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ORIGINAL CLINICAL SCIENCE

# Long-term outcome and bridging success of patients evaluated and bridged to lung transplantation on the ICU

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**KEYWORDS:**
lung transplantation;
survival;
CLAD;
ICU;
bridging

**BACKGROUND:** Evaluating and bridging patients to lung transplantation (LTx) on the intensive care unit (ICU) remains controversial, especially without a previous waitlist status. Long term outcome data after LTx from ICU remains scarce. We compared long-term survival and development of chronic lung allograft dysfunction (CLAD) in elective and LTx from ICU, with or without previous waitlist status.

**METHODS:** Patients transplanted between 2004 and 2018 in 2 large academic Dutch institutes were included. Long-term survival and development of CLAD was compared in patients who received an elective LTx (ELTx), those bridged and transplanted from the ICU with a previous listing status (BTT), and in patients urgently evaluated and bridged on ICU (EBTT).

**RESULTS:** A total of 582 patients underwent a LTx, 70 (12%) from ICU, 39 BTT and 31 EBTT. Patients transplanted from ICU were younger than ELTx (46 vs 51 years) and were bridged with mechanical ventilation ($n = 42$ (60%)), extra corporeal membrane oxygenation ($n = 28$ (40%)), or both (n = 21/28). Bridging success was 48% in the BTT group and 72% in the EBTT group. Patients bridged to LTx on ICU had similar 1 and 5 year survival (86.8% and 78.4%) compared to elective LTx (86.8% and 71.9%). This was not different between the BTT and EBTT group. 5 year CLAD free survival was not different in patients transplanted from ICU vs ELTx.

**CONCLUSION:** Patients bridged to LTx on the ICU with and without prior listing status had excellent short and long-term patient and graft outcomes, and was similar to patients electively transplanted.
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Lung transplantation (LTx) is a lifesaving treatment in carefully identified patients with end-stage lung disease with respiratory failure.[1] Patients are referred for LTx when there is chronic, progressive end-stage lung disease despite optimal treatment.[2] The majority of patients receive a LTx electively, after rigorous evaluation and variable time on the waiting list, meanwhile receiving the best disease specific care at home until donor lungs become available.

Donor shortage has led to increased time on the waiting list and significant disease progression during the waiting period with respiratory failure, occasionally resulting in requirement of admission to the intensive care unit (ICU) for mechanical support as a bridge to LTx. During the last decades the number of patients bridged on ICU to LTx by either mechanical ventilation or extra-corporeal membrane oxygenation (ECMO) has increased.[3] Where in 2003, 3.7% of patients in the US were transplanted from the ICU, this was 16.5% in 2019.[4,5] A similar trend is observed within the Eurotransplant region.[6] This might be the result of the introduction of the Lung Allocation Score (LAS) to prioritize patients for LTx, by substantial improvement in ECMO-techniques, and increased experience with bridging patients to LTx.

Bridging patients on ICU to LTx is accepted, but remains debated, mainly due to reported inferior 1 year survival rates when compared to electively transplanted patients,[7] despite increasing success in the more recent era.[8]

Especially controversial is LTx from ICU in patients without a previous listing status requiring urgent evaluation and listing. Patients with unexpected acute respiratory failure requiring mechanical ventilation or ECMO, are not universally considered for LTx unless they have been evaluated previously. The main arguments are the limited evaluation potential of the patient, high mortality risk, limited organ availability and scarce data on post-transplant survival or transplant function.[9] Nevertheless, some centers report acceptable outcome in selected cases of urgent evaluation and LTx on ICU.[10,11] In this retrospective study we aimed to assess long term survival and chronic lung allograft dysfunction (CLAD) of patients bridged to LTx on ICU (BTT) in comparison to elective LTx (ELTx). In addition, we compared survival and transplant function of the BTT group to patients without a previous listing status who underwent urgent evaluation and bridging to LTx on ICU (EBTT).

## Material and methods

### Patients

The Medical Ethical Commission approved the study (NL-202000736), and according to the Central Committee on Research Involving Human Subjects (CCMO), this retrospective study is beyond the scope of the Medical Research Involving Human Subjects Act (WMO). The study complies with the ISHLT Ethics Statement. All consecutive patients who underwent a single or bilateral LTx in the University Medical Center Groningen (UMCG) or in the Erasmus Medical Center (Erasmus MC) in the Netherlands between April 2004 and December 31, 2017 were included. Written informed consent was received from all patients or their legal first-degree relatives. Data from patients who died or were removed from the waiting list, including those urgently evaluated and bridged for LTx on the ICU, was collected. Patients were categorized: ELTx; elective LTx, BTT: bridging to LTx on ICU with a previous listing status, ELBTx; evaluated and bridged to LTx on ICU without a previous listing status.

### Evaluation for LTx

Diagnostic evaluation was performed in all recipients according to the International Society of Heart and Lung Transplantation (ISHLT) consensus document.[2] All patients were discussed in the multidisciplinary LTx team (MDT), prior to listing. The MDT involved at least an intensivist, anaesthesiologist, cardiothoracic surgeon and LTx physician. Patients bridged on ICU were closely monitored on a daily basis. Clinical deterioration of to-be-bridged patients resulted in re-assessment and discussion in the MDT. Patients no longer eligible for LTx were removed from the waiting list.

For potential LTx recipients without a previous listing status, one of the transplant physicians would routinely visit the patient on the ICU in the referring center, and discuss the LTx trajectory with the referring physician, intensivist, relatives and if possible with the patient.

Patients considered for urgent evaluation and LTx had isolated respiratory failure, with no realistic chance of recovery. Left heart failure, significant coronary disease, obesity (body mass > 30kg/m2), active or recent malignancy, renal failure including renal replacement therapy and significant liver injury were all absolute contra-indications. For urgent evaluation age of 60 years was the upper limit. Patients with a combination of relative contra-indications such as diabetes, hypertension and other co-morbidities were not considered. Patients unable to wean from non-invasive or invasive ventilation after prolonged treatment were considered, under the circumstances that a patient had no infection or the time to clear an infection; based on inflammatory markers, negative cultures including broncho-alveolar lavage (BAL), negative viral nasopharyngeal swab or viral diagnostics on BAL.

Severe neurological impairment should have been excluded in order to qualify for LTx from the ICU. Therefore, patients were preferentially awake during bridging so they could be mobilized daily. If awake bridging was not feasible, daily wake up calls were required and clinical condition was more frequently and strictly re-assessed. If blood transfusions were necessary, weekly checks of panel reactive antibody formation were performed. Highly sensitized recipients were no longer deemed candidates. All potential transplant candidates were discussed in the MDT before transferring the patient to the transplant center for further evaluation, listing and bridging to LTx. The decision to list patients was made unanimously taking all different views and standpoints of the team members into account.

Evaluation of patients on the ICU was as similar as possible as patients that were electively assessed. Evaluation included extensive blood-tests; white blood count, renal and liver parameters, vitamin status, PSA, M-protein screening, virology status, 24 hours urine examination and panel reactive antibodies. Extensive cultures were performed. In addition, all patients underwent CT scans of thorax, abdomen and CT sinuses and brain. If indicated additional abdominal ultrasound and liver fibroscan were performed. All patients with pulmonary fibrosis underwent a total body PET-CT. All patients had a right hearth catheterization and if over 50 years of age a coronary angiogram was performed. Electrocardiogram, trans thoracic or trans-oesophageal echocardiography were performed to assess cardiac function. Dental specialists assessed and treated potential oral infectious foci. Gastro and/or colonoscopy was only performed upon indication.

## Bridging to LTx

Patients were bridged on ICU with mechanical ventilation (MV), extra-corporeal membrane oxygenation (ECMO) or a combination of MV and ECMO. ECMO was performed with a PermanentLife Support (PLS) or Cardiohelp HLS module 7.0 (Maquet, Rastatt, Germany). Percutaneous or surgical jugular, subclavian or femoral arteries (17-21-F) or veness (21-29-F) were cannulated. Avalon cannulas (AVALON ELITE Bi-Caval Dual Lumen Catheter, Maquet) were used in 10 patients. Unfractionated heparin was administrated during ECMO with a partial thromboplastin time between 60 and 80 seconds.

## Transplant care

Routine pre-transplant evaluation, waiting list visits, and post-transplant follow-up were performed in either the University Medical Center Groningen or in the Erasmus University Medical Center. Postoperatively all patients received standard immunosuppression according to the local protocol; consisting of 20 mg of Basiliximab induction on day 0 and 4, and maintenance immunosuppression; tacrolimus, prednisolone and mycophenolate mophetil. Patients received prophylactic therapy for pneumocystis pneumonia; cotrimoxazole, CMV: (val)ganciclovir (5mg/kg OD) and antifungal: non-liposomal Amphotericin B nebulization.

Chronic lung allograft dysfunction (CLAD), the obstructive type bronchiolitis obliterans syndrome (BOS), restrictive allograft syndrome (RAS) and mixed BOS/RAS phenotype were defined according to the international ISHLT/ATS/ERS clinical practice guideline.[12]

## Statistical analysis

Continuous variables were presented as median [25th-75th percentiles], and categorical variables as numbers ($n$) with percentages (%). Patient, clinical and donor characteristics were collected by use of electronic patient records. Patients characteristics included age, sex, indication for transplantation (divided in emphysema or alfa-1-antitrypsin deficiency, cystic fibrosis or bronchiectasis, pulmonary fibrosis, pulmonary hypertension, transplantation or other), and type of transplantation (unilateral vs bilateral). Clinical characteristics included LAS score at transplant, high-urgent status or high LAS (>50) status, clinical wait for transplantation and if yes duration of the clinical wait for LTx, BTT using ECMO or mechanical ventilation, duration of ICU admission and duration of hospital admission. Clinical wait for LTx was calculated from the first day of ICU admission in our centers to time of LTx. Duration of ICU admission and hospital admission were calculated from time of LTx to ICU discharge and hospital discharge, respectively. Donor characteristics included donor age, sex, cause of death (divided in intracranial hemorrhage, trauma, cardiac arrest, brain tumor, suicide, meningitis or other), donor smoking status and if ever smoker number of packyears, donor type (heart-beating as opposed to non-heart-beating) and donor PO2. Differences between groups were compared using a Fisher's exact test for categorical variables and ANOVA or Mann-Whitney U test for continuous variables depending on the distribution. Normality of continuous variables was tested using the Shapiro-Wilk test. Survival and freedom from CLAD were assessed by Kaplan Meier analyses and statistical testing was performed using a log-rank test. Patients that underwent re-transplantation were censored in the survival analyses. In the analyses on freedom from CLAD patients were censored at time of death or end-of follow-up.

We subsequently performed Cox-regression analyses on patient survival and CLAD-free survival adjusting for between-group differences. Statistically significant differences in patient characteristics (age, gender, indication, type of transplantation) and donor characteristics (donor age, donor type and donor packyears) were incorporated in the adjusted models. Due to limited numbers it was only feasible to adjust the cox-regression model comparing BTT and EBTT for patient differences. Differences in clinical characteristics (such as clinical wait) were not incorporated as these were related to and colinear with the test groups. Hazard ratios (HR) with [95% confidence intervals] were reported as well as $p$-values. Two-sided $p$-values $< 0.05$ were regarded as statistically significant. All statistical analyses were performed with Stata version 11.2.

## Results

A total of 693 patients were referred, evaluated electively, and listed for LTx (Figure 1). During the studied time period 551 transplantations were performed in this group. In the same period, 43 patients were referred for urgent evaluation, of whom 31 were eventually transplanted, resulting in a total number of 582 transplantation between 2004 and 2017.

Of the referred and electively evaluated and listed patients, in total 100 (14.4%) patients died on the waiting list or were delisted. In total, 51 patients were delisted. Most patients were delisted because they were either clinically stable or showed improvement of lung function (e.g., due to novel CFTR treatment) and often requested by the patient ($n$ = 11), followed by development of malignancy ($n$ = 10) or development of cardio-vascular events with end-organ failure as a consequence ($n$ = 9). Less frequently patients were delisted due to relapse in smoking or drug abuse ($n$ = 2), age $\geq$ 65 ($n$ = 4), BMI 30kg/m2 ($n$ = 3) development of renal failure ($n$ = 2), uncontrolled infection ($n$ = 3), osteoporotic fractures limiting mobility ($n$ = 2) psychiatric dysregulation ($n$ = 2) and deconditioning ($n$ = 3).

Eighty-one patients out of this group (13.7%) were bridged on ICU. Thirty-nine (48%) patients received a LTx, 42 (52%) patients died on ICU while waiting.

## Waiting list mortality

Characteristics of patients deceased on the waiting list are shown in Table 1. In total 154 of 748 (20.6%) of all

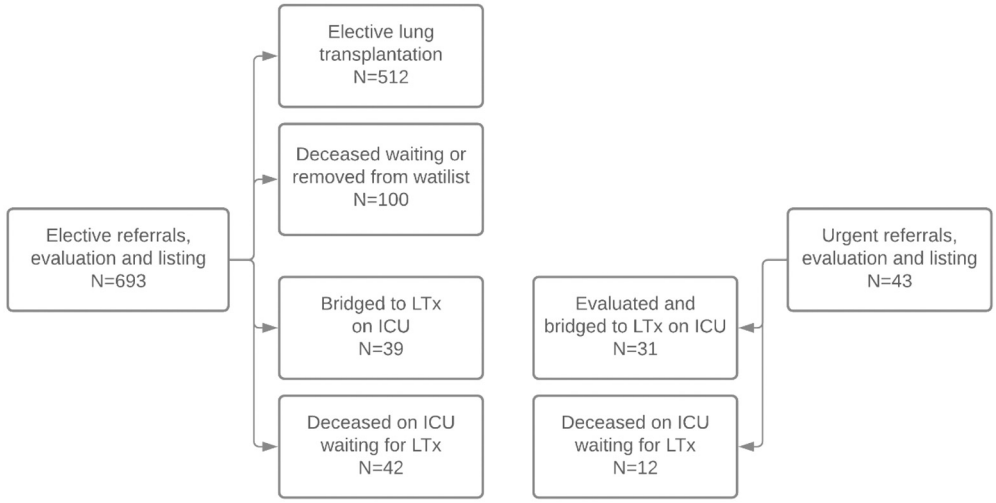


**Figure 1** Flowchart of patients included.

the patients referred and listed did not make it to LTx. The majority of these 154 patients had COPD. Patients with a previous listing status and not bridged to LTx were on average older than patients who were intentionally bridged. Pulmonary fibrosis and cystic fibrosis (CF) were the most common diagnoses in the patients who were deemed fit for a bridging trajectory on the ICU but did not make it to transplant. From the 43 patients in the EBTT group 12 (28%) patients died waiting, due to multiple organ failure ($n$ = 3), sepsis ($n$ = 4), Right heart failure ($n$ = 3), pneumothorax ($n$ = 1), and post anoxic encephalopathy ($n$ = 1).

## Lung transplantation

Between 2004 and 2018 a total of 582 patients received a LTx (Table 2). Seventy patients (12%) were transplanted from the ICU. The patients bridged on the ICU were more frequently male, younger and received more frequently a bilateral LTx compared to the patients in the ELTx group. In the ELTx group the majority were COPD patients (42.3%), followed by pulmonary fibrosis (31%) and CF (15%). In the patients transplanted from ICU pulmonary fibrosis (48.6%) was the most common diagnosis followed by COPD (25.7%) and CF (13.9%). The LAS was significantly higher in the patients bridged to LTx on ICU compared to ELTx (median 84.4 vs 34.7, $p < 0.001$). The median time of mechanical support pre-transplantation was 26 [13-48] days. Patients transplanted electively had a significantly shorter post-operative stay on the ICU, and total hospital admission time when compared to patients transplanted from ICU. Donors of patients transplanted from ICU were on average younger, but had smoked on average more packyears when compared to donors for the patients in de ELTx group.

## Bridging to LTx on the ICU

From the seventy patients that were transplanted from ICU, 39 (56%) were in the BTT-group and 31 (44%)

**Table 1** Characteristics of Patients Deceased or Removed From the Waiting List in ELTx, BTT and EBTT Groups

| | Deceased or removed ELTx group ($n$ = 100) | Deceased BTT group ($n$ = 42) | Deceased EBTT group ($n$ = 12) | $p$-value |
|---|---|---|---|---|
| Patient Characteristics | | | | |
| Male gender | 36 (36%) | 18 (42.9%) | 6 (50%) | 0.50 |
| Age (years) | 58 [49-64] | 48 [36-53] | 50 [28-58] | <0.001 |
| Indication | | | | |
| Emphysema/A1AD | 50 (49.5%) | 3 (7.1%) | 0 (0%) | <0.001 |
| Cystic Fibrosis/ bronchiectasis | 4 (4%) | 16 (38.1%) | 4 (33.3%) | |
| Pulmonary Fibrosis | 23 (22.8%) | 20 (47.6%) | 7 (58.3%) | |
| Pulmonary hypertension | 23 (22.8%) | 3 (7.1%) | 1 (8.3%) | |
| Re-transplantation | 0 (0%) | 0 (0%) | 0 (0%) | |
| Other | - | - | - | |
| Clinical wait for LTX | 7 (6.9%) | 42 (100%) | 12 (100%) | <0.001 |
| Duration clinical wait (days) | 16 [2-29] | 12 [5-20] | 24 [15-39] | 0.88 |
| Bridging with ECMO | - | 15 (36%) | 8 (67%) | 0.07 |

**Table 2** Patient Characteristics Transplanted Electively and From ICU

| | ELTx ($n$ = 512) | BTT /EBTT ($n$ = 70) | $p$-value |
|---|---|---|---|
| Recipient Characteristics | | | |
| Male gender | 246 (46.9%) | 43 (61.4%) | 0.03 |
| Age (years) | 51.4 [45.9-60.3] | 45.8 [35.6-57.0] | <0.001 |
| Indication | | | 0.005 |
| Emphysema/A1AD | 222 (42.3%) | 18 (25.7%) | |
| Cystic Fibrosis/bronchiectasis | 79 (15.0%) | 11 (13.9%) | |
| Pulmonary Fibrosis | 163 (31.0%) | 34 (48.6%) | |
| Pulmonary hypertension | 45 (8.6%) | 2 (2.9%) | |
| Re-transplantation | 5 (1%) | - | |
| Other | 11 (2.1%) | 5 (7.1%) | |
| Type of transplantation | | | 0.002 |
| Unilateral | 108 (20.5%) | 4 (5.7%) | |
| Bilateral | 406 (77.2%) | 66 (94.3%) | |
| LAS score at transplant | 34.7 [32.1-40.1] | 84.4 [49.5-90.3] | <0.001 |
| HU status or high LAS (>50) | 151 (29.6%) | 60 (85.7%) | <0.001 |
| Clinical wait for LTX | 47 (9.2%) | 70 (100%) | <0.001 |
| Duration clinical wait (days) | 57 [34-120] | 26 [13-48] | <0.001 |
| LTX from ECMO | - | 28 (40%) | |
| LTX from MV | - | 42 (60%) | |
| Duration ICU admission (days) | 5 [3-18] | 18 [8-33] | <0.001 |
| Duration hospital admission (days) | 32 [24-54] | 52 [33-91] | <0.001 |
| Donor Characteristics | | | |
| Heartbeating donor | 341 (68.8%) | 60 (85.7%) | 0.006 |
| Male gender | 207 (41.7%) | 34 (48.6%) | 0.23 |
| Age (years) | 55.1 [45.9-60.3] | 49.6 [35.6-57.0] | 0.04 |
| Donor cause of death: | | | 0.49 |
| Intracranial haemorrhage | 341 (68.8%) | 43 (61%) | |
| Trauma | 73 (14.7%) | 14 (20%) | |
| Cardiac Arrest | 38 (7.7%) | 4 (6%) | |
| Brain tumour | 9 (1.8%) | 2 (3%) | |
| Suicide | 15 (3%) | 3 (4%) | |
| Meningitis | 4 (0.8%) | 0 (0%) | |
| Other | 16 (3%) | 4 (6%) | |
| Donor ever smoker | 199 (41.2%) | 29 (45%) | 0.60 |
| Donor packyears (if donor ever smoker) | 15 [5-22] | 20 [12-30] | 0.04 |
| Donor PO2 (kPa) | 61 [52-67] | 61 [53-70] | 0.57 |
| Ex-vivo Lung Perfusion | 15 (2.9%) | 1 (1.4%) | 1.00 |

EBTT-group. Characteristics for both the BTT and EBTT groups are summarized in Table 3. There were no significant differences between the groups regarding age, and indication diagnoses. Median LAS score was higher in EBTT group compared to the BTT group. Despite the time used for evaluation during bridging, there was no significant difference in the total bridging time to LTx. Duration of ICU and hospital admission after LTx was also not different between the BTT and EBTT groups. In both groups a significant amount of patients were bridged by MV alone, BTT-group; 69.2% and EBTT group; 48.4%. Veno-venous ECMO was used in 19 patients, and combined with MV in 14 patients, while 9 patients were bridged with veno-arterial ECMO, and combined with MV in 7 patients. In total 16 patients were awake, 4 patients were awake and sedated intermittently, while 8 patients received full sedation on ECMO. Average bridging success, defined as patients bridged on the ICU and received a LTx was 59%. In the EBTT group bridging success was significantly higher compared to the BTT group (72% vs 48%, $p < 0.05$). Patients that deceased during bridging on the ICU were more frequently treated with ECMO and more frequently had CF as underlying diagnosis. Causes of bridging failure were sepsis and/or multiorgan failure (52%), progressive respiratory failure and pneumothorax (11%), progressive cardiac failure (11%), massive pulmonary or intra-cranial bleeding (11%), failure to stabilize patient with ECMO or failed resuscitation (7%), refractory fungal infection (6%) and progressive airway stenosis (2%).

Figure 4 shows the number of LTx, patients who were delisted or deceased on the wait list annually in the studied time period. The amount of LTx increased over time. In addition, bridging patients to LTx paralleled this trend in recent years. However, LTx from ICU concerned a small portion of the total number of annual LTx. Wait list mortality and/or delisting (including failed bridging) decreased over time.

**Table 3** Characteristics of Patients in the BTT and EBTT Groups

| | BTT group ($n$ = 39) | EBTT group ($n$ = 31) | $p$-value |
|---|---|---|---|
| Recipient Characteristics | | | |
| Male gender | 20 (51.3%) | 23 (74.2%) | 0.08 |
| Age (years) | 49.4 [37.7-57.0] | 50.3 [33.3-57.1] | 0.69 |
| Indication | | | 0.27 |
| Emphysema/A1AD | 12(30.8%) | 6 (19.4%) | |
| Cystic Fibrosis/bronchiectasis | 7 (18.0%) | 4 (12.9%) | |
| Pulmonary Fibrosis | 18 (46.2%) | 21 (67.7) | |
| Pulmonary hypertension | 2 (5.1%) | - | |
| Re-transplantation | - | - | |
| Other | | | |
| Type of transplantation | | | 0.60 |
| Unilateral | 2 (5.1%) | 2 (6.4%) | |
| Bilateral | 37 (94.9%) | 29 (93.6%) | |
| LAS score at transplant | 56.7 [42.8-87.7] | 89.9 [76.5-91.1] | 0.04 |
| HU status or high LAS (>50) | 32 (82.1%) | 28 (90.3%) | 0.50 |
| Clinical wait for LTX | 39 (100%) | 31 (100%) | - |
| Duration clinical wait (days) | 23 [10-40] | 36 [13-49] | 0.75 |
| Bridging with ECMO | 12 (30.8%) | 16 (51.6%) | 0.09 |
| VV-ECMO | 6 (50%) | 13 (81%) | - |
| Combined with MV | 4 (67%) | 10 (63%) | |
| Avalon Cathether 27-30 FR | 4 (67%) | 6 (38) | |
| V.Jug/V.Fem catheter | 1 (17%) | 4 (25) | |
| V.Fem/V.Fem catheter | 1 (17%) | - | |
| VA-ECMO | 6 (50%) | 3 (19%) | - |
| Combined with MV | 5 (83%) | 2 (67%) | |
| A.Subclav/V.Jug catheter | 1 (17%) | 2 (67%) | |
| A.Fem/V.Jug catheter | 3 (0%) | 1 (33) | |
| A.Fem/V.Fem catheter | 2 (33%) | - | |
| Renal failure at time of transplant | 0 (0%) | 0 (0%) | - |
| Liver failure at time of transplant | 0 (0%) | 0 (0%) | - |
| Complete evaluation | 39 (100%) | 31 (100%) | - |
| Duration ICU admission (days) | 23 [11-46] | 16 [6-31] | 0.83 |
| Duration hospital admission (days) | 56 [39-105] | 48 [31-88] | 0.81 |

## Survival

In the total group the 1 year, 5 year and 10 year survival was 87, 72.9 and 58%, respectively. The median survival was 11,7 years. In the patients transplanted electively 1 year, 5 year and 10 year survival was 86.8%, 71.9%, and 58.0% respectively (Figure 2A). This was not different in the patients bridged and transplanted from the ICU, (1 year: 86.8%, 5 year: 78.4%, 10 year: 53.4%, P Log rank = 0.88). Nor was 1 year and 5 year survival of patients in the BTT group different from the EBTT group (92.3% and 83.8% vs 79.3% and 71.3% respectively, P Log rank = 0.92) (Figure 2B). Patients bridged using MV also had similar survival to patients bridged using mechanical support; that is, ECMO or a combination of ECMO and MV, P Log-rank 0.92.

Cox regression analyses showed similar results, with survival in the patients bridged and transplanted from the ICU being not different from ELTx after adjusting for differences in patients characteristics (HR 1.03 [0.65-1.64], $p$ = 0.89) or patient and donor characteristics (HR 2.04 [0.89-4.67], $p$ = 0.09). Similarly, survival in EBTT was not different from BTT after adjusting for differences in patient characteristics (HR 1.25 [0.52-3.04], $p$ = 0.62).

## Chronic lung allograft dysfunction (CLAD)

At follow-up 112 patients developed CLAD. Sixty-six patients were excluded for this analysis because they died within 3 months after LTx. In the total cohort, 1-, 5- and 10 years CLAD free survival was 98.0%, 82.3%, and 63.6% respectively. CLAD free survival was not significantly different between the ELTx group and BTT/EBTT groups, P Log-rank = 0.37, as shown in Figure 3. There was no difference in CLAD free survival between the BTT and EBTT groups, P Log-rank = 0.33, Figure 3.

Cox regression analyses showed similar results, with CLAD-free survival in the patients bridged and transplanted from the ICU being not different from ELTx after adjusting for differences in patients characteristics (HR 0.78 [0.39-1.55], $p$ = 0.48) or patient and donor characteristics (HR 1.44 [0.43-4.93], $p$ = 0.55). Likewise, CLAD-free survival in EBTT was not different from BTT after adjusting for

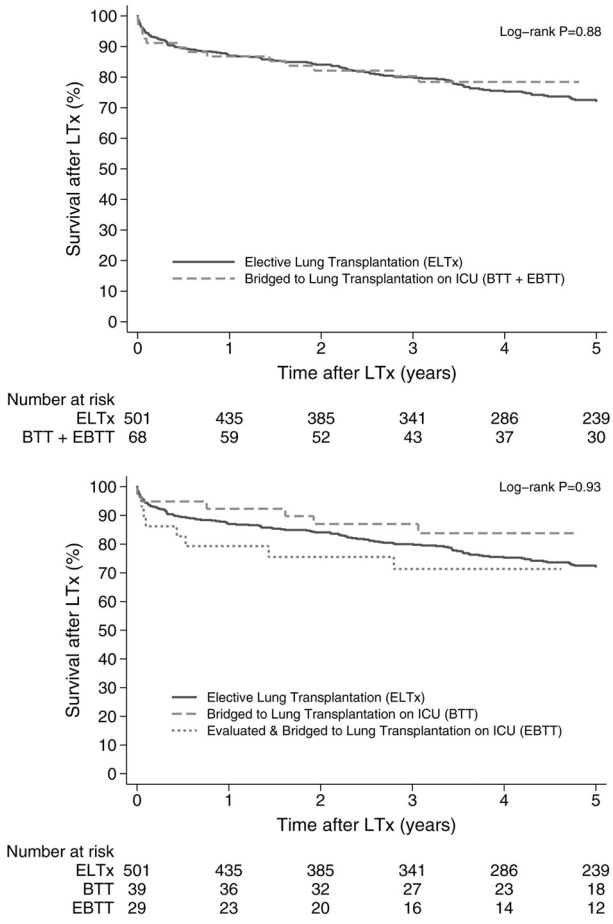


**Figure 2** Survival analyses after LTx 2A Elective LTx vs bridged to LTx on the ICU 2B Elective LTx vs bridged to LTx on the ICU vs evaluated and bridged to LTx on the ICU

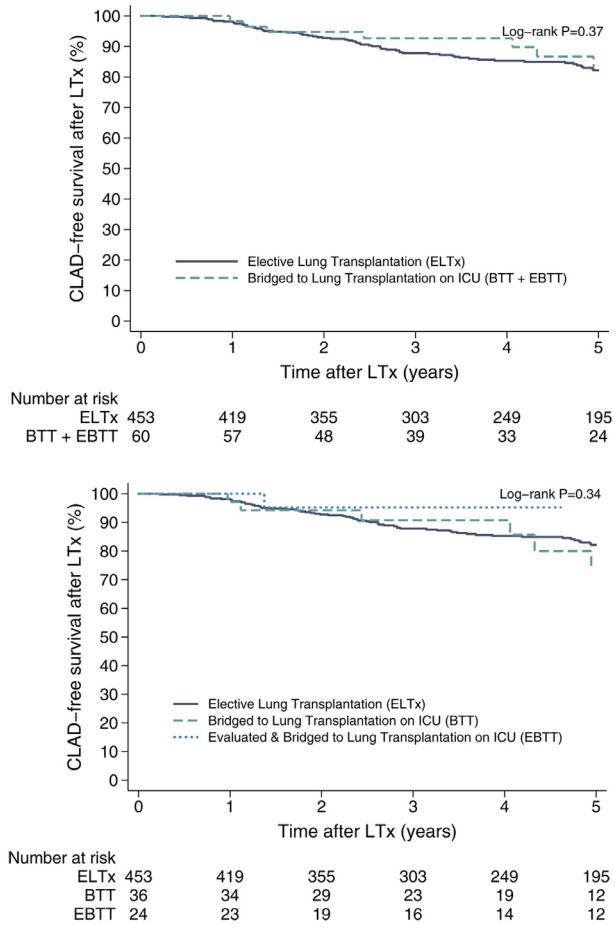


**Figure 3** nA. CLAD free survival after LTx 3A Elective LTx vs bridged to LTx on the ICU 3B Elective LTx vs bridged to LTx on the ICU vs evaluated and bridged to LTx on the ICU

differences in patient characteristics (HR 0.32 [0.06-1.79], $p = 0.20$).

## Discussion

In this retrospective study we assessed long term patient survival and graft function in patients bridged to LTx in the ICU, and found that it was equivalent to patients transplanted electively. Patients that were urgently referred, evaluated and bridged to LTx on the ICU had equally good outcomes.

Patients selected for LTx from ICU underwent extensive evaluation, but not very different from electively referred patients. Unfortunately, there was only referral data available of the UMCG. These data showed that only a limited number of patients (6,6%) is referred for

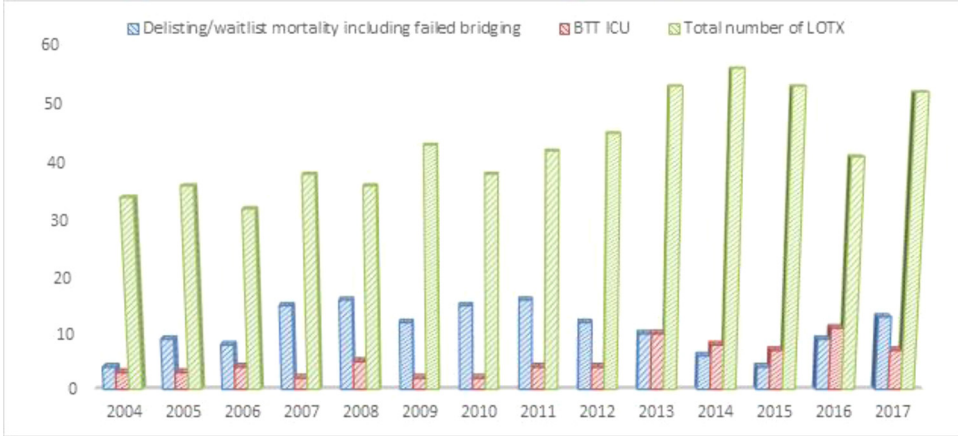


**Figure 4** Total number of LTx, patients bridged to LTx on the ICU, and the total number of patients delisted or who died on the waiting list. BTT, bridged to transplantation; ICU, Intensive Care Unit; LTx, lung transplantation

urgent evaluation and bridging to LTx. We speculate that the number of patients referred and rejected is higher, since in daily clinical practice the transplant physicians discusses potential LTx recipients on a regular base with referring physicians, while eventually this may not have led to a referral of the patients. In addition, 66% of the urgently referred patients were accepted for evaluation and listing.

The 1 year survival of 87% in this study was comparable to international outcomes,[1] and was similar in patients bridged to LTx and in patients evaluated and bridged to LTx on the ICU. Initial 1 year survival rates of patients bridged to LTx were inferior to non-bridged patients, an analysis performed between 1987 and 2008 in UNOS (United Network for Organ Sharing database) showed a 1-survival of 62% for patients on MV and 50% on ECMO.[7,13] The 1 year survival improved over time ranging from 57.6% to 93%.[14] Improvements in techniques, shift from preferentially veno-arterial-ECMO to veno-venous-ECMO, increased experience, the general implementation of (ambulatory) ECMO, and the more recent strategies for bridging may have resulted in improved outcomes over time.[15-17]

The long term survival in this Dutch cohort at 5 and 10 years was 72.9 % and 58% respectively (favorable compared to ISHLT registry data of 5 years of 55.8%, and 10 years survival of 34.1%). These mid and long term results are in agreement with observations from other experienced centers.[18,19] Mid-term and long-term survival outcomes after bridging to LTx on ICU are scarce. Hayanga et al. reported 5 year survival rates of 42% in patients on MV and 66% in patients on combined MV and ECMO.[16] In addition, Benazzo et al. reported 5 year survival of 60% in the more recent era (2010-2017).[8] The 5 year survival in this population bridged and transplanted from ICU was 78,4% and is comparable to the outcome in our elective transplanted cohort. Thus, in the current era bridging patients to LTx results in acceptable outcomes compared with non-bridged patients regarding survival, despite being significantly more ill.

Bridging to LTx is becoming increasingly standard of care, urgent evaluation for LTx on the ICU remains considered controversial. In most centers lack of a previous listing status is an absolute contra-indication as the evaluation potential in this situation is considered limited and long-term outcome data remain scarce. Nonetheless, in recent years multiple cases and cases series have been published on urgent evaluation and bridging to LTx, mostly in ARDS patients and more recently in patients with COVID-19 ARDS.[10,11,20,21]

A series of urgently evaluated and bridged patients to LTx was described by Orsini et al. in France, 52 patients were described along with 49 patients bridged to LTx with prior listing status. One and 3 year survival rates were 67.5% and 59.4%, but were not compared to their electively transplanted patients. Survival, like in our cohort, was not affected by prior listing status. Several important differences between this French and our cohort are; The French cohort consisted mostly of CF-patients (>65%), few patients on ECMO (34%), and the waiting time to LTx was significantly shorter (4 vs 26 days).

Harano, et al. compared outcomes of 39 patients that underwent urgent LTx for ARDS compared to a propensity score matched LTx controls. ECMO prior to LTx was used in 77% of patients. One year (82.1%) and 3 years (69.2%) survival was comparable with the matched controls. Outcomes regarding graft function were not reported.

Short and mid-term outcomes in 130 urgently evaluated and listed patients were reported by Tang et al., and propensity matched outcomes were found to be similar, also at 5 years after transplantation.[22] Graft function was similar in both groups, but with large uncertainty and a trend towards inferior pulmonary outcome in the urgently evaluated group. To our knowledge, this is the first paper to demonstrate that patients survival, and CLAD free survival was excellent, without differences between elective and bridged patients. Although patients bridged on ICU had a high urgency status and/or high LAS, this did not resulted in accepting more marginal donor organs. The latter is supported by the non-significant difference in donor pO2 and ex-vivo lung perfusion procedures. Regarding donor selection we in general accepted donors with extended criteria. However, donor organs with multiple extended criteria were not accepted for patients transplanted from the ICU. Generally similar donor organs were accepted for patients bridged to transplantation on the ICU as for elective transplantation, as shown in Table 1.

Survival is determined multifactorial and influenced by experience and improved surgical techniques, early recognition and management of post-transplant complications like bleeding and primary graft dysfunction. Improved prophylaxis and treatment of infections, better immunosuppressive regimes, close follow-up for development of cardiovascular comorbidity, chronic kidney disease and low threshold to investigate for malignancies, may have resulted in the good outcome in our cohort.

Although we showed that patients bridged successfully to LTx have good outcomes, not all patients made it to LTx. In our cohort bridging success was 72%. The reported bridging success of patients ranges from 50% to 90%.[14,20,22,23] The variable bridging success might be related to center experience and patient selection, and there might be an important role for donor availability. The short median waiting time to urgent LTx of 4 days in the study by Orsini et al, compared 26 days in our series will likely influence bridging success. This study showed that in the majority of patients bridging failure on ICU was due to severe infection with multi organ failure, bleeding complications or cardiac failure despite receiving mechanical support with ECMO. Furthermore, the amount of patients transplanted from ICU increased. This is in part due to increased experience and technical possibility, but also as this is better facilitated by the LAS system introduced in the Netherlands in 2014. Nonetheless, only a small proportion of LTx concerned BTT.

The percentage wait list mortality and/or removal (including failed bridging) remained stable over time, especially since introduction from the LAS system in 2014. In a comprehensive paper by van Hoffman et al, waiting list dynamics and lung transplantation outcomes

after introduction of the LAS in The Netherlands were evaluated.[24] From 2014 the relative waitlist mortality remained stable in the Netherlands. Although the absolute numbers of death on the waitlist increased, so did the total amount of transplants. The increase in the number of transplantations may be attributed to more frequent acceptation of donor lungs with extended criteria within the Eurotransplant region as shown by Smits et al.[25] As a result of more transplantations the percentage waitlist mortality did not change. Furthermore, it was shown that slightly more patients were delisted since the introduction of the LAS era. All in all there is no evident signal that increased bridging to transplantation including urgent evaluation increased waiting list mortality, but this needs to be re-evaluated over time.

Despite that patients had longer admission time on the ICU, and that they were more ill (high LAS score), bridging success was higher in patients without prior listing status. We speculate that the higher bridging success represents the pre-selection of this group. They were only considered for urgent evaluation when they had generally good health and active lifestyle before becoming critically ill and had rehabilitation potential. The urgent evaluations were more frequently performed in recent years and the increased bridging success may reflect increased experience.

There are limitations to our study. Urgent assessment and bridging to lung transplant in ICU should be considered only in centers with experience, a high number of transplant per year, and with low mortality rate on the waiting list. We have to acknowledge that patients who underwent this procedure were highly selected and this selection process is key for the success. All patients were treated on ICU's in various centers as a bridge to recovery, and transplant teams were consulted when recovery was no longer realistic. In general, these patients had rehabilitation potential and had an active lifestyle. All patients were visited by the transplant team in the referring center, and discussed in the MDT prior to transfer and evaluation of the patients in the ICU of the transplant center. Often the potential for adequate evaluation is criticized. Our experience is that adequate evaluation is challenging but possible. Some patients are awake and able to communicate, and extensive conversations can be performed with relatives of the patients to assess candidacy. During the waiting time for LTx, listing status was routinely evaluated by the MDT. Data of patients who were referred to both centers but not evaluated would have given more insight on the selection of candidates, since the group of patients without a previous listing status was highly selected. Furthermore, the LAS was introduced in 2014 in the Netherlands and this has increased the number of LTx from ICU. LAS introduction might have influenced patient selection.

In conclusion, we report excellent short and long-term patient and graft survival between patients bridged to LTx on the ICU, independent of previous waiting list status and despite relatively long waiting time for suitable donor organs. LTx should be considered as a treatment option in selected patients with end stage lung disease and chronic respiratory failure on ICU in centres with specific expertise.

## Author contributions

C.Tji Gan; study design, data analysis, writing of manuscript, Rogier A.S. Hoek; data analysis, writing of manuscript Wim van der Bij; study design, data analysis, writing of manuscript Caroline Van De Wauwer; data analysis, writing of manuscript Michiel E. Erasmus; study design, data analysis, writing of manuscript Annemiek Oude Lansink-Hartgring; data analysis, writing of manuscript Joep M. Droogh; data analysis, writing of manuscript Leonard S. Seghers; data analysis, writing of manuscript Bas J. Mathot; data analysis, writing of manuscript Edris A.F. Mahtab; data analysis, writing of manuscript Jos A. Bekkers; data analysis, writing of manuscript Dinis Dos Reis Miranda; data analysis, writing of manuscript Erik A.M Verschuuren; study design, data analysis, writing of manuscript Merel E. Hellemons; study design, data analysis, writing of manuscript.

Table 1: A1AD: alfa-1-antitrypsin deficiency, ELTx; elective lung transplantation, BTT; bridged and transplanted from the ICU with a previous listing status, EBTT; patients urgently evaluated and bridged to lung transplantation on ICU, ECMO; Extra-corporeal Membrane Oxygenation, LTx; Lung transplantation.

Table 2; A1AD: alfa-1-antitrypsin deficiency, LAS; Lung Allocation score (for patients transplanted in the LAS system), HU; High Urgent, LTx; Lung transplantation, EVLP; ex vivo lung perfusion ELTx; elective lung transplantation, BTT; bridged and transplanted from the ICU with a previous listing status, EBTT; patients urgently evaluated and bridged to lung transplantation on ICU, ECMO; Extra-corporeal Membrane Oxygenation, MV; mechanical ventilation, kPa; kilopascal.

Table 3; A1AD: alfa-1-antitrypsin deficiency, LAS; Lung Allocation score, HU; High Urgent, LTx; Lung transplantation, ECMO; extra corporal membrane oxygenation. MV; mechanical ventilation. VV; veno-venous, VA; veno-arterial, Jug; Jugular, Fem; Femoral, Subclav; subclavian, V; vene, A; artery * < 0.05** 2 patients were converted from VV to VA-ECMO.

Patients were referred, evaluated and listed on the waiting list, either electively ($n$ = 693) or urgently ($n$ = 43). In the total group 512 patients received a LTx electively (ELTx), 100 patients died waiting or were removed from the waiting list. From 81 elective patients bridged on the ICU 39 patients received a LTx (BTT). From the urgent referrals, 31 patients were evaluated, listed and bridged on ICU (EBTT), 12 patients died waiting for LTx. A total of 70 patients were bridged to LTx on the ICU. LTx = lung transplantation.

## Disclosure statement

The authors have no conflicts of interest to declare.

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