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Original Research

Frequency of Unplanned Readmissions Following Lung Transplantation During the SAR-COV-2 Pandemic When Hospital Resources Were Strained

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Abstract

Despite the concerted efforts by lung transplant recipients (LTR) and their medical teams, hospital readmissions are common in the first year following transplantation. Reasons for unplanned readmissions include allograft rejection, infections, and respiratory failure before the SARS-COV-2 pandemic. Clinical predictors of readmissions have changed over time with the higher risk factors of acceptable criteria for recipients and donors. We aimed to assess more recent readmission rates based on group classifications to better understand specific groups that are at risk for various readmissions during the SARS-COV-2 pandemic when hospital resources were strained. A retrospective analysis for LTR at UCSD was performed from 1/1/2018 to 6/30/2022. We recorded the baseline demographics; LAS at the time of lung transplant; mechanical ventilation prior to lung transplant; the need for VV-or VA-ECMO prior

to or after lung transplantation; categories for UNOS listing (groups A, B, C, D); PGD grade 3 based on the ISHLT definition; and acquisition of serious donor-derived infections. We recorded the primary reason for all the readmissions and the duration of admission. Descriptive statistics were used for the analysis of this 4.5-year patient cohort. 149 LT were performed. 29 were single LTR while 120 were bilateral LTR. Median age of 57 years, 63 patients (42%) were female. Indications for transplantation included 28 (19%) group A, 19 (13%) group B, 12 (8%) group C, and 90 (60%) group D. The median length of follow-up following lung transplant was 1.7 years. Collectively, there were 73 patients (49%) that required readmissions. On average, there are 2.5 readmissions per patient for our cohort. Most common reasons for unplanned readmission included infections, transplant-related (transplant rejection, other complications of transplant, etc.), and GI Related. This was primarily seen in the group D cohort. The median hospital LOS at readmission was 3.8 days (4 hours to 34.6 days). Despite infection being the leading cause of readmission, only 11 cases were related to COVID-19 infection. No death occurred with a readmission. Groups B and D appear to be at a higher risk for readmission, irrespective of the pre-LT LAS and need for mech vent or VV-ECMO.

Keywords
Lung transplant; readmissions; covid-19; pandemic

1. Introduction

Lung transplantation is a therapeutic surgical option for selected patients with severe pulmonary disease who are refractory to medical therapy and continue to have progressive clinical deterioration [1]. An ongoing challenge in lung transplantation is the balancing act between an appropriate degree of immunosuppression to minimize allograft rejection and infectious complications. The routine practice has been to follow protocols on dosing of standard triple-drug maintenance immunosuppression with corticosteroids, antimetabolites, calcineurin inhibitors, and prophylactic medications to cover for Aspergillus, cytomegalovirus, and pneumocystis jiroveci pneumonia. Despite the concerted efforts by lung transplant recipients and their medical teams, adverse events requiring hospital readmissions in the first year can occur in up to 60.1% of cases [2, 3]. This is twice the rate of kidney and liver transplant recipient readmission rates [4, 5]. Infections have been reported as the main culprit of unplanned readmissions within the first year followed by allograft rejection, pleural effusion, and respiratory failure [2, 3]. Predictors of the readmissions include male gender, initial discharge to a long-term care facility.

As of March 16, 2023, globally there are 760,360,956 confirmed cases of COVID-19 with 6,873,477 deaths (0.9%) [6]. Efforts were made to maintain lung transplant activity irrespective of the increased COVID-19 rates [7]. Knowing the higher unaccounted risk factors that are not computed into the mortality model for the lung allocation score, herein we aimed to assess the risk of readmissions based on group classifications to better understand specific groups that are at risk for various readmissions and their frequency of readmission during a period when hospital resources were strained due to the SARS-COV-2 pandemic.

2. Methods

We reviewed the medical records for all the patients who underwent lung transplantation at UC San Diego from 1/1/2018 to 6/30/2022. The study was approved by our institutional review board (IRB). We excluded multi-organ transplant recipients and those who died prior to their initial discharge. We defined readmission as a use of hospital resources, to include short stays of observation. We recorded the baseline demographics; lung allocation score (LAS) value and percentile at the time of lung transplant; and risk factors attributed to poor outcomes such as the need for high flow nasal cannula, non-invasive positive pressure ventilation, or mechanical ventilation before lung transplant; need for VV-or VA-ECMO before or after lung transplantation; categories for UNOS listing (groups A, B, C, D; see Table S1), concomitant cardiac surgery; PGD grade 3 at time 72 hours based on the International Society for Heart and Lung Transplantation (ISHLT) definition; acquisition of serious donor-derived infections; and return to the operating room. We recorded the primary reason for all the readmissions and duration of admission. Descriptive statistics were used for the analysis of this 4.5-year patient cohort. Additionally, Pareto analysis was utilized to help determine the volume of the various readmission reasons. Overall survival time was calculated from the date of the lung transplant to the date of the last follow-up or death.

During the pandemic, all candidates and donors were tested for COVID-19 by nasal PCR (recipient) or BAL PCR (donor) prior to pursuing lung transplantation. Given this is only an evaluation of readmissions, lung transplant recipients tested positive for COVID-19, but did not warrant an admission were not included in the analysis.

2.1 Immunosuppression Protocol

Lung transplant recipients receive induction therapy with the administration of monoclonal interleukin (IL-2) receptor antibody basiliximab (Simulect, Novartis Pharmaceuticals) at doses of 20 mg immediately prior to and on postoperative day 4 of lung transplantation. Additionally, administration of 500 mg of methylprednisolone during the operation immediately prior to perfusion, followed from the first operative day at 125 mg of methylprednisolone every 8 hours. On post-operative day 2, an enteral route prednisone was administered at a dose of 0.2 mg/kg per day. Mycophenolate mofetil (Cellcept, Hoffman-La Roche) was administered at 1,000 mg pre-operative and commenced immediately after lung transplantation on post-operative day 0 in a dose of 2 grams per day. Tacrolimus route on administration was an enteral route and the target Tac levels were maintained between 10 and 12 ng/mL in the first 3 months and further adjusted to target Tac levels between 8 and 12 ng/mL in the first year. After the first year, if there were no episodes of acute cellular rejection, the target Tac levels were between 6 and 8 ng/mL. Sirolimus (Rapamune, Pfizer Inc) was provided on a case-by-case basis and only started 3 months after lung transplantation. The sirolimus dose and target range was varied according to the clinical indications and concomitant azole use. Target ranges were monitored through high-performance liquid chromatography-tandem mass spectrometry.

3. Results

Between 1/1/2018 and 6/30/2022, 149 lung transplants were performed. 29 were single transplant while 120 were bilateral lung transplant recipients. Median age 57 years, 63 patients

(42%) were female. Indications for transplantation included 28 (19%) group A, 19 (13%) group B, 12 (8%) group C, and 90 (60%) group D [Table 1]. 26 patients (17.4%) underwent concomitant cardiac surgery with their lung transplantation. 76 patients (51%) were removed from the analysis due to death or not having experienced a readmission event. 20 patients (13%) died during this time period, however none of them died during a readmission event. The use of mechanical ventilation, use of extracorpeal membrane oxygenation, development of primary graft failure grade 3, unplanned return to the operating room, and serious donor-acquired lung infections are shown in Table 1. The median length of follow-up following a lung transplant was 1.7 years (IQR 0.93-2.8, MIN 0.02, MAX 4.5).

Table 1 Baseline characteristics.

Age, median (IQR; years)	57 (IQR; 46, 63)
Female gender	63 (42%)
UNOS Native Lung Disease Groupings	
Group A	28 (19%)
Group B	19 (13%)
Group C	12 (8%)
Group D	90 (60%)
Lung Allocation Score at the time of transplantation, median (Percentile; 90^{th}, 95^{th}, 99^{th})	43.9 (88.6, 90.7, 94.1)
Risk Factors Attributed to Poor Outcome with Previous Publications	
Mechanical ventilation at time of transplant	18 (12%)
VV- or VA-ECMO prior to or after lung transplant	17 (11.4%)
PGD grade 3 at time 72 hours	1 (0.007%)
Unplanned return to the operating room	11 (7%)
Donor acquired high risk infection	3 (2%)

Collectively, there were 73 patients (49%) that required readmissions. These 73 patients accounted for 184 readmissions, 19 (10%) of which were in the Emergency Department. On average, there are 2.5 readmissions per patient for our cohort. The median hospital LOS at readmission was 3.8 days (MIN 4 hours, MAX 34.6 days). The most common reasons for unplanned readmission included 61 Infection (33%), 44 Transplant-related (24%) (transplant rejection, other complication of transplant, etc.), and 40 GI-related (22%) [Table 2, Figure 1]. Although infections were the most common cause of readmission, COVID-19 accounted for only 11 cases (18.33% of infections) Table S2. Lung transplantation with concomitant valvular surgery and coronary artery bypass grafts concomitant with lung transplantation (17.4%); and VV-ECMO bridge to lung transplantation (11.4%) had readmission rates of 46.2%. Readmissions were primarily seen in the Group D cohort with the absolute number, but highest in Group B based on the percentage of readmissions [Figure 2]. Table S3 indicates the readmissions based on different UNOS groups. All readmissions were treated with standard-of-care approaches to the particular indications for admission. No deaths during a readmission occurred during this study period.

Table 2 Reason for Readmission.

Reason for Readmission	# of Readmissions	# of Unique Patients	Median LOS (days)	IQR LOS (days)	MIN LOS (days)	MAX LOS (days)
Infection	61	35	4.94	3.14-11.79	0.94	34.63
Transplant Related	44	29	3.64	2.7-6.77	0.17	26.85
GI Related	40	33	3.16	2.2-4.91	0.94	21.22
Cardiovascular	9	9	2.10	1.85-6.97	1.19	13.55
Renal	8	6	4.91	2.74-7.03	0.38	9.54
Psychosocial	4	2	2.53	1.78-3.38	1.47	3.98
Metabolic	4	4	3.82	3.06-4.43	2.19	4.85
Hematological	4	1	5.86	2.58-8.74	1.03	9.09
Pulmonary	4	4	1.55	1.01-2.27	0.99	2.83
Neurological	3	3	4.07	3.66-6.73	3.25	9.40
Pain, Specified or Unspecified	2	2	2.42	2.19-2.65	1.96	2.88
Methemaglobinemia	1	1	1.89	1.89-1.89	1.89	1.89
Musculoskeletal	1	1	2.46	2.46-2.46	2.46	2.46

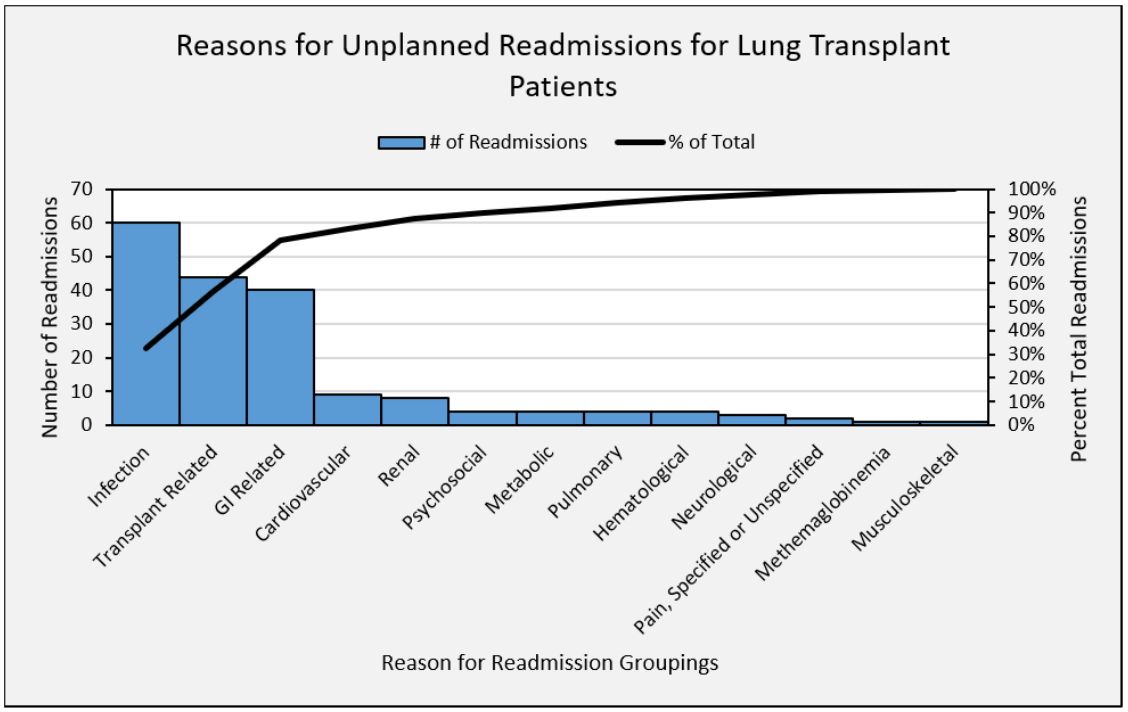

Figure 1 Reason for the unplanned readmissions after lung transplantation.

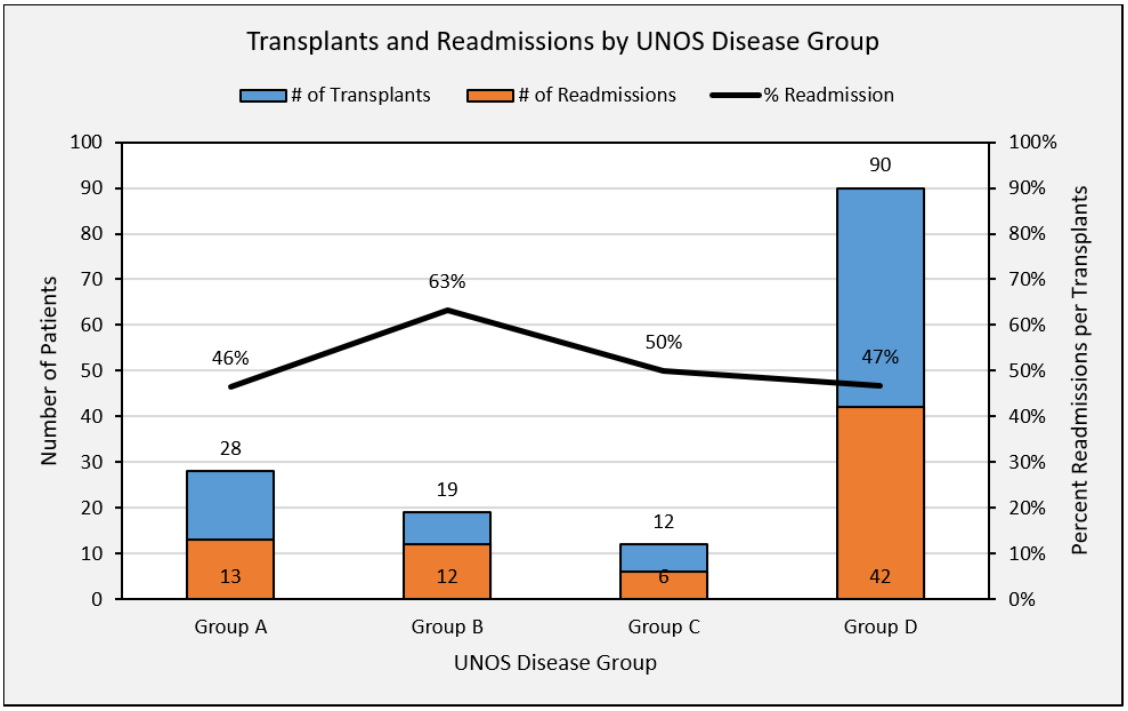

Figure 2 Readmission rates based on the different UNOS disease groups.

4. Discussion

Despite the concerted efforts by lung transplant recipients (LTR) and their medical teams, adverse events requiring hospital readmissions in the first year are expected. Unlike other solid organ transplants, there is limited data for rates and predictors for readmissions after lung transplantation. Lushaj et al. have shown that the first readmission post-transplant admission within 60 days had a mortality rate that is 1.6 times higher than those readmitted after 60 days [2]. Disposition to a long-term care facility was associated with greater than 3 unplanned readmissions within the first year of lung transplantation [3]. Lung transplant recipients requiring multiple patient readmissions resulted in lower overall survival [2, 3]. Readmission rates have been reported as high as 60% [2, 3]. Both prior readmission publications for lung transplantation are from 2016. The reports by Courtwright and Lushaj did not show differences for specific populations in need of lung transplants having higher rates of readmissions like us. There are a few other important differences to comment on.

The median LAS at the time of transplantation for Courtwright et al was 41.6 (IQR 36.3-50.2). Lushaj et al. did not report the median LAS. Our cohort of LTR has median LAS at the time of transplantation of 43.9 (IQR 37.5-65.4), with a 90^{th}, 95^{th}, and 99^{th} percentile LAS of 88.6, 90.7, and 94.1 respectively. We specifically highlight having patients in our cohort with LAS scores ≥ 90^{th} percentile given they typically have lower survival in the first year of transplant, thereby more likely to have higher readmission rates [8]. Despite the SARS-COV-2 pandemic, we continued to perform lung transplantation with concomitant valvular surgery and coronary artery bypass grafts concomitant with lung transplantation (17.4%); and VV-ECMO bridge to lung transplantation (11.4%). These are at higher rates than some larger lung transplant programs [9]. The rate of readmissions for this subset of the cohort was 46.2%.

Lushaj et al showed that 50% of the patients underwent bilateral lung transplants. 92% were readmitted (5.3 times per patient) with a median time from discharge to first readmission being 71 days (IQR 28 to 240). LAS and air leaks for longer than 5 days were contributing factors for readmission, but not PGD grade 3 or ICU length of stay. Respiratory infections (89% of cases) were the most likely cause of readmission but did not clearly delineate between native lung infection versus allograft infection versus opportunistic infections. 41% of the LTR who had been readmitted died at the end of the study period compared to 21% of the LTR who died without needing readmissions. The first readmission occurring within 60 days resulted in 1.6 times greater mortality compared to those readmitted after 60 days. Table S2 provides the main infections our cohort developed to warrant readmission.

Courtwright reported lower LAS, but high readmissions and mortality rates than our study. 193 patients were transplanted, but they did not report the number of single versus bilateral lung transplants. 40% were readmitted in the first year following a lung transplant. 15% had 3 or more readmissions. The median number of hospitalizations in the first year of transplant 3 (IQR 1-4) time to first readmission, is slightly higher than ours. 62 p LTR (32%) were discharged to an LTAC. The LTR discharged to LTAC were typically readmitted more than 3 times within the study period. Initial readmission was related to infection 25.7% of the time and 35.8% for subsequent readmission readmissions. Surgical complications (25.7%) and "Other" category (27.2%) for other primary reasons for first readmission. 28.5% died during the study period.

Neither Courtwright nor Lushaj noted any differences between underlying disease states and outcomes for readmissions. Knowing the higher unaccounted risk factors that are not computed into the mortality model for the LAS, one aim was to assess the risk of readmissions based on group classifications to better understand specific groups that are at risk for various readmissions, and their frequency of readmission. Readmissions were primarily seen in the group D cohort with the absolute number, but highest in Group B based on the percentage of readmissions. PGD grade 3, concomitant cardiac surgery, utilization of ECMO did not contribute to any need for readmission.

The policy reported by Lushaj et al. at the University of Wisconsin was to keep the patients locally for approximately 1 week after discharge [2]. Based on their findings, they concluded that the patient may need to be local for 2 weeks. Our program requires LTR to stay locally for 3 months. None of our patients were discharged to long-term-care facilities. Those deemed to have a higher risk profile after their transplant were seen twice weekly for 3-4 weeks. If stable, they would be seen every week for another month and subsequently to twice monthly and then monthly thereafter. Laboratory assessments are performed every month irrespective of the time from transplantation.

Logan et al. noted a 15.5% mortality in their lung transplant cohort [10]. Age, gender, nor race were statistically different between those who died versus those who survived. The degree of immunosuppressed state was not indicated. Our study is a more contemporary evaluation of readmission rates for lung transplant recipients during a period when hospital resources were strained due to the SARS-COV-2 pandemic. We had only 11 read mission during this study period related to COVID-19. Contrary to their findings, we had no deaths related to COVID-19.

Our study has several limitations in that it is a single-center study. Compared to Courtwright and Lushaj, our sample size is smaller, but our LTR severity of illness is found to be higher. This is a short-term follow-up for readmissions by comparison. We will need to follow the patients for a longer period to determine long-term graft and patient survival. Standard of care was provided for all readmissions, so a controlled analysis for various reasons for the outcomes cannot be provided.

Author Contributions

Mr. Justin Cole provided the statistical and data analytics and interpretation of results. Dr. Eugene Golts provided writing of the drafts, a review of the results, and edits. Mr. Michael Bernales provided his data extraction expertise and ensured that we had access to the data needed to support the associated analytics. Ms. Dina Shirazi provided background information, a review of the results, and edits. Ms. Deepa Kurup provided a review of the results and edits. Ms. Sarah Golts provided background information, a review of the results, and edits. Dr. Gordon Yung provided a review of the results and edits. Dr. Aarya Kafi provided a review of the results and edits. Dr. Christine M. Lin provided a review of the results and edits. Dr. Travis Pollema provided a review of the results and edits. Dr. Kamyar Afshar provided concept generation, draft writing, data analytics, and interpretation of results, and edits.

Competing Interests

The authors have declared that no competing interests exist.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Table S1: UNOS Lung Disease Diagnosis Groups.
2. Table S2: Main Infections that Contributed to Readmission.
3. Table S3: Reasons for Readmission by UNOS Disease Groups.

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