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Research Article

Lung Transplantation in A Low-Volume Center: The Antwerp University Hospital Experience

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Introduction

Lung transplantation remains the treatment of choice for selected patients with end-stage pulmonary diseases, such as Chronic Obstructive Pulmonary Disease (COPD), alpha1-antitrypsin deficiency emphysema, bronchiectasis (Brect), Cystic Fibrosis (CF), interstitial fibrosing lung diseases such as idiopathic pulmonary fibrosis (IPF), and pulmonary arterial hypertension. The possibility of lung transplantation may be offered in these patients when no other treatment options are available to improve their clinical status, when there is no other organ dysfunction and they fulfill classical acceptance criteria for transplantation without clear contra-indications [1]. Since the beginning of successful lung transplantation in the early nineties, results have improved with a 1-, 3- and 5 y survival of 81.4%, 66.8% and 55.8% respectively [2]. In a more recent era (2008-2013) the 1-y and 5-y survival further improved to 85% and 70% respectively [3]. The outcome of lung transplantation seems to be dependent on several significant additional risk factors that may negatively impact the 1- and/or 5-y survival such as prior lung surgery, performing a single lung transplant compared to a double lung transplant, the underlying diagnosis, with IPF having the worst outcome, ventilator dependency, extracorporeal membrane oxygenation started before transplantation, hospitalization, older donor and recipient age, higher recipient BMI. Next to classical donor and recipient specific risk factors, also a lower center transplant volume over the last 3 y has been identified as a significant risk for worse outcome [3]. This was further corroborated in a recent study by Jawitz et al. in which the authors demonstrated that a low volume center (defined as <40 lung transplantations per year) was associated with an increased early mortality [4]. Although it seems acceptable that less experience may lead to worse outcome results, there are conflicting data in the literature. Indeed, in a study by Yang et al., the authors published excellent results with a 1-, 3-

and 5-y survival of 88, 72 and 72% respectively, whereas only 25 lung transplantations were performed between 2006 and 2012 [5]. At the same time the official transplantation report from Taiwan, published in 2011, mentioned a 1-y and 3-y survival of 65 and 56% respectively [5], demonstrating indeed huge differences in outcome.

The literature therefore seems to present different outcome results from low volume lung transplantation centers, therefore, we report here the results of the Antwerp University hospital (Belgium) lung transplantation program, also representing a low volume center.

Keywords: CLAD; Low volume center; Lung transplantation; Survival

History of The Antwerp University Hospital (UZA) Lung Transplantation Program

The history of lung transplantation in the Antwerp University Hospital is very atypical, with the first lung transplantation performed in 1997, however, till the end of 1999 only 5 lung transplants were carried out. Then the program was interrupted for the first time due to staffing problems, with complete loss of referrals. In 2003, the program was restarted and again interrupted in 2011 for the same reasons. In that time span only 14 procedures were performed. After an interval of 4y, the program was again re-initiated in 2015 and interrupted in 2016, with 15 transplantations performed. It was then decided to re-invest in a dedicated team of physicians and after an external observation and training period, the program restarted in 2019 and till the end of 2023, 25 procedures were performed in 24 patients (1 redo operation), meaning 2-7 lung transplantations per year. The results of this last period will now be further elaborated and contrasted with the results in the period 2015-2016 (15 procedures). These two periods also represent two different teams of surgeons and transplant physicians, although the follow up protocols and immunosuppressive treatments were in general comparable.

Patients and Methods

Study Protocol

We performed a retrospective study including all patients who underwent lung transplanted between Jan 1st 2015 and Dec 31st 2023, with follow up till June 30th, 2024. All necessary data were retrieved from the patient charts and from the UZA lung transplantation database. The study was approved by the Institutional review board of the Antwerp University Hospital, with the informed consent waved.

Recipient and Donor Selection

All recipients were selected according to the international selection criteria and there were no exceptions to these criteria (1, 6). Donor lungs came from brain death donors (DBD, n=29) and from donation after cardiocirculatory death donors (DCD, n=11, all DCD-III) (7), according to the existing law and ethical issues in the respective donor countries. The Eurotransplant organization was responsible for the selection of the best matched receptor, once a possible lung donor was announced in their network.

Lung Transplant Protocol

All patients underwent induction therapy with basiliximab and were started on triple immunosuppression consisting of tacrolimus, mycophenolate and corticosteroids. Antiviral prophylaxis was provided with aciclovir/ganciclovir depending on Cytomegalovirus (CMV) status of donor and receptor for a minimum period of 3 months, and trimethoprim/sulfamethoxazol was used as prophylactic agent against Pneumocystis infection. Inhaled (liposomal) amphotericin B was used to prevent fungal infections up to 3 months after transplantation. Antibiotics were based on pre- and perioperative cultures. After hospital discharge, patients were regularly seen at the outpatient clinic, according to the local protocol. During every control visit, blood sampling with calcineurin trough level, spirometry and chest X ray were performed. A chest CT scan was routinely done at discharge (around 4-6 weeks), 3, 6, 12, 18 and 24 months and further yearly or in between in case of new opacities on chest X ray, new (respiratory) symptoms and/or FEV_1 decline. Bronchoscopy with transbronchial biopsies and broncho-alveolar lavage was performed after 4-6 weeks, 3, 6, 12 and 24 months, thereafter or in between only per indication (see above).

Statistical Analysis

Continuous data are expressed as means ± standard deviation. Proportions are presented as number and/or percentage, with a range where applicable. Cumulative survival and Chronic Lung Allograft Dysfunction (CLAD)-free survival are determined via the Kaplan-Meier method. Between group variables were compared with a Mann-Whitney U test. Prism software (Graphpad Prism® 8.4.3; 2024, Boston) was used for statistical analysis. A p value of <0.05 was considered significant.

Results

All patients from 2015-2023 (40 procedures in 38 patients)

Patient and donor characteristics are summarized in table 1. There were 38 first lung transplantations, and 2 redo transplantations because of end-stage CLAD. The mean follow up is 1266 (± 1030) days. The overall 1-, 3- and 5-y patient survival is 87, 80 and 75% respectively with a median survival of 8 years. The 1-y conditional survival is 92 and 85% respectively at 3 and 5 years (Figure 1). The CLAD-free survival in 34 evaluable patients (living > 3 months) was 100, 96, 87 and 55% respectively at 1, 3, 5 and 7 years post

transplantation (Figure 2). Since there seems to be a difference in outcome between the two different era's, these were also analyzed separately.

2015-2016 era (15 transplant procedures in 15 patients)

Data are summarized in Table 1. All patients (7 males) underwent a double lung transplantation via clamshell incision. The underlying indications were: COPD (n=6), IPF (n=3), CF (n=2), occupational-induced ILD, alpha-1 antitrypsin deficiency, non-CF bronchiectasis and veno-occlusive disease (VOD) (all n=1). The mean receptor and donor age were 52 (±16) and 49 (±12) y respectively. There were 7 male and 8 female donors, with 1 female to male and 2 male to female transplants. The mean waitlist time was 118 (±80) days. A young patient with IPF was transplanted from ECMO on the intensive care unit (ICU). Ten of 15 patients (66.7%) died during the follow up period, after a mean of 1307 (±1342) days, due to surgical/perioperative complications (n=4, 26.6%), infection (Tuberculosis, n=1 and Covid-19, n= 2), acute lung failure due to antibody mediated rejection (n=1) and CLAD (n=2). A mean number of 4 transbronchial biopsies sessions were performed per patient (range 0-11). One patient had a single episode of A2 rejection, whereas 1 had recurrent A2 and 3 had recurrent A1 acute rejection [8], all treated with a 3-day course of high dose IV pulsed steroids, followed by an oral taper and optimalisation of their immunosuppressive drug treatment. The mean follow up time was 1878 (±1364) days. Survival at 1, 3 and 5 y is 73, 67 and 60% respectively (Figure 1). Conditional 1-y survival is 90 and 82% at 3 and 5 years respectively. CLAD-free survival is 100% at 5 years in 11 evaluable patients (living > 3 months post procedure), however, later on most patients developed CLAD as evident from Figure 2.

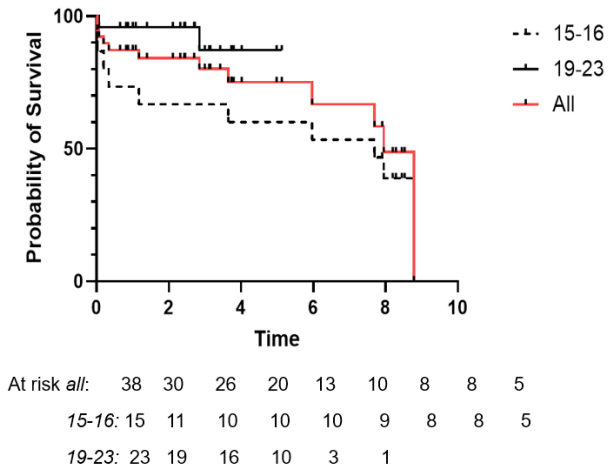

Figure 1: Patient survival (in years) from 2015-2023 (n=38)* and in 15-16 (n=15), and 2019-2023 (n=24)**. There is a significant difference in survival between 15-16 and 19-23 (p=0.048). * 2 redo transplant patients in the whole period; ** 1 redo patient in this period, after a first transplant in the same period and another redo after a first transplant in the previous period [15,16].

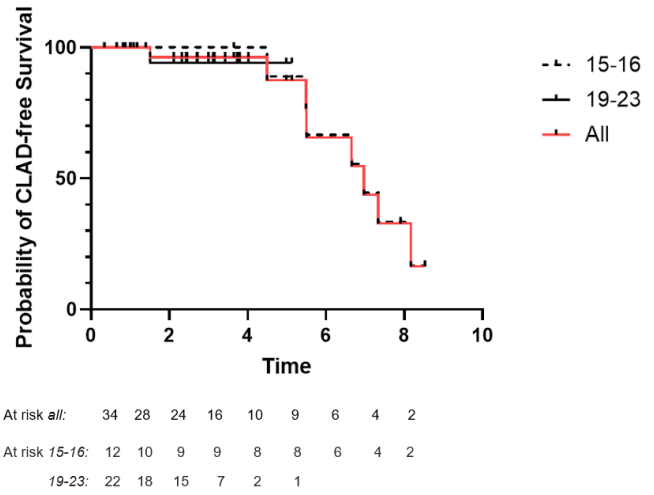

Figure 2: Clad-free survival (in years) from 2015-2023 (n=34 evaluable patients) and in the 2015-2016 (n=12 evaluable patients) and 2019-2023 era (n=22 evaluable patients).

Characteristic	**All (2015-2023) (n=40)**	**2015-2016 (n=15)**	**2019-2023 (n=25)**	**P value**
Receptor age (y)	55 (±14)	52 (±16)	55 (±12)	NS
Receptor sex (M/F)	14/26	7/8	7/18	NS
Receptor BMI	23.0 (±3.6)	23.2 (±4.5)	22.8 (±3.1)	NS
Diagnosis:				
COPD	21 (52%)	6 (40%)	15 (60%)	
ILD	8 (20%)	4 (26.7%)	4 (16%)	
CF	3 (8%	2 (13.3%)	1 (4%)	NS
PAHT	2 (5%)	1 (6.7%)	1 (4%)	
Redo transplant	2 (5%)	0	2 (8%)	
Other	4 (10%)	2 (13.3%)	2 (8%)	
Waiting time (days)	162 (±182)	118 (±80)	187 (±219)	P=0.05
Transplant procedure:				
Double lung	38	15	23	NS
Single lung	2	0	2	
Donor age (y)	45 (±16)	49 (±12)	45 (±16)	NS
Donor Sex (M/F)	16/24	7/8	9/16	NS

Donor BMI (kg/m^2)	25.0 (±5.4)	24.8 (±4.2)	25.1 (±6.1)	NS
Type of Donor (DBD/ DCD)	29/11	12/3	17/8	NS
Causes of receptor mortality: Surg./perioperative CLAD ALF due to AMR Infection	 6 (15%) 2 (5%) 1 (2.5%) 3 (7.5%)	 4 (26.6%) 2 (13% 1 (6%) TBC (n=1) COVID-19 (n=2)	 2 (8%) - - - -	-
LAS	39 (30-90)	41 (31-90)	37 (30-79)	NS
Mean follow-up (days)	1266 (±1030)	1878 (±1364)	899 (±515)	P=0.0038
TBB sessions	3.6 (0-11)	4 (0-11)	3.3 (0-10)	NS
Patient Survival (%) @ 1 y 3 y 5 y	 87 80 75	 73 67 60	 96 87 87	P=0.048

Numbers with standard deviation or percentage or range in brackets. BMI = body mass index, COPD = chronic obstructive pulmonary disease, ILD = interstitial lung diseases (including idiopathic pulmonary fibrosis), CF = cystic fibrosis, PAHT = pulmonary arterial hypertension, DBD = donation after brain death, DCD = donation after cardiocirculatory death, Surg = surgical, CLAD = chronic lung allograft dysfunction, ALF = acute lung failure, AMR = antibody mediated rejection, TBC = Tuberculosis, LAS = lung allocation score, TBB = transbronchial biopsy. P value compares era 2015-16 with 2019-23

Table 1: Characteristics of donors/receptors.

2019-2023 era (25 transplant procedures in 24 patients)

All patients (7 males), except 2, underwent a double lung transplantation (18 clamshell incisions), with as underlying disease: COPD (n=15), interstitial lung disease (n=4), redo transplantation for bronchiolitis obliterans syndrome (n=2), CF, sarcoidosis, pulmonary arterial hypertension and pleuroparenchymal fibroelastosis following graft versus host disease (all n=1). The mean receptor and donor age were 55 (±12) and 45 (±16) y. There were 9 male and 16 female donors, with 5 female to male and 3 male to female transplantations. The mean waitlist time was 187 (±219) days. One patient with IPF was transplanted while being ventilated on the ICU. The mean follow up time was 899 (±515) days, which was significantly shorter compared to the first era (p=0.0038). Patient and donor characteristics are summarized in table 1. A mean of 3.2 (range 0-10) transbronchial biopsy sessions were performed. Seven patients developed a single episode of A1 rejection, 3 an A2, whilst 2 patients had recurrent A2 and 1 patient recurrent A1 acute rejection [8]. These episodes were all treated as mentioned above. Cumulative graft survival at 1, 3 and 5 y is 92, 85 and 85% respectively, whereas patient survival was 96, 87 and 87% respectively (Figure 1). The conditional 1-y survival is 90% at 3 and 5 years. Two patients died due to perioperative complications (8%). No other deaths have occurred. There is a significant improvement in survival in the 2019-2023 era compared to 2015-2016 (p=0.048). The CLAD-free survival is 100% at 1 y and 96% at 2, 3, and 4 years (Figure 2).

Discussion

Although the first lung transplantation in the Antwerp University Hospital was already performed in 1997, there have been many ups and downs in the program. In fact, during the first 18 years, only 18 lung transplantations were performed, by the same surgeon but

with an unstable follow up team. This led to multiple interruptions of the program. Despite of all these problems, there was a learning curve that became of interest later in the program, as evidenced by this report. In 2015 there was another start up, with a different team compared to the latest era (2019 till now). Despite all these above cited difficulties, in the current era (from 2019 on) the results are excellent, although the transplant experience remains rather low (with only a maximum of 7 lung transplantations per year). The team is, however, stable now, and the lead surgeon (JMHH) is much more experienced as a thoracic surgeon with skills in sleeve resections, tracheal surgery and aortic procedures. Clam shell incision is avoided as much as possible (72% in the latest era versus 100% in 2015-16), lobar and redo transplantation were also introduced, and this, all together, results in a good survival.

The survival from 2015 on is better that the internationally registered results from ISHLT, certainly when we analyze the figures conditional to 1 y survival, where in our program the 5-y survival was 85%, compared to 70% in the ISHLT registry database [3]. In the 2019-2023 era, 1-, 3- and 5-y patient survival is also better compared to ISHLT data: 96, 87 and 87% versus 85, 69 and 59% respectively [3,9,10]. There is a significantly improved survival in the latest era, compared to the previous era (p=0.048), which is mainly due to a lower perioperative mortality in the latest period (8% versus nearly 27%) since 1-y conditional survival is comparable up to 5 years after the procedure. Otherwise there are no significant differences in donor and receptor characteristics between the 2 periods, except the waiting time that was longer in the latest era. Although an increasing number of DCD donors was used in the latest era, (32% versus 20%), there was no significant difference with the previous era, moreover, there is no evidence that this type of donors leads to a different receptor survival [11].

These excellent results contradict the ISHLT registry data, in which it is clearly stated that a low volume center is a risk factor for a worse survival outcome compared to a high output center [4,5]. Also other studies have pointed to the role of the center volume. For instance in the paper by Yang et al., including >10,000 patients from the UNOS registry at 71 transplant centers, the mean annual center volume was 22/y, and the authors demonstrated that a higher volume center (>33 cases per year) was associated with better 1-y survival, with no additional benefit with further increase in center volume. They also showed that only 23/71 centers reached the volume threshold of at least 33 cases per year [12]. In another study from Kilie et al., the authors showed that low volume centers (cut off 33 cases per year) were found to have a 1.56 increased risk for 90 day, and a 1.1 and 1.22 increased risk for 1-year mortality (excluding 90 day mortality) and 10 year mortality (excluding 1 y deaths) [13]. On the other hand, some authors point to a good outcome, even with a low volume of lung transplantations per year. These data are, however, mainly coming from Asian cohorts. In a first paper, Yang et al. published their results from 25 consecutive double lung transplantations, performed over 6.5 years. They showed a survival of 88, 72 and 72% at 1, 3 and 5 y respectively [5]. Chida et al. reported their results with 21 lung transplantations performed over a 12 year period, with a 5-y survival of 84.8% [14]. In a recent paper, Chida et al reported the results of all lung transplantations (n=658) in Japan performed between 2000 and 2021, divided into low volume (<8 lung transplantations per year, n=5 centers) and higher volume centers (≥8 lung transplantations per year, n=4 centers). There was no difference in 90 day and 1-y mortality between higher and lower volume centers, taking into account that their definition of high volume (>8 procedures/y) still represents a rather low volume. Moreover, case volume did not reveal a significant difference in long-term survival between the high and low volume centers although the low volume centers had wide differences for long-term outcomes [15].

These papers and our own data only proof that also a low volume center with a dedicated team and a well-organized follow up can present good results, sometimes even better than in some high volume centers, where the number of procedures and patients in follow up may exceed the center's capacity, leading to no additional benefit with increasing volume [13]. We not only present good survival data, also our CLAD-free survival is high, although we must recognize that patient numbers are still low and follow up in the second era is somewhat short to take real conclusions. In fact, in the first evaluated era, we had no CLAD during the first 5 years, but afterwards, most patients developed CLAD, albeit late in their course after transplantation. This, however, did not lead to a high prevalence of CLAD-related mortality (n=2). In the second era, CLAD prevalence is also low, however, conclusions remain restricted due to the low patient numbers and shorter follow up period. If we consider all 34 eligible patients from 2015 on (surviving >3 months) and a mean follow up of 1442 (±982) days, then the CLAD-free survival is 100, 96 and 87% at 1, 3 and 5 y respectively. In a recent comparative trial between cyclosporin and tacrolimus as first line treatment, CLAD occurred in 39% in the cyclosporin group and 13% in the tacrolimus group at 36 months post transplantation [16]. This data is consistent with our CLAD prevalence, although it is commonly accepted that the prevalence of CLAD is about 30% after 3 and 50% after 5 years [3]. We have no explanation for our relative low prevalence of CLAD. Our immunosuppressive protocol is not different from other centers, although we do use tacrolimus as first line calcineurin blocker. We hypothesize that the good education of our patients, the very strict instructions to call or to come to the emergency department (with a low travel distance) in case of a new problem and our overall close follow-up may have a role to play.

In Conclusion

Although generally accepted that outcome results are worse in a low volume center, we can offer hope for other low volume lung transplantation centers as our results are excellent and even superior compared to the ISHLT registry database. Strict patient and donor selection, adequate surgery, follow up and in general, a dedicated team, is of utmost importance and may not only benefit individual patients but certainly also all important outcome measures in a low volume center.

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