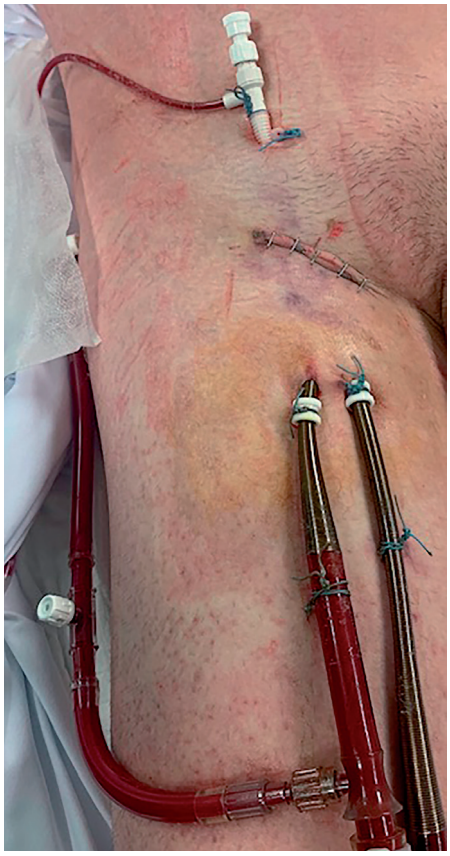

Figure 4. *Prolonged postoperative veno-arterial extracorporeal membrane oxygenation support in the groin: 15 Fr arterial and 17 Fr venous cannulas were placed in the right common femoral artery and vein with an 8 Fr distal reperfusion line. Prolonged postoperative veno-arterial extracorporeal membrane oxygenation support is started immediately after transplantation prior to leaving the operating room in recipients with pulmonary hypertension and in patients with questionable graft function at the end of implantation.*

Donor characteristics are reported in Table 3. Fourteen donor lungs came from within Croatia and the remaining 5 came from abroad. As expected, donors were younger than recipients (p=0.002). The mean age of donors was 38±14, ranging from 14 to 56 years. There were more females among donors than among recipients (p=0.045). Gender mismatch was observed in 9 (47%) transplanted patients. There were 15 (79%) identical ABO blood group matches. All the four compatible ABO matches were from O donors for either A or B recipients. High-risk CMV mismatches (D+/R) were observed in 3 (16%) cases. Donor reports revealed PaO_2 at 100% FiO_2 in the range from 233 to 637 mmHg. During procurement, blood gas analyses were reassessed. In case of PaO_2<300 mmHg with 100% FiO2 and 5 mmHg of positive end-expiratory pressure, the lungs were rejected. Following a satisfactory blood gas analysis, final decision to continue with lung transplantation was made in each case after visual inspection of the explanted lungs (Figure 5).

Table 3. Lung transplantation donor characteristics.

	N=19
Age (years)	38±14
Female	11 (58%)
Height (m)	1.70±0.09
Weight (kg)	72±15
BMI (kg/m^2)	24±3
Arterial hypertension	7 (37%)
Diabetes	1 (5%)
Smoking	5 (26%)
pO_2 (mmHg)	466±101
pCO_2(mmHg)	40 (28-75)

BMI, body mass index; pO_2 partial pressure of oxygen; pCO_2 partial pressure of carbon dioxide

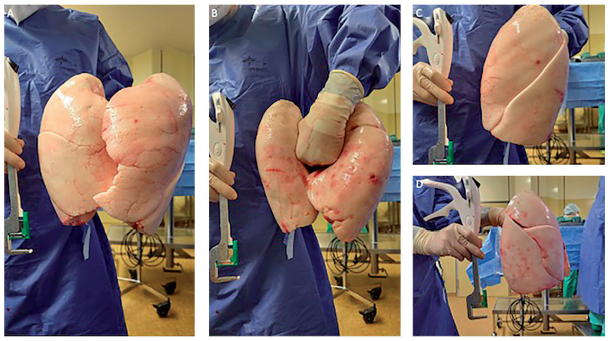

Figure 5. *Final decision to continue with lung transplantation was made during lung procurement based on blood gas analysis, palpation, compliance assessment, and visual inspection of the explanted lungs: (A) anterior view of the explanted lung with the linear stapler aside to aid in size assessment; (B) posterior view; (C) left lateral view; (D) right lateral view.*

All patients received bilateral lung transplantation. Lung volume reduction was undertaken in 5 (26%) patients. Lung volume reduction was based on surgeons' preference. In these cases, the middle lobe and lingula were resected. Lung ischemia times ranged from 237 to 475 min on the right side and 329 to 575 min on the left side. Prolonged ECMO support was necessary in two cases. One was related to high-grade PGD immediately after transplantation. The other one did not show any signs of diffuse lung edema on chest radiograph. Prolonged ECMO support was started immediately after transplantation prior to leaving the operating room. Both patients were successfully weaned from support. One was weaned after four days, and the other one, only one day after transplantation.

The need to reexplore the chest cavity for bleeding was necessary in one (5%) patient. The patient was taken back to the operating room due to an excessive chest tube output on the same day of transplantation. Bleeding was surgically managed, and the patient recovered fully. There was one ECMO related complication requiring an intervention. It was related to leg ischemia due to right external iliac artery thrombosis after peripheral VA ECMO removal. Surgical thrombectomy was performed without any further sequels for the patient.

Hospital stay, mechanical ventilation duration and ICU days are reported in Table 4. High-grade PGD at 72 hours after transplantation is characterized with diffuse lung edema on chest radiograph. Most patients were grade 0 and the incidence of high-grade PGD was low. Detailed information on each grade is reported in Table 4. There were no cases of PGD grade 2 at 72 hours following transplantation.

Table 4. *Outcome measures.*

		N=19
Mechanical ventilation (h)		105±58
ICU time (days)		6 (4-15)
In-hospital stay (days)		32 (21-62)
PGD grade at 72 hours	0	16 (84%)
	1	1 (5%)
	3	2 (11%)

PGD, primary graft dysfunction; ICU, intensive care unit

There were no operative deaths. All patients were successfully discharged from the hospital after the index procedure. Two patients transplanted in December 2022 were recovering well but still in the hospital while this manuscript was in preparation. There were no late deaths except for one. The patient died 18 months after transplantation due to sepsis and multiorgan failure. Compliance to medical therapy was a major issue in this case.

DISCUSSION

In this article, we report our initial experience with lung transplantation at the Zagreb University Hospital Center, Zagreb, Croatia. Lung transplantation was the only solid organ transplantation that was not routinely performed in Croatia until recently. Since April 2021, lung transplantations are routinely performed at our center and Croatian patients no longer need to travel abroad for lung transplantation. Based on the results of this study, we can say that lung transplantation was safely performed at our center and the initial outcomes are encouraging. Further follow-up is needed to give an insight into long-term results.

Survival is probably the most robust and straight forward assessment of outcome after lung transplantation. Large registries can easily provide information on survival estimates based on multicenter international data. The ISHLT registry has accumulated data on more than 64,000 lung transplant recipients. It annually reports survival estimates and has become a quality benchmark in the field. According to the recent registry report, the median survival for adult recipients since 2010 is 6.7 years, but bilateral lung recipients appear to have a better median survival than single lung recipients (7.8 *versus* 4.8 years) (2). However, it is not entirely clear if the survival advantage is directly related to the choice of procedure or rather to the recipient characteristics. Better allograft longevity and overall favorable outcomes of lung transplantation today are a result of refinement in the processes of recipient and donor selection, surgical techniques, immunosuppression, and other post-transplant treatment regimens. Despite these improvements, survival outcomes of lung transplantation recipients remain inferior to those of other solid-organ transplant procedures. For instance, the median survival after heart transplantation is around 12 years (13).

The underlying diagnosis has a major impact on survival after transplantation. Certain diagnoses carry higher risks of operative complications and PGD. It is important to emphasize that some diagnoses are linked to particular age groups. Recipients with chronic obstructive pulmonary disease are older and they have the best one-year survival but lower ten-year survival compared to those with cystic fibrosis or primary pulmonary hypertension (14). Recipients with primary pulmonary hypertension have the lowest one-year survival but their ten-year survival approaches those with cystic fibrosis (2). In the more recent epoch of lung transplantation, improvement in one-year survival is notable, although the difference is not so obvious at 5 years. This might be due to management strategies that have been more effective at reducing early complications rather than the later ones.

Primary graft dysfunction is still one of the main risks at short-term outcome after lung transplantation. It is a form of acute respiratory distress syndrome characterized with diffuse alveolar damage, which occurs between early hours and a few days after transplantation. In the ISHLT registry, PGD is defined as lung injury that occurs within the first 72 hours following lung transplantation as reflected by the appearance of diffuse lung edema on chest x-ray. A grading system for PGD incorporates the PaO_2/FiO_2 ratio and chest radiograph findings (12). Severe PGD is the most common cause of early mortality after lung transplantation and has also been associated with later allograft dysfunction (5). It accounts for more than 20% of deaths in the first 30 days (2,15). Several groups have shown that severe PGD is associated with increased perioperative mortality and impaired 1-year survival rates (16). Proper intraoperative allograft management is crucial to avoid PGD. Based on the ISHLT PGD working group data, severe graft dysfunction is observed in up to 20% of patients within 72 hours after lung transplantation (12). In our patient cohort, we observed severe graft dysfunction in only 2 (11%) patients. One of these patients was managed with VA ECMO support immediately after transplantation before leaving the operating room. Weaning from ECMO was successful within four days of transplantation.

The optimal strategy and use of extracorporeal circulation during lung transplantation has been a matter of ongoing discussion. Some centers apply intraoperative support only in unstable patients, whereas others use it routinely. In our center, we opted for routine intraoperative VA ECMO support in all our transplant cases. Cardiopulmonary bypass has been a more traditional approach mainly used in the early days of lung transplantation, whereas VA ECMO came into use at a later date. When used properly, the side effects associated with routine application of intraoperative central VA ECMO are nonsignificant (17).

Lung transplantation does not necessarily require the use of extracorporeal circulation. However, the use of intraoperative VA ECMO guarantees hemodynamic and respiratory stability during single-lung ventilation period. This is particularly important in patients with severe pulmonary hypertension and those with preexisting hemodynamic instability. It also facilitates lung protective ventilation strategies and allows for prolonged and controlled reperfusion of the newly implanted allograft. Finally, a routine use of intraoperative VA ECMO support has been associated with exceptionally low PGD rates and even improved survival, particularly in patients with primary pulmonary hypertension (6,17).

Chronic lung allograft dysfunction and infections are the leading cause of death and the main limiting factor in long-term survival after lung transplantation. Up to 30% of fatal outcomes are due to CLAD (2). There are two main phenotypes of CLAD: bronchiolitis obliterans syndrome (BOS), so called oCLAD, and restrictive allograft syndrome (RAS), so called rCLAD plus mixed forms. Survival after the onset of BOS is about 50% after only three years (2). Our understanding of CLAD mechanism and risk factors is still insufficient. Currently available therapies for CLAD are not effective. Infections led by bacterial bronchitis and pneumonia are the most common complications at all time points after lung transplantation. Fungi, CMV, community acquired respiratory viruses and mycobacteria all contribute to the overall infectious burden (18-21).

Matching age, height, and size are established requirements in a lung allocation program to ensure successful transplantation and optimal outcomes. Conventionally, ABO blood group identical matching has been used in lung allocation. Sometimes an ABO compatible donor is used instead of an ABO identical one due to the scarcity in donors and the individual assessment of each recipient. Matching an ABO compatible donor rather than identical to the recipient did not reveal any negative consequences in our limited experience. It has been reported that recipients who receive ABO compatible matched allografts show a similar survival rate to recipients who receive ABO identical ones (22). ABO blood group compatible matching might potentially shorten lung transplant waiting list times. Other donor and recipient factors considered during matching include human leukocyte antigen status, gender, CMV, Epstein Barr virus and toxoplasma serology, smoking status, and screening through bronchoscopy and chest x-ray.

An overall shortage of lung donors remains a major limiting factor for the number of transplants performed annually (23). *Ex vivo* lung perfusion technology allows for lung perfusion and reconditioning in an environment which may reduce lung injury in some cases. This might allow for transplantation from donors previously deemed unsuitable (24,25). Recently, studies are emerging on new target temperature for static lung preservation. Conventionally, lungs are preserved on ice for about 6 to 9 hours before transplantation at 4°C. This limits availability of organs across locations where the distance would prolong ischemia time beyond the 9-hour threshold. It has been reported that increasing the static storage temperature to 10°C preserves mitochondrial function and reduces mitochondrial injury in animal models (26,27). A successful clinical application has been reported in five human lung transplant recipients after up to 16 hours of static storage at 10°C (26).

This was a non-randomized retrospective observational study with all the limitations associated with the study design. There were only 19 subjects in the study, making it a small sample size study; therefore, statistical comparisons were not feasible. The study might be underpowered to make strong conclusions on the matter. A larger sample with longer follow-up is warranted.

CONCLUSION

The results of our study have shown once again that lung transplantation is a feasible option for patients with end-stage lung disease refractory to medical therapy. Not only it is feasible but safe and effective. Even under the circumstances of the novel coronavirus pandemic, we managed to establish a lung transplantation program at our center. An imperative to perform life-saving lung transplantations was a major driver in this process. Regional hospitals and pulmonologists are urged to refer their patients with advanced stage non-malignant lung disease for lung transplantation evaluation to our center. Only with the support from referring physicians will the program continue its grow that long term.

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SAŽETAK

TRANSPLANTACIJA PLUĆA U KLINIČKOM BOLNIČKOM CENTRU ZAGREB U HRVATSKOJ

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Cilj: Transplantacija pluća postala je standard skrbi za pacijente s nizom nemalignih plućnih bolesti u završnom stadiju. Cilj ovog istraživanja bio je izvijestiti o sigurnosti i izvedivosti transplantacije pluća u Kliničkom bolničkom centru Zagreb u Hrvatskoj. ***Metode:*** U ovu retrospektivnu opservacijsku studiju uključeni su svi uzastopni pacijenti koji su bili podvrgnuti transplantaciji pluća u Kliničkom bolničkom centru Zagreb od travnja 2021. do prosinca 2022. godine. Jedini kriterij za uključivanje bio je kirurški zahvat transplantacije pluća. Zabilježene su demografske i operativne karakteristike pacijenata, kao i rani ishodi, uključujući 30-dnevnu smrtnost, boravak u bolnici, boravak na jedinici intenzivne njege, trajanje mehaničke ventilacije i incidenciju primarne disfunkcije presatka. Stupanj primarne disfunkcije presatka ocijenjen je na temelju kriterija Međunarodnog društva za transplantaciju srca i pluća 72 sata nakon transplantacije ocjenama od 0 do 3. ***Rezultati:*** Tijekom dvadesetjednomjesečnog razdoblja istraživanja transplantacija je uspješno primijenjena u 19 pacijenata. Nije bilo 30-dnevne smrtnosti. Dogodila se jedna kasna smrt 18 mjeseci nakon transplantacije. Medijan boravka u bolnici bio je 32 dana, u rasponu od 21 do 62 dana. Prosječno trajanje mehaničke ventilacije bilo je 105±58 h, a medijanboravka u jedinici intenzivne njege bio je 6 dana, u rasponu od 4 do 15 dana. Samo dva (11 %) bolesnika imala su primarnu disfunkciju presatka najvišeg stupnja 3. Od preostalih bolesnika 16 (84 %) ih nije imalo nikakav (stupanj 0), a jedan (5%) bolesnik imao je blagi, stupanj 1. ***Rasprava:*** U ovom članku prikazujemo naše početno iskustvo s transplantacijom pluća. Transplantacija pluća bila je jedina od transplantacija solidnih organa koja se donedavno u Hrvatskoj nije rutinski izvodila, s napomenom da je prva transplantacija pluća u Hrvatskoj učinjena još 2003. godine u Klinici za torakalnu kirurgiju Jordanovac, ali se program transplantacije nije tada nastavio. Od travnja 2021. godine transplantacije pluća rutinski se izvode u našem centru i hrvatski pacijenti više ne moraju putovati u inozemstvo radi transplantacije pluća.Sveukupni nedostatak donora pluća i dalje je glavni ograničavajući čimbenik za broj transplantacija koje se izvode na godinu. Svega 20%-30% doniranih pluća iskoristi se za transplantaciju. Potrebno je kontinuirano unaprjeđenje i razvoj strategija koje će povećati broj donora i uporabljivih plućnih presadaka. ***Zaključak:*** Naši rezultati pokazuju da se transplantacija pluća sigurno izvodi u Kliničkom bolničkom centru Zagreb. Početni rezultati bez operativnog mortaliteta su ohrabrujući. Daljnje praćenje i iskustvo potrebni su za donošenje zaključaka o dugoročnim ishodima naših pacijenata s transplantacijom pluća.

Ključne riječi: transplantacija pluća, završni stadij bolesti pluća, ekstrakorporalna membranska oksigenacija, primarna disfunkcija plućnog presatka, preživljenje, operativna smrtnost