Kennedy Jessica (Orcid ID: 0000-0003-2086-743X)

ORIGINAL RESEARCH

OUTCOMES OF NON-CYSTIC FIBROSIS RELATED BRONCHIECTASIS POST LUNG TRANSPLANTATION.

Jessica Kennedy[1,2,3] BBiomedSc. MBBS, FRACP

Anne Walker[1,4] MBBS, GradCertClinTch

Claire M. Ellender[1,5] BSc, MBBS, FRACP

Kate Steinfort[1] MBBS, MMed(CritCare)

Catherine Martin[6] BSc, PhD

Catherine Smith[6] BSc (Hons), MPH, MSc (App Stats)

Gregory Snell[1] MBBS, FRACP

Helen Whitford[1] MBBS, FRACP

[1]Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Melbourne, Australia.

[2]School of Medicine, Dentistry and Health Science, Melbourne University, Melbourne, Australia.

[3]Department of Respiratory and Sleep Medicine, Austin Hospital, Melbourne, Australia.

[4]Department of Thoracic Medicine, Royal Adelaide Hospital, South Australia, Australia

[5]Department of Respiratory & Sleep Medicine, Princess Alexandra Hospital, Brisbane, Australia

[6] Pubic Health and Preventative Medicine, Monash University, Melbourne, Australia.

CONTRIBUTIONS OF AUTHORS:

- Dr Jessica Kennedy, Consultant Respiratory and Sleep Physician: Principal investigator, Project plan, Data collection, Literature review, Primary author, Presenter at conference presentations to date; TSANZ SIG Oral 2016, Vic Branch TSANZ Oral 2016 & ATS Poster discussion 2017.
- Dr Annie Walker, Respiratory and Sleep Advanced Trainee: Co-author, Literature review, Data collection
- Dr Claire Ellender, Consultant Respiratory and Sleep Physician: Assistance with project design, Data collection, Review of manuscript

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/imj.15256

- D. Kate Steinfort, Anaesthetics Registrar: Data collection
- Dr Catherine Martin, Biostatistician, Monash University: Data analysis and interpretation
- Ms Catherine Smith, Biostatistician, Monash University: Data analysis and interpretation
- Dr Greg Snell, Consultant Respiratory and Lung Transplantation Physician: Manuscript review.
- Dr Helen Whitford, Consultant Respiratory and Lung Transplantation Physician: Supervisor of project, Project design, Plan, Analysis and Write up.

ACKNOWELDGEMENTS:

The authors wish to acknowledge the contribution of the Alfred Hospital Lung transplantation team for the patient care and maintaining the registry from which the cohort was sourced for this research.

GRANT SUPPORT: Nil

DECLARATION OF INTEREST STATEMENT: There are no conflicts of interest.

CORRESPONDING AUTHOR:

Dr Jessica Kennedy

Department of Respiratory and Sleep Medicine

Austin Hospital, 145 Studley Rd, Heidelberg VIC 3084, Melbourne, Australia

Phone number: +61394963688

Fax number: +61394965124

Email: jessicalouisekennedy@icloud.com

Abstract word count: 243

Main text word count: 2425

Introduction

The term bronchiectasis describes the abnormal dilatation of the bronchial lumen, which can lead to a clinical syndrome of chronic suppurative cough and recurrent respiratory tract infections.[1] Cystic-fibrosis (CF) is a well-recognised cause of bronchiectasis, however the majority of cases are not related to CF (referred to as non-CF bronchiectasis) and can be attributed to childhood infections, inherited and acquired immunodeficiency states, connective tissue and inflammatory diseases, cilia abnormalities, gastric reflux and obstructive lung diseases. In a proportion of cases, the aetiology is unclear. In many

patients with bronchiectasis, progression to respiratory failure is slow; however, a proportion progress rapidly leading to reduced quality of life and survival.[2,3] Whilst difficult to accurately define, the prevalence of bronchiectasis associated hospitalisations is increasing.[1,4-6]

Bilateral lung transplantation is a recognised treatment for end-stage lung disease, including CF and non-CF bronchiectasis.[3] The proportion of patients with non-CF bronchiectasis that receive lung transplantation is small (2.7%) compared with CF (15.8%) and therefore are often combined into one cohort in the literature.[7] However there are differences between the two populations, with the non-CF bronchiectasis population typically being older, female and with co-existing Chronic Obstructive Pulmonary Disease (COPD).[4] The five-year survival of non-CF bronchiectasis patients post lung transplantation varies dramatically from 34% to 73%.[8-11]

Thus, the aim primary of this study was to examine the time to and cause of lung allograft loss in non-CF bronchiectasis patients compared to CF and other end-stage lung disease cohorts following transplantation. The secondary aim was to describe the admission rates of patients with non-CF bronchiectasis post transplantation. The hypothesis was that non-CF bronchiectasis (hereafter referred to as bronchiectasis) patients have a higher admission rate and worse survival post transplantation than CF patients.

Methods

Study population

A retrospective analysis of consecutive patients undergoing lung transplantation between 01 January 2008 and 31 December 2013 at the Alfred Hospital, Melbourne was performed. The cohort was generated from the centres prospectively maintained lung transplant registry. Patients were excluded if age was less than 18 years or the encounter was for re-transplantation. Primary indication for transplant was determined based on the medical record and the final histopathology report from the explanted lung. Primary indication was categorised as: Obstructive Lung Disease (OLD), Interstitial Lung Disease (ILD), Cystic Fibrosis (CF), Pulmonary Hypertension/Congenital heart disease (PH) and Bronchiectasis. All patients post transplantation received standard care as previously described.[12] See Figure 1 for CONSORT diagram. The study was conducted in accordance with the Human Research and Ethics Committee (HREC457/14).

Mortality and Lung Allograft Loss

Lung allograft loss was classified as death or re-transplantation with (a) a functional graft or (b) chronic lung allograft dysfunction (CLAD). Data for this analysis was censored on 01 April 2018. CLAD was defined according to the International Society of Health and Lung Transplant (ISHLT) definition as; a sustained decline in FEV1 or FVC in combination with histological and radiological findings with no alternate diagnosis found, encompassing both bronchiolitis obliterans syndrome (BOS) and restrictive allograph syndrome (RAS).[13,14] CLAD was then sub-categorized either with or without predominant infective features. Death with a functional graft was sub-classified as death due to non-respiratory sepsis, neurological, malignant or unknown.

Morbidity Case Control Sub-Group

In order to evaluate health care utilisation more detailed data collection was performed on a sub-group from the larger dataset. To generate the sub-group, the 22 bronchiectasis patients were gender matched with 22 patients from each of OLD, CF and ILD diagnostic groups, using a random number generator. For each patient, the electronic medical record was searched for hospital admissions from date of transplantation to a censor date of 01 January 2015. Routine procedural admissions were excluded. The primary cause for each admission was categorised according to ISHLT criteria as either: primary sepsis, allograft dysfunction (rejection) or other.[15] The length of stay (days) including days on hospital in the home was used to calculate the total inpatient days. After randomisation, complete admission data was unavailable in 10 patients, leaving the sub-group analysis population of n = 78 patients. Complete case notes were not accessible in 9 patients and 1 patient died during the immediate post transplantation period.

Statistical Analysis

Time to lung allograft loss or death with a functioning graft was assessed using Kaplan-Meier log-rank-test and Cox Proportional Hazard Model, with pre-defined sub-group analysis planed for cause of death or allograft loss. All-cause mortality and allograft loss was analysed using a competing risk analysis. The morbidity analysis used negative binomial regression to generate Incidence Rate Ratios (IRR), to accurately compare admissions rates accounting for the variability in time that a person was exposed to the risk of an admission (i.e. transplant date to censor 01 Jan 2015). Statistical significance was defined as $p < 0.05$ using two-tailed tests. Statistical analysis was performed on all available data using STATA version 14.

Results

Population

A total of 341 patients met the selection criteria, with a median follow-up time of 5 years (range: 14 days to 10 years), 171 (50%) being male, and the average age at transplantation was 50 years. Table 1 shows baseline characteristics by disease group. OLD represented the largest disease group (n = 149, 44%), followed by ILD, CF, bronchiectasis and PH. Double lung transplantation was conducted in 307 (90%) patients. The aetiology of the bronchiectasis cohort included 3 prior stem cell transplant or GVHD, 3 autoimmune disease, 3 immunoglobulin deficiency, 8 post infective, 1 congenital bronchial web, 4 idiopathic (see supplementary Table S3). In the OLD group 12 (8%) had concurrent bronchiectasis, however this was not the predominant pathological feature and were therefore analysed in the OLD group (see supplementary Table S4).

Lung Allograft Loss

There were 155 instances of lung allograft loss of which 136 were death and 19 were re-transplantations. For the entire cohort, graft survival was 93% at 1 year, 71% at 3 years and 61% at 5 years (see Figure 2). At 5-years, the graft survival for the bronchiectasis group was significantly lower (32%) compared with OLD (64%), CF (69%), ILD (55%), PHT (62%), (p=0.008). Adjusting for age at transplantation and gender, all groups had a reduced hazard ratio (HR) for allograft loss compared to bronchiectasis on multi-variate analysis (see supplementary Table S1). Excluding the 2 bronchiectasis patients with immunoglobulin deficiency did not significantly change the reduced bronchiectasis survival rates.

Cause of Lung Allograft Loss

Of those who experienced allograft loss, CLAD without infective features was the leading cause in 45% of cases (n = 70), followed by CLAD with infective features in 24% (37), other causes in 10% (16) and non-respiratory sepsis in 5% (8). Data was missing in 24 (15%) of the allograft loss cases (see Table 2). In the bronchiectasis cohort, allograft loss from CLAD with infective features at 2 years was significantly higher compared to CF HR 0.23 (95% CI: 0.09-0.64, p = 0.004), PH HR 0.11 (95% CI: 0.01-0.85, p= 0.04), OLD HR 0.24 (95% CI: 0.10-0.55, p = 0.001) and ILD HR 0.18 (95% CI: 0.06-0.50, p = 0.001), see supplementary table 1 for adjusted and unadjusted survival analysis. Allograft loss due to CLAD without infective features was not different in the bronchiectasis cohort when compared to OLD HR 0.85 (95% CI: 0.34-2.15, p = 0.74), CF HR 0.97 (95% CI: 0.37-2.59, p = 0.96), ILD HR 1.04 (95% CI: 0.39-2.77, p = 0.94) and PH HR 0.61 (95% CI: 0.15-2.52, p = 0.49). The cause of allograft loss in the bronchiectasis group is shown in supplementary table 2.

Morbidity Case Control Sub-Group

Of the 78 patients included in the morbidity sub-group analysis, 59% were male with a median age of 53 years (range 18 to 70 years), the demographic are shown in supplementary table 3. The acute admission incident rate ratio (IRR), which assesses the number of admissions per patient per year post transplantation, was 2.24 times higher in the bronchiectasis group than the admission IRR for OLD (95% CI: 1.21-4.14, p = 0.010) and 2.22 times higher than the admission IRR for ILD (95% CI: 1.21-4.06, p = 0.009), and 1.5 times that for CF, however this was not statistically significant (95% CI: 0.81-2.83, p = 0.19) as shown in figure 3. Bronchiectasis patients spent 45.81 days in hospital per person year after transplantation compared with CF 18.21 days, OLD 12.46 days, and ILD 12.45 days.

Discussion

Lung transplantation remains an option for end stage bronchiectasis, however this study supports the hypothesis that bronchiectasis patients have a reduced survival and increased complications due to respiratory sepsis compared to patients undergoing lung transplantation for other chronic lung diseases. The post transplantation survival of all patients in this cohort (93% at 1-year and 61% 5-years) is comparable to the ISHLT Registry for the period between January 1990 and June 2014 (80% at 1-year

and 54% at 5-years).[7] The 5-year survival for CF patients in this study (69%), is comparable with 2016 ISHLT reported 5-year survival (60%).[7] However, the 32% 5-year survival in the bronchiectasis group in this study is substantially lower than other similar sized bronchiectasis cohorts published to date, with 5-year survival between 60-73%.[8,9,16-18] Interestingly, Nathan *et al.*[11] reported a cohort of 37 patients with a 34% 5-year survival; this cohort had a similar proportion of patients with antibody deficiency (5/37, 13%) as in the current study (3/22, 13%). There is a trend in the literature that 5-year survival for bronchiectasis patients is higher in cohorts where the proportion of patients with antibody deficiency is lower. [8,9,16-18] The small numbers in our bronchiectasis cohort, prevented a mortality sub-group analysis comparing proven antibody deficiency bronchiectasis versus other bronchiectasis causes.

Bronchiectasis patients had longer and more frequent hospital admissions, averaging 2.11 admissions per person year and 45 days in hospital per person year post transplantation. Previous literature regarding bronchiectasis post transplantation survival has not examined admission rate or duration for comparison, which is a novel insight provided by this paper and warrants replication. We postulate that increased admissions because of respiratory sepsis, could be a marker for premature graft loss and result in a reduced quality of life for these patients.

The main limitations of this study are the retrospective medical history review, single centre, and small sample sizes. Microbiology and cytomegalovirus status was not a focus of this investigation, which is a limitation as *Pseudomonas aeruginosa* colonization has been associated with negative post-transplant outcomes.[19] Whilst there was a standardised approach to immunosuppression post transplantation at this institution, the exact pharmacotherapy used over time was not considered in this analysis and is a potential confounder.

Previous reports from our institution have raised the possibility of incorporating less immune suppression regimens for profound immunodeficiency states such as X-link agammaglobulinemia.[20] Given the findings of this study, potential areas for further investigation include a detailed review of immunoglobulin status pre- and post-transplantation, particularly regarding those with primary antibody deficiency. Furthermore, a meta-analysis may be useful to clarify the impact of immunodeficiency status on bronchiectasis survival.

Conclusion

This study found lower 5-year survival in patients with non-CF bronchiectasis undergoing lung transplantation compared to other indications. Additionally, there was a higher rate of allograft loss due to CLAD with infective features, increased rates of hospital admissions and longer length of stay. Furthermore, given the disparity in post-transplantation outcomes for CF and bronchiectasis, these groups should be considered distinct aetiologies when post-transplant survival outcomes are reported.

References

1. Redondo M, Keyt H, Dhar R, Chalmers JD. Global impact of bronchiectasis and cystic fibrosis. Breathe (Sheff) 2016;12(3):222-35.
2. Loebinger MR, Wells AU, Hansell DM, Chinyanganya N, Devaraj A, Meister M, et al. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. Eur Respir J 2009;34(4):843-9.
3. Hayes D, Jr., Meyer KC. Lung transplantation for advanced bronchiectasis. Semin Respir Crit Care Med 2010;31(2):123-38.
4. Ringshausen FC, de Roux A, Pletz MW, Hämäläinen N, Welte T, Rademacher J. Bronchiectasis-associated hospitalizations in Germany, 2005-2011: a population-based study of disease burden and trends. PLoS One 2013;8(8):e71109.
5. Seitz AE, Olivier KN, Steiner CA, Montes de Oca R, Holland SM, Prevots DR. Trends and burden of bronchiectasis-associated hospitalizations in the United States, 1993-2006. Chest 2010;138(4):944-9.
6. Kwak HJ, Moon JY, Choi YW, Kim TH, Sohn JW, Yoon HJ, et al. High prevalence of bronchiectasis in adults: analysis of CT findings in a health screening program. Tohoku J Exp Med 2010;222(4):237-42.
7. Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-third Adult Lung and Heart-Lung Transplant Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. J Heart Lung Transplant 2016;35(10):1170-84.
8. Beirne PA, Banner NR, Khaghani A, Hodson ME, Yacoub MH. Lung transplantation for non-cystic fibrosis bronchiectasis: analysis of a 13-year experience. J Heart Lung Transplant 2005;24(10):1530-5.
9. Rademacher J, Ringshausen FC, Suhling H, Fuge J, Marsch G, Warnecke G, et al. Lung transplantation for non-cystic fibrosis bronchiectasis. Respir Med 2016;115:60-5.
10. Birch J, Sunny SS, Hester KLM, Parry G, Kate Gould F, Dark JH, et al. Outcomes of lung transplantation in adults with bronchiectasis. BMC Pulm Med 2018;18(1):82.

11. Nathan JA, Sharples LD, Exley AR, Sivasothy P, Wallwork J. The outcomes of lung transplantation in patients with bronchiectasis and antibody deficiency. J Heart Lung Transplant 2005;24(10):1517-21.

12. Paraskeva MA, Westall GP, Pilcher D, McGiffin D, Levvey BJ, Williams TJ, et al. The Alfred Hospital Lung Transplant Experience. Clin Transpl 2014:99-108.

13. Meyer KC, Raghu G, Verleden GM, Corris PA, Aurora P, Wilson KC, et al. An international ISHLT/ATS/ERS clinical practice guideline: diagnosis and management of bronchiolitis obliterans syndrome. Eur Respir J 2014;44(6):1479-503.

14. Verleden GM, Raghu G, Meyer KC, Glanville AR, Corris P. A new classification system for chronic lung allograft dysfunction. J Heart Lung Transplant 2014;33(2):127-33.

15. Husain S, Mooney ML, Danziger-Isakov L, Mattner F, Singh N, Avery R, et al. A 2010 working formulation for the standardization of definitions of infections in cardiothoracic transplant recipients. J Heart Lung Transplant 2011;30(4):361-74.

16. Birch J, Hester K, Parry G, Gould KF, Dark JH, Meachery G, et al. Outcomes of lung transplantation for bronchiectasis. In: European Respiratory Society Annual Congress; 2012.

17. Christie G, Rao J, Hilton C. Lung Transplantation for non cystic fibrosis bronchiectasis. Thorax 2000;55(Suppl 3):A8.

18. Rusanov V, Fridman V, Wille K, Kramer MR. Lung Transplantation for Cystic Fibrosis and Non-cystic Fibrosis Bronchiectasis: A Single-Center Experience. Transplant Proc 2019;51(6):2029-34.

19. Orfanos S, Gomez C, Baron S, Dufeu N, Coltey B, Thomas P, et al. Impact Of Gram Negative Bacteria Airway Recolonization On The Occurrence Of Chronic Lung Allograft Dysfunction After Lung Transplantation In A Population Of Cystic Fibrosis Patients. Am. J. Respir. Crit. Care Med. 2017;195.

20. Barnes S, Kotecha S, Douglass JA, Paul E, Hore-Lacy F, Hore-Lacey F, et al. Evolving practice: X-linked agammaglobulinemia and lung transplantation. Am J Transplant 2015;15(4):1110-3.

Figure legends

Figure 1. CONSORT diagram. ITT, intention to treat.

Figure 2 represents the allograft loss as a function of time since lung transplantation ranging between 01 January 2008 and 31 December 2013 with data being censored at 01 April 2018.

Figure 3 represents the admission rate per patient per year post transplantation for each diagnostic group compared with Bronchiectasis (IRR ± 95% confidence interval). BRO = Bronchiectasis, OLD = Obstructive Lung Disease, ILD = Interstitial Lung Disease and CF = Cystic Fibrosis.

Table 1. Baseline Characteristics

	All	OLD	CF	BRO	ILD	PH	p-value
Number	341	149	69	22	80	21	
Male sex	171 (50%)	60 (40%)	36 (52%)	13 (59%)	52 (65%)	10 (48%)	0.008
Age	50.4 ± 13.9	58.3 ± 6.4	30.9 ± 8.6	47 ± 14.1	56.3 ± 9.2	40.4 ± 12.7	<0.001
BMI (kg/m^2)	23.4 ± 4.6	23.6 ± 4.5	20.5 ± 3.3	22.4 ± 4.3	26.1 ± 4.4	23.6 ± 4.5	<0.001
Transplant type							
SLT	28 (8%)	9 (6%)	-	-	19 (24%)	-	
DLT	307 (90%)	140 (94%)	69 (100%)	21 (95%)	59 (74%)	18 (86%)	
HLT	5 (2%)	-	-	1 (5%)	1 (1%)	3 (14%)	
LKT	1 (<1%)	-	-	-	1 (1%)	-	

Values expressed as; number (%) or mean +/- standard deviation. Age (years) at date of transplantation; BMI, body mass index within 6 months prior to transplant; SLT, single lung transplant; DLT, double lung transplant; HLT, heart and lung transplant; LKT, lung and kidney transplant. BRO, non-cystic fibrosis bronchiectasis; OLD, Obstructive Lung Disease; ILD, Interstitial Lung Disease; CF, Cystic Fibrosis; PH Pulmonary Hypertension.

Table 2. Post transplantation outcomes

	All Patients n=341	OLD n=149	CF n=69	BRO n=22	ILD n=80	PH n=21
State at Censor						
Alive	186 (55%)	86 (58%)	42 (61%)	5 (23%)	40 (50%)	13 (62%)
Deceased	136 (40%)	58 (39%)	19 (27%)	15 (68%)	37 (46%)	7 (33%)
Re-transplanted	19 (5%)	5 (3%)	8 (12%)	2 (9%)	3 (4%)	1 (5%)
Lung Allograft Loss Cause						
Missing	24 (15%)	9 (14%)	1 (4%)	3 (18%)	9 (23%)	2 (25%)
Infective CLAD	37 (24%)	15 (24%)	7 (26%)	8 (47%)	6 (15%)	1 (13%)
Non-infective CLAD	70 (45%)	29 (46%)	16 (59%)	5 (29%)	17 (43%)	3 (38%)
Non-respiratory sepsis	8 (5%)	4 (6%)	1 (4%)	0 (0%)	1 (3%)	2 (25%)
Other	16 (10%)	6 (10%)	2 (7%)	1 (6%)	7 (18%)	0 (0%)

Values expressed as number (%) unless otherwise stated. OLD = Obstructive Lung Disease, CF = Cystic Fibrosis, BRO = Bronchiectasis, ILD = Interstitial Lung Disease, PHT = Pulmonary Hypertension & Congenital Heart Diseases, CLAD = chronic lung allograft dysfunction.

Supplementary Table 1 – Survival analysis of allograft (mortality or re-transplant)

Table S1. Multivariate Analysis – Survival analysis of allograft (mortality or re-transplant)

				Unadjusted		Adjusted for age and sex		
Diagnostic Group	**N**	**Median time followed (days)**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
BRO	22	1192	1					
OLD	149	1812	0.42	0.25-0.72	0.002	0.39	0.22-0.70	0.002
CF	69	2028	0.37	0.20-0.68	0.001	0.41	0.21-0.79	0.008
ILD	80	1741	0.54	0.31-0.95	0.03	0.50	0.27-0.90	0.02
PH	21	2015	0.37	0.16-0.86	0.02	0.39	0.17-0.90	0.03

BRO, non-cystic fibrosis bronchiectasis; OLD, Obstructive Lung Disease; ILD, Interstitial Lung Disease; CF, Cystic Fibrosis; PH Pulmonary Hypertension. HR, Hazard Ratio; 95%CI, 95th confidence interval.

Supplementary Table 2 – Bronchiectasis Aetiology and Cause of Lung Allograft Loss

Table S2. Bronchiectasis Aetiology and Cause of Lung Allograft Loss

	Cohort size	Number with Allograft loss	Cause of allograft loss			
			Infective CLAD	Non-infective CLAD	Non-Resp sepsis	Other
Idiopathic	4	4	2	1	0	1
Post infectious	8	6	5	1	0	0
Immunodeficiency	3	2	1	1*	0	0
Autoimmune	3	3	1	1+1*	0	0
Stem cell	3	1	1	0	0	0
Congenital Web	1	1	0	1	0	0

17 patients with lung allograft loss – 15 deceased and 2 re-transplanted.

Non-Resp sepsis = non respiratory sepsis. CLAD = chronic lung allograft dysfunction.

* patient re-transplanted

Supplementary Table 3 – Demographics of morbidity case control sub-group

Table S3. Demographics of morbidity case control sub-group

	OLD	CF	BRO	ILD
Number	22	22	21	22
Male sex	13 (59%)	13 (59%)	13 (62%)	13 (59%)
Age	60 ±6.33	33 ±9.8	48 ±12.9	55 ±10.18
BMI (kg/m^2)	24 ±3.5	20 ±3.4	22 ±4	26 ±4.8
Transplant type				
SLT	2 (9%)	0	0	5 (23%)
DLT	20 (91%)	22 (100%)	21 (100%)	16 (73%)
HLT	0	0	0	1 (4%)

Values expressed as; number (%) or mean +/- standard deviation. Age (years) at date of transplantation; BMI, body mass index within 6 months prior to transplant; SLT, single lung transplant; DLT, double lung transplant; HLT, heart and lung transplant. BRO, non-cystic fibrosis bronchiectasis; OLD, Obstructive Lung Disease; ILD, Interstitial Lung Disease; CF, Cystic Fibrosis;

Supplementary Table S4 – Aetiology of OLD, including those with minor concurrent bronchiectasis.

Table S4. Aetiology of Obstructive Lung Disease

	OLD =149	Concurrent BRO n=12
COPD/EMP	130 (87%)	9
A1AT	15 (10%)	1
Asthma	4 (3%)	2

Values expressed as number (%). OLD, Obstructive Lung Disease; COPD, Chronic obstructive pulmonary disease; EMP, Emphysema; A1AT, Alpha-1antitrypsin deficiency.

OUTCOMES OF NON-CYSTIC FIBROSIS RELATED BRONCHIECTASIS POST LUNG TRANSPLANTATION.

BACKGROUND:

Lung transplantation is a recognised treatment for end-stage lung disease due to bronchiectasis. Non-CF bronchiectasis and CF are often combined into one cohort, however outcomes for non-CF bronchiectasis patients varies between centres, and in comparison to those for CF.

AIMS:

To compare lung transplantation mortality and morbidity of bronchiectasis (non-CF) patients to those with CF and other indications.

METHODS:

Retrospective analysis of patients undergoing lung transplantation between 01 January 2008 - 31 December 2013. Time to and cause of lung allograft loss was censored on 01 April 2018. A case-note review was conducted on a sub-group of 78 patients, to analyse hospital admissions as a marker of morbidity.

RESULTS:

341 patients underwent lung transplantation, 22 (6%) had bronchiectasis compared to 69 (20%) with CF. The 5-year survival for the bronchiectasis group was 32%, compared to CF 69%, obstructive lung disease (OLD) 64%, pulmonary hypertension 62% and ILD 55% ($p = 0.008$). Lung allograft loss due to CLAD with predominant infection was significantly higher in the bronchiectasis group at 2 years. The rate of acute admissions was 2.24 higher in the bronchiectasis group when compared to OLD ($p = 0.01$). Patients with bronchiectasis spent 45.81 days in hospital per person year after transplantation compared with 18.21 days for CF.

CONCLUSIONS:

Bronchiectasis patients in this study had a lower 5-year survival and poorer outcomes in comparison to other indications including CF. Bronchiectasis should be considered a separate entity to CF in survival analysis.

KEY WORDS: Bronchiectasis, respiratory tract diseases, lung transplantation, morbidity

ORIGINAL RESEARCH

OUTCOMES OF NON-CYSTIC FIBROSIS RELATED BRONCHIECTASIS POST LUNG TRANSPLANTATION.

Jessica Kennedy[1,2,3] BBiomedSc. MBBS, FRACP

Anne Walker[1,4] MBBS, GradCertClinTch

Claire M. Ellender[1,5] BSc, MBBS, FRACP

Kate Steinfort[1] MBBS, MMed(CritCare)

Catherine Martin[6] BSc, PhD

Catherine Smith[6] BSc (Hons), MPH, MSc (App Stats)

Gregory Snell[1] MBBS, FRACP

Helen Whitford[1] MBBS, FRACP

[1]Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Melbourne, Australia.

[2]School of Medicine, Dentistry and Health Science, Melbourne University, Melbourne, Australia.

[3]Department of Respiratory and Sleep Medicine, Austin Hospital, Melbourne, Australia.

[4]Department of Thoracic Medicine, Royal Adelaide Hospital, South Australia, Australia

[5]Department of Respiratory & Sleep Medicine, Princess Alexandra Hospital, Brisbane, Australia

[6] Pubic Health and Preventative Medicine, Monash University, Melbourne, Australia.

CONTRIBUTIONS OF AUTHORS:

- Dr Jessica Kennedy, Consultant Respiratory and Sleep Physician: Principal investigator, Project plan, Data collection, Literature review, Primary author, Presenter at conference presentations to date; TSANZ SIG Oral 2016, Vic Branch TSANZ Oral 2016 & ATS Poster discussion 2017.
- Dr Annie Walker, Respiratory and Sleep Advanced Trainee: Co-author, Literature review, Data collection

- Dr Claire Ellender, Consultant Respiratory and Sleep Physician: Assistance with project design, Data collection, Review of manuscript
- D. Kate Steinfort, Anaesthetics Registrar: Data collection
- Dr Catherine Martin, Biostatistician, Monash University: Data analysis and interpretation
- Ms Catherine Smith, Biostatistician, Monash University: Data analysis and interpretation
- Dr Greg Snell, Consultant Respiratory and Lung Transplantation Physician: Manuscript review.
- Dr Helen Whitford, Consultant Respiratory and Lung Transplantation Physician: Supervisor of project, Project design, Plan, Analysis and Write up.

ACKNOWELDGEMENTS:

The authors wish to acknowledge the contribution of the Alfred Hospital Lung transplantation team for the patient care and maintaining the registry from which the cohort was sourced for this research.

GRANT SUPPORT: Nil

DECLARATION OF INTEREST STATEMENT: There are no conflicts of interest.

CORRESPONDING AUTHOR:

Dr Jessica Kennedy

Department of Respiratory and Sleep Medicine

Austin Hospital, 145 Studley Rd, Heidelberg VIC 3084, Melbourne, Australia

Phone number: +61394963688

Fax number: +61394965124

Email: jessicalouisekennedy@icloud.com

Abstract word count: 243

Main text word count: 2425

Figure 1

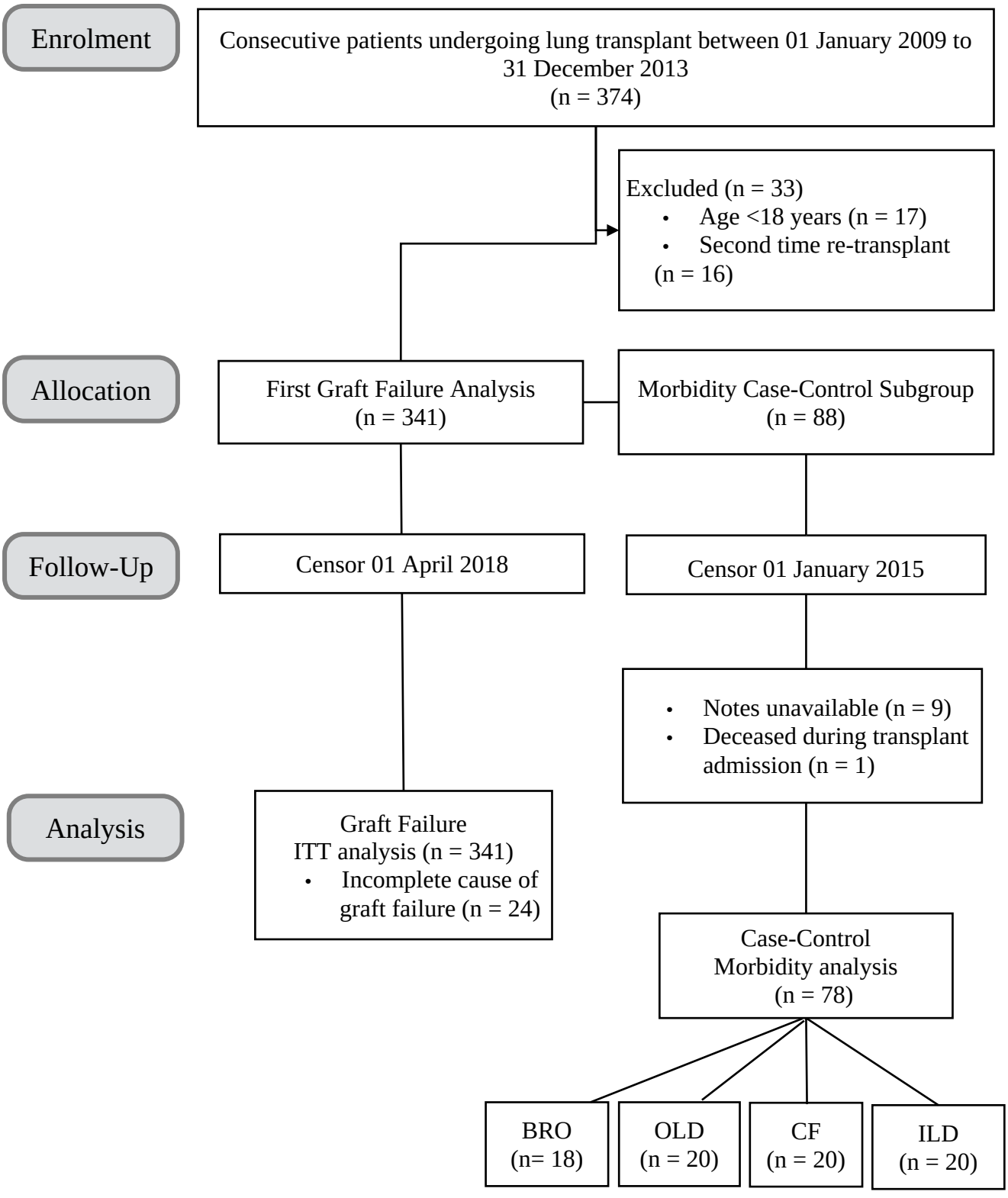
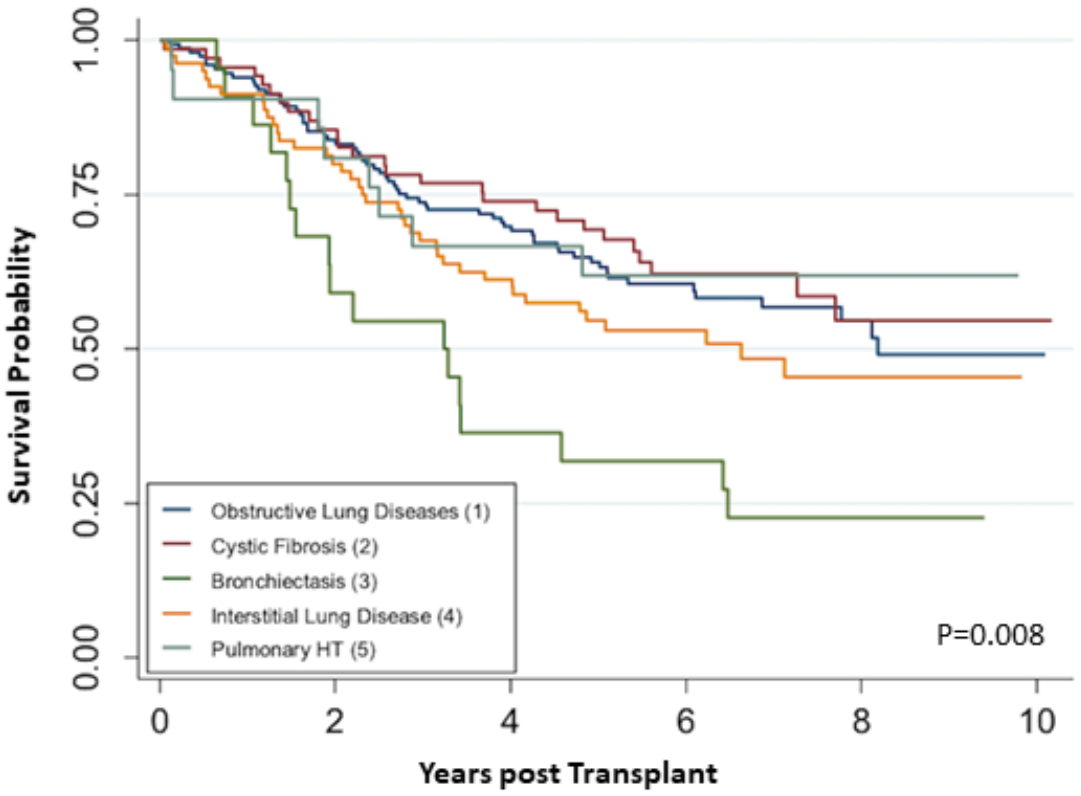


Figure 1. CONSORT diagram. ITT, intention to treat.

Figure 2. Primary Allograft Survival



At Risk (Events)

Diagnosis						
OLD (1)	149 (24)	125 (21)	104 (12)	56 (4)	22 (2)	3
CF (2)	69 (10)	59 (8)	50 (7)	29 (2)	12 (0)	3
BRO (3)	22 (9)	13 (5)	8 (1)	7 (2)	2 (0)	0
ILD (4)	80 (16)	64 (15)	49 (6)	26 (3)	9 (0)	0
PH (5)	21 (4)	17 (3)	14 (1)	10 (0)	5 (0)	0

Figure 2: Primary allograft survival, for each lung transplant indication diagnosis, as a function of time since lung transplantation for consecutive lung transplant recipients between 01 January 2008 and 31 December 2013. Data censored on 01 April 2018.

Figure 3 – Acute admission incident rate ratio

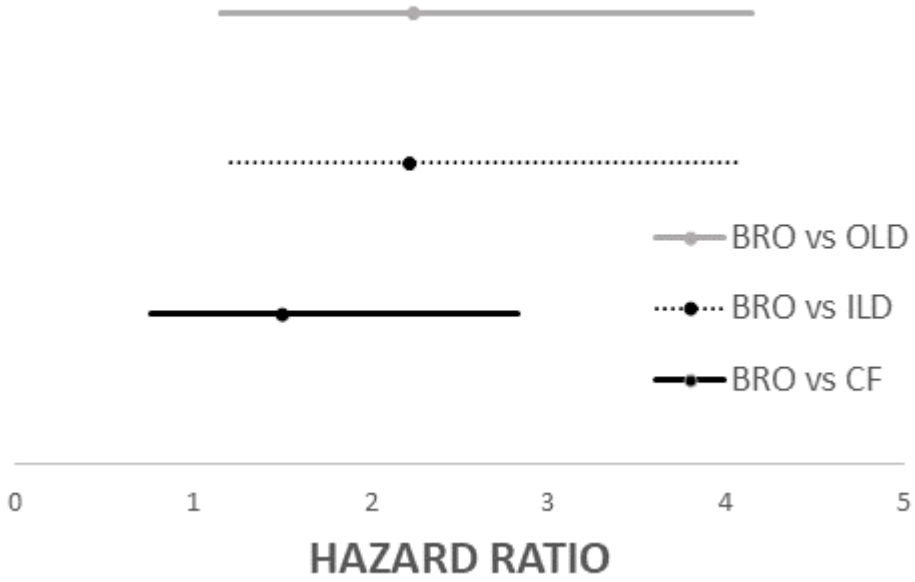


Figure 3 represents the admission rate per patient per year post transplantation for each diagnostic group compared with Bronchiectasis (IRR ± 95% confidence interval). BRO = Bronchiectasis, OLD = Obstructive Lung Disease, ILD = Interstitial Lung Disease and CF = Cystic Fibrosis.