ORIGINAL ARTICLE

Association between diverticular disease requiring surgical intervention and mortality in the postlung transplant population - a retrospective cohort study

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SUMMARY

Lung Transplant recipients are at increased risk of complicated diverticular disease. We aim to assess the rate of diverticular surgery in a postlung transplantation population and identify risk factors for surgery. We performed a retrospective cohort study of lung transplant recipients from 2007 to 2011. Demographic variables were evaluated with the Mann–Whitney U and chi-squared tests. Cox regression was performed to evaluate 1- and 2-year landmark survival, assess predictor variables of diverticular surgery and evaluate impact of surgery on CLAD development. Of 17 of 158 patients (10.7%) underwent diverticular-related surgery. Surgical patients had significantly worse survival than nonsurgical patients at 1 year [aHR 2.93 (1.05–8.21), $P = 0.041$] and 2 year [aHR 4.17 (1.26–13.84), $P = 0.020$] landmark analyses. Transplant indication of alpha-1 antitrypsin disease and cystic fibrosis were significantly associated with the need for diverticular surgery. Emergent surgery was associated with poorer survival [aHR 5.12(1.00–26.27), $P = 0.050$]. Lung transplant patients requiring surgery for complicated diverticular disease have significantly poorer survival than those who do not require surgery. Surgery was more common in patients transplanted for A1AT and CF. Optimal assessment and risk stratification of diverticular disease is necessary to prevent excessive morbidity and mortality following transplantation.

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Introduction

Gastrointestinal complications are common after lung transplant and can be a major source of morbidity and mortality for these recipients [1]. Lung transplant recipients are at higher risk of developing diverticular disease and related complications when compared to an age-matched general population [2]. The broad spectrum of diverticular disease described in lung transplant recipients ranges from uncomplicated diverticulitis to colonic perforation and death [3–6]. Although the increased incidence of diverticular disease and related complications has been reported previously, the specific impact on post-transplant outcomes remains unclear and no factors have been identified which accurately predict the development of complicated diverticulitis.

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Diverticulosis has long been characterized as a disease of the elderly with epidemiologic studies showing an incidence of < 30% in those under 40 as compared with >60% in those over the age of 60 [7–9]. Although there is a high prevalence of diverticular disease, it is diagnosed coincidentally in the majority of people during imaging or procedures performed for other reasons. Most people in the general population with diverticular disease remain asymptomatic with only about twenty to thirty percent ever developing symptoms and less than that ever requiring any intervention [10]. Although no factors have been able to accurately predict complications related to diverticular disease, studies in the general population have found an association with age, male sex, obesity, concomitant hypertension and atherosclerotic disease [11–15]. The increase in average lung transplant recipient age makes it likely that this problem will be increasingly prevalent among this population. Since the implementation of the lung allocation score (LAS), the indications for lung transplant have changed such that idiopathic pulmonary fibrosis (IPF) and other interstitial lung diseases (ILDs) have become the most common indication for lung transplantation, allowing for the most urgent patients with advanced lung disease to receive lung transplantation quickly [16]. The indirect resulting trend over recent years is an increasingly ageing lung transplant population as more than half of patients transplanted for IPF are over the age of 60 as opposed to previously more common indications such as CF where approximately 70% of patients are under the age of 35 [17].

Within the lung transplant population, the prevalence of diverticular-related gastrointestinal complications is highly variable, ranging from 10% to as high as 50% of transplanted patients [18–20]. When diverticulitis occurs in lung transplant recipients, it tends to occur early in the post-transplant period and is more likely to be associated with severe complications, such as perforation, peritonitis and need for surgical intervention, than in the general population [18,19]. Our aim is to assess the rate of complicated diverticular disease requiring surgery in our post-lung transplantation population, to identify any risk factors that might be associated with its development and to determine the effect on post-transplant outcomes including graft survival and rejection.

Materials and methods

Study design and population

We conducted a retrospective cohort study that included all adult (≥18 years) lung transplant recipients at Loyola University Medical Center between January 1, 2007 and December 31, 2011. The presence of pretransplant diverticular disease was identified from pretransplant screening colonoscopy, which all patients over the age of 50 or with prior GI disease are required to receive as part of the evaluation process. Post-transplant diverticular disease and related surgery was identified using ICD-9 codes and manual chart review. Patients without pretransplant screening colonoscopy documenting presence or absence of diverticular disease to allow for comparison post-transplant and those who expired in the immediate postoperative period (≤30 days) were excluded from the analysis. Additional data collected included baseline demographic data, presence or absence of coronary artery disease (CAD) and diabetes mellitus (DM) as well as cumulative acute rejection (CAR) score. The CAR score was calculated, as has been previously described, as the sum of acute rejection episodes (i.e. A0 is a score of 0, A1 is a score of 1, etc.) and was dichotomized at ≥ 3 [21].

Immunosuppression

A standard maintenance immunosuppression regimen was utilized at our institution during the study period and included induction immunosuppression with an IL-2 receptor antagonist (daclizumab or basiliximab), a calcineurin inhibitor (tacrolimus or cyclosporine), an antiproliferative agent (mycophenolate or azathioprine), and corticosteroids. Changes to individual immunosuppression therapy were determined on a case-by-case basis at the discretion of the treating physician to target protocolized trough goal levels of calcineurin inhibitor (10–15 for tacrolimus and 30–350 for cyclosporine within the first year post-transplant), protocolized steroid dose (in the absence of infection/rejection episodes, steroids tapered from 1 g daily of methylprednisolone intra-op to a post-op goal of 5 mg prednisone daily by 6 months post-transplant), and based on clinical signs/symptoms for antiproliferative agents (i.e. infection, leukopenia). This study was reviewed and approved by the Loyola University Chicago Health Sciences Division Institutional Review Board for the Protection of Human Subjects LU204872.

Statistical analysis

Baseline demographics are expressed as means with standard deviations for normally distributed continuous variables, median and interquartile range for non-normally distributed continuous variables and percentages for categorical variables. Comparisons of baseline demographics

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were made using Pearson's χ^2 for categorical variables, student's *t*-test for continuous variables that were normally distributed and Mann–Whitney U for continuous variables that were not normally distributed. One-year and 2-year landmark survival analyses were performed as previously described [22] utilizing a Cox proportional hazards regression model. This method involves including only patients who have survived to the landmark time and defining the outcome of interest up to the landmark analysis time. All univariable predictors with $P < 0.15$ or with previously demonstrated significant clinical impact were included in the final multivariable survival models. Cox regression modelling was also utilized to assess predictor variables for diverticular surgery, impact of surgery on time to CLAD development and impact of surgery urgency on postsurgical survival. Results were considered statistically significant with a two-sided *P*-value of < 0.05. All statistical analyses were performed using IBM SPSS (IBM Corp. IBM SPSS Statistics for Macintosh, Version 24.0. Released 2016. Armonk, NY, USA).

Results

Patient characteristics

A total of 201 patients were transplanted during the selected time frame (Fig. 1). Of these, 158 had a documented pretransplant colonoscopy and were included in the analysis. Seventy-eight of 158 patients (49.4%) had documented diverticular disease prior to transplant. Twenty-five patients had a diagnosis of diverticulitis post-transplant, 17 of whom underwent surgery for complications because of diverticular disease. Of the 17 patients requiring surgery, 10 patients had known diverticular disease identified pretransplant and seven patients had no diverticular disease identified on pretransplant screening. Table 1 shows baseline demographics of the patients who required diverticular surgery versus those who did not require surgery. There was a significant difference in pulmonary diagnosis between the surgical and nonsurgical groups with a higher percentage of patients in the surgical group transplanted for alpha-1 antitrypsin (17.6%) and cystic fibrosis (17.6%) in contrast to only 2.8% each in the nonsurgical group ($P = 0.003$).

The details of surgery site and type, immunosuppression regimen and changes, and surgical outcomes are reported in Table S1. Sixteen of 17 surgical patients had diverticulitis of the colon. The most common procedure was a Hartmann's, which nine of 17 underwent. Additionally, all but one patient had either their calcineurin inhibitor or their anti-metabolite stopped or decreased. Surgery was emergent in 10 of 17 patients and 2 of 17 patients died within 30 days of surgery from direct complications.

Predicting diverticular surgery

In univariable modelling, pulmonary diagnosis of A1AT and CF were independently associated with the need for diverticular surgery [HR 5.53 (1.32–23.21, $P = 0.019$ and HR 4.93 (1.18–20.65), $P = 0.029$, respectively]. In a multivariable model, both diagnoses remained significantly associated with diverticular surgery [A1AT: HR 6.76 (1.51—30.29), $P = 0.013$, CF: HR 6.24 (1.35–28.80),

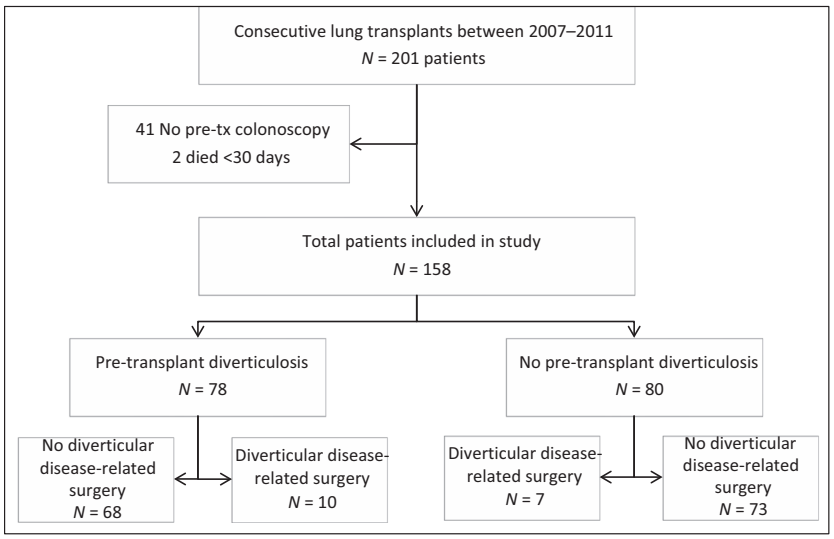

Figure 1 Flow chart of patients included in the study.

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Table 1. Cohort baseline demographics.

	Overall n = 158	No diverticular surgery, n = 141	Diverticular surgery n = 17	P-value
Age, years, median (IQR)	59 (52.8–64)	59 (53–64)	60 (50–65.5)	0.782
Female sex, n (%)	79 (50)	70 (49.6)	9 (52.9)	0.797
Race, n (%)				
White	133 (84.2)	119 (84.4)	14 (82.4)	
Black	15 (9.5)	14 (9.9)	1 (5.9)	0.400
Hispanic	7 (4.4)	5 (3.5)	2 (11.8)	
Other	3 (1.9)	3 (2.1)	0	
LAS, median (IQR)	38.96 (33.57–48.28)	38.58 (33.66–48.31)	42.38 (33.26–49.05)	0.588
Transplant type, n (%)				
Single	96 (60.8)	84 (59.6)	12 (70.6)	
Double	49 (31.0)	44 (31.2)	5 (29.4)	0.389
Re-do	13 (8.2)	13 (9.2)	0	
Transplant indication, n (%)				
COPD	59 (37.3)	54 (38.3)	5 (29.4)	
ILD	69 (43.7)	63 (44.7)	6 (35.3)	0.003
A1AT	7 (4.4)	4 (2.8)	3 (17.6)	
CF	7 (4.4)	4 (2.8)	3 (17.6)	
Other	16 (10.1)	16 (11.3)	0 (0)	
Induction, n (%)				
None	44 (27.8)	41 (29.1)	3 (17.6)	0.494
Daclizumab	73 (46.2)	63 (44.7)	10 (58.8)	
Basiliximab	41 (25.9)	37 (26.2)	4 (23.5)	
Antiproliferative agent*				
Azathioprine	110 (69.6)	98 (69.5)	12 (70.6)	0.940
Mycophenolate	47 (29.7)	42 (29.8)	5 (29.4)	
Calcineurin inhibitor*				
Cyclosporine	12 (7.6)	11 (7.8)	1 (5.9)	0.902
Tacrolimus	145 (91.8)	129 (91.5)	16 (94.1)	
BMI, median (IQR)	25.68 (22.88–28.71)	25.76 (22.85–28.73)	25.61 (23.23–28.42)	0.892
CAD-positive, n (%)	32 (20.2)	29 (20.6)	3 (17.6)	0.777
DM-positive, n (%)	16 (10.1)	14 (9.9)	2 (11.8)	0.813
Pretransplant diverticulosis, n (%)	78 (49.4)	68 (48.2)	10 (58.8)	0.409
Surgery, n (%)				
Emergent		-	10 (58.8)	
Nonemergent		-	7 (41.2)	
CAR score ≥ 3, n (%)	60	52 (36.9)	8 (47.1)	0.414

BMI, body mass index; CAD, coronary artery disease; CAR, cumulative acute rejection; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; A1AT, alpha-1 antitrypsin disease; CF, cystic fibrosis; BOS, bronchiolitis obliterans; PAH, pulmonary arterial hypertension; ILD, interstitial lung disease; DM, diabetes mellitus; IQR, interquartile range; LAS, lung allocation score.

*Overall total 157 instead of 158 because one subject not on immunosuppression.

P = 0.019] while age >65 years at time of transplant also had an increased risk, but did not reach statistical significance [HR 3.01 (0.94–9.62) P = 0.064] (Table 2).

Survival after diverticulitis and diverticular surgery

The 25 patients who developed diverticulitis had worse survival than patients who did not develop diverticulitis, although this did not reach significance [median 44.2 months (IQR 34.2–54.2) vs. median 55.9 months (IQR 51.3–60.7), P = 0.091]. The 17 patients who underwent diverticular surgery did so at a median of 143 days post-transplant (IQR 16–233 days). The median survival after surgery was 21.8 months (IQR 8.4–28.8 months). Diverticular surgery was independently associated with poorer survival at 1-year landmark survival analysis [Table 3 and Fig. 2a, aHR = 2.93 (1.05–8.21), P = 0.041]. This relationship increased at the 2-year landmark survival analysis, [Table 4 and Fig. 2b, aHR 4.17 (1.26–13.84), P = 0.020], Fig. 2b). Overall, having diverticulosis

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Table 2. Cox regression analysis for predictors of diverticular surgery.

	Univariate analysis		Multivariate analysis	
Variable	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age > 65	1.93 (0.68–5.52)	0.217	3.01 (0.94–9.62)	0.064
Race (ref: White)		0.465		
Black	0.64 (0.08–4.85)	0.664		
Hispanic	3.10 (0.71–13.66)	0.136		
Sex (ref: male)	1.13 (0.43–2.92)	0.808		
Indication (ref: COPD)		0.018		0.011
ILD	1.08 (0.33–3.56)	0.893	1.04 (0.32–3.42)	0.951
A1AT	5.53 (1.32–23.21)	0.019	6.76 (1.51–30.29)	0.013
CF	4.93 (1.18–20.65)	0.029	6.24 (1.35–28.80)	0.019
LAS	0.99 (0.96–1.03)	0.754		
BMI	0.39 (0.05–2.96)	0.364		
CAD	0.92 (0.26–3.21)	0.898		
DM	1.03 (0.23–4.50)	0.972		
Induction therapy (Ref: None)		0.625		
Daclizumab	1.88 (0.52–6.87)	0.339		
Basiliximab	1.48 (0.33–6.63)	0.611		
Antiproliferative Agent (AZA vs. MPA)	0.88 (0.30–2.55)	0.817		
Calcineurin inhibitor (CSA vs. TAC)	0.83 (0.11–6.25)	0.856		
CAR ≥ 3 at 1 year	1.42 (0.55–3.69)	0.469		
Pretransplant diverticulosis (ref: no)	1.45 (0.55–3.80)	0.455		
Prediagnosed CLAD	0.21 (0.03–1.61)	0.134	0.18 (0.02–1.47)	0.110

identified on pretransplant screening colonoscopy was not associated with a survival difference post-transplant (Fig. 3a). For those patients who underwent surgery for diverticular disease, having identified diverticulosis on pretransplant screening colonoscopy had no effect on post-transplant survival in a 1-year landmark analysis (Fig. 3b). Finally, emergent surgical intervention was associated with poorer survival than nonemergent surgical intervention [HR 5.12 (1.00–26.27), $P = 0.050$, Fig. 4].

CLAD and diverticular surgery

In evaluating the impact of diverticular surgery on the subsequent development of CLAD, 1-year landmark analysis revealed that diverticular surgery was not significantly associated with the subsequent development of CLAD [aHR 1.86 (0.78–4.40), $P = 0.159$], while acute rejection at 1 year was associated with a significantly higher risk of subsequent development of CLAD [aHR 2.13 (1.15–3.94), $P = 0.016$, Table S2, Figure S1].

Discussion

Diverticular disease requiring surgical intervention is a major cause of morbidity and mortality following lung transplantation. The major finding of this investigation is that lung transplant patients who undergo intra-abdominal surgery for complications related to diverticular disease have significantly poorer survival than those patients who do not require surgery. The over fourfold increase in mortality in this group of lung transplant recipients remained despite adjusting for other comorbidities. Additionally, patients undergoing transplantation for A1AT or CF were at an over fivefold increased risk of developing diverticular disease necessitating surgical intervention compared to patients with other indications for lung transplantation.

In our cohort, 10% of patients required surgery for complicated diverticular disease. This rate is consistent with previous investigations of patients with diverticular disease post-transplantation which have found surgical rates varying from 4.5% (8) [20], to as high as 40% [20,23]. This increase in complicated diverticular disease following transplant is significantly higher than what has been described in the general population. Qasabian *et al.* compared the incidence of severe diverticulitis in a cohort of 953 patients who were postheart, lung or heart-lung transplant to the general population and found a substantially increased risk among transplant patients with an incidence ratio of 22.2 when compared to an age-matched general population (95% CI 9.9–50, $P < 0.001$) [2]. Complications from diverticular disease

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Table 3. Univariate and multivariate Cox regression analysis for 1-year landmark survival.

1-year landmark Cox regression analysis for survival				
	Univariate analysis		Multivariate analysis	
Variable	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age ≥ 65	2.47 (1.02–5.98)	0.045	2.01 (0.80–5.05)	0.138
Race (ref: White)		0.826		
Black	0.38 (0.05–2.82)	0.344		
Hispanic	0.98 (0.13–7.24)	0.980		
Sex (ref: male)	0.99 (0.44–2.21)	0.981		
Indication (ref: COPD)		0.880		
ILD	0.66 (0.25–1.74)	0.402		
A1AT	0.98 (0.12–7.59)	0.978		
CF	1.13 (0.25–5.16)	0.877		
Retransplant	1.57 (0.43–5.72)	0.492		
LAS	1.01 (0.97–1.03)	0.989		
BMI ≥ 30	0.68 (0.16–2.89)	0.603		
CAD	0.59 (0.18–1.99)	0.401		
DM	0.54 (0.13–2.31)	0.408		
Induction therapy (ref: none)		0.627		
Daclizumab	0.74 (0.31–1.80)	0.510		
Basiliximab	0.49 (0.10–2.38)	0.378		
Antiproliferative Agent (AZA vs. MPA)	0.58 (0.20–1.60)	0.284		
Calcineurin Inhibitor (CSA vs. Tac)	0.56 (0.08–4.12)	0.566		
CAR ≥ 3 at 1 year	1.31 (0.59–2.92)	0.511		
Pretransplant diverticulosis (ref: no)	1.04 (0.47–2.32)	0.916		
Diverticular Surgery at 1 Year	3.58 (1.33–9.62)	0.011	2.93 (1.05–8.21)	0.041

also appear to develop early in the post-transplant period. In our study, median time to surgery was less than six months, with 100% occurring within the first two years. This is consistent with prior studies [24]. However, while the aforementioned studies have evaluated the rate and severity of complicated diverticular disease in lung transplant patients as well as surgical morbidity and mortality in this population compared to a nonimmunosuppressed population, the current investigation is novel in its evaluation of the impact that surgery, as a treatment for complicated diverticular disease, has on overall post-transplant survival when compared to transplant recipients who do not develop this complication.

Following transplantation, there are a variety of risk factors that could account for the increased incidence of diverticular disease that we observed. The most commonly considered risk factor post-transplant is the addition of anti-rejection medications, and more specifically, corticosteroids. Lung transplant recipients in particular tend to receive increased amount of anti-rejection medications and corticosteroids in order to achieve higher levels of immunosuppression compared to not only the age-matched general population, but also other solid organ transplant recipients [19,25]. These recipients may receive large doses of corticosteroids in order to treat rejection. Interestingly, patients in this investigation who required surgery tended to have higher CAR scores, although this did not reach statistical significance. Beaver *et al.* evaluated a series of four lung transplant recipients who developed complicated diverticulitis leading to colon perforation and the need for surgical intervention after transplant. In their cohort, complicated diverticular disease was associated with corticosteroid use, and those that developed this complication had a 50% mortality rate [26]. Steroids have been implicated in several other investigations in the development of diverticulitis and other colonic pathology. Several transplant centres reported an increased incidence of colon perforation after treatment for acute rejection. In a series of nontransplant patients who suffered a colonic perforation secondary to diverticulitis, 22% were discovered to have been receiving corticosteroids [27–29]. Rapid taper of corticosteroids after treatment of acute rejection and steroid sparing maintenance regimens to reduce cumulative steroid exposure might be beneficial to minimize the risk of gastrointestinal complications such as complicated diverticular disease.

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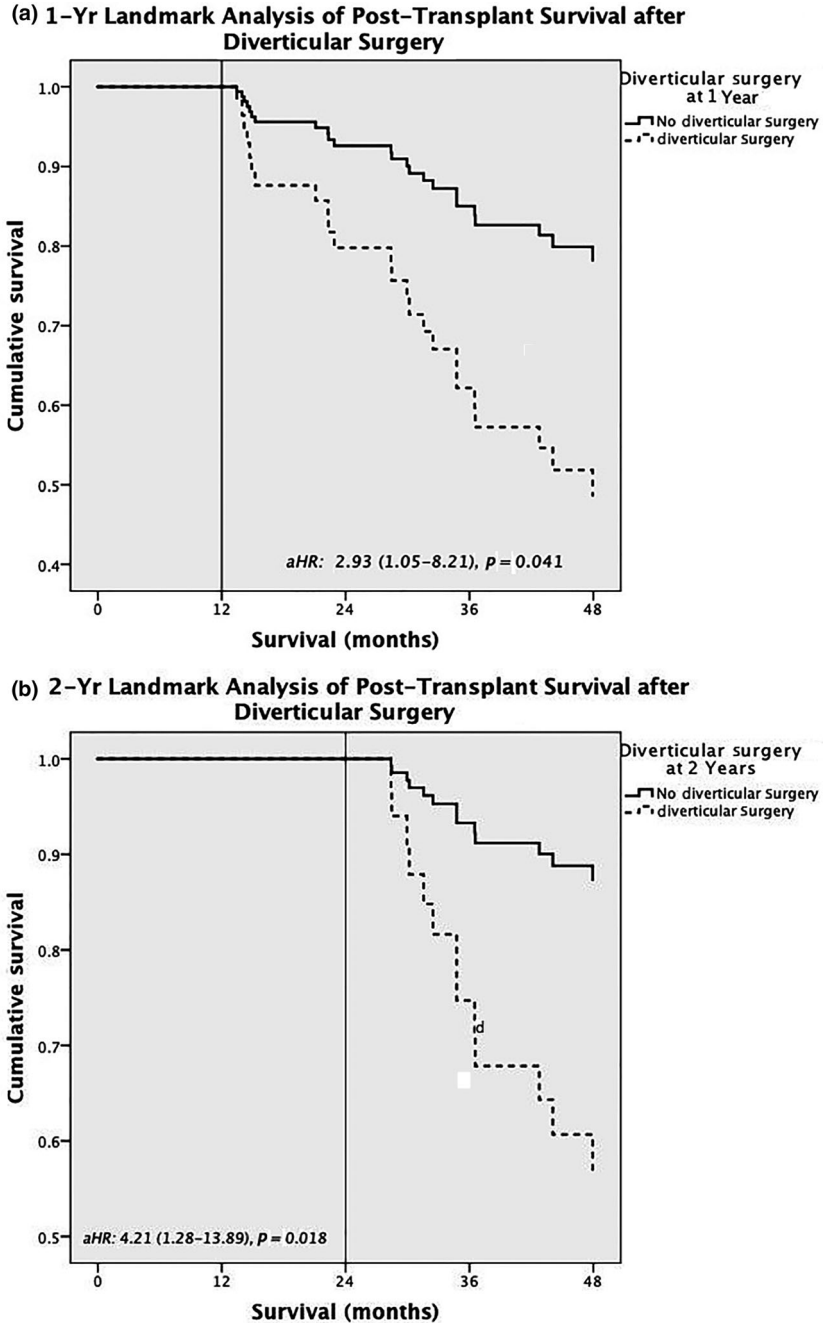

Figure 2 Multivariate Cox regression analysis of post-transplant survival after diverticular surgery by (a) 1-year and (b) 2-year landmark survival analysis. Vertical reference lines indicate the landmark time set for each analysis. Covariates for final multivariable analysis for (a) include age and diverticular surgery by 1 year. Adjusted hazard ratios for all variables included in the final multivariable 1-year landmark analysis are reported in Table 3. Covariates for final multivariable analysis for (b) include cumulative acute rejection score at 2 years, pre-existing CLAD and diverticular surgery at 2 years. Adjusted hazard ratios for all variables included in the final multivariable 1-year Landmark analysis are reported in Table 4.

An interesting finding was that about 40% of the patients who underwent surgery for complicated diverticular disease did not have a pre-existing diagnosis of diverticulosis. This might be due, in part, to incomplete evaluation pretransplant as several of those patients went on to develop R-sided disease and two even had small intestine involvement. However, the *de novo* development of not only diverticulosis, but also progression to

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Table 4. Univariate and multivariate Cox regression analysis for 2-year landmark survival.

2-year landmark Cox regression analysis for survival				
	Univariate analysis		Multivariate analysis	
Variable	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age	0.98 (0.93–1.03)	0.462		
Race (ref: White)		0.923		
Black	1.04 (0.13–8.09)	0.968		
Hispanic	2.06 (0.27–16.05)	0.489		
Sex (ref: male)	1.48 (0.48–4.54)	0.489		
Indication (ref: COPD)		0.740		
ILD	0.57 (0.17–1.94)	0.368		
A1AT	1.62 (0.43–9.72)	0.988		
CF	1.36 (0.28–6.55)	0.704		
Retransplant	0.43 (0.05–3.53)	0.435		
LAS	0.98 (0.93–1.03)	0.417		
BMI $\geq$ 30	0.67 (0.09–5.16)	0.700		
CAD	0.35 (0.04–2.69)	0.313		
DM	1.02 (0.23–4.60)	0.981		
Induction therapy (ref: none)		0.228		
Daclizumab	0.38 (0.13–1.15)	0.086		
Basiliximab	0.98 (0.94–1.06)	0.982		
Antiproliferative agent (AZA vs. MPA)	0.78 (0.10–6.04)	0.812		
Calcineurin inhibitor (CSA vs. Tac)	0.93 (0.12–7.14)	0.943		
CAR $\geq$ 3 at 2 years	2.63 (0.86–8.05)	0.090	2.47 (0.81–7.53)	0.111
Pretransplant diverticulosis (ref: no)	2.41 (0.74–7.82)	0.145		
Diverticular surgery at 2 years	4.78 (1.47–15.60)	0.009	4.17 (1.26–13.84)	0.020
CLAD diagnosis prior to surgery	2.67 (0.89–7.97)	0.079	2.96 (0.97–9.03)	0.056

diverticulitis and related complications is an area that, while previously recognized, requires more exploration [30]. There are multiple reasons why transplant patients might be at increased risk of *de novo* or aggressive diverticular disease. Beginning with the perioperative period, transplant recipients are at a higher risk for bowel ischaemia, especially if cardiopulmonary bypass is utilized during the transplant operation [31–33]. Additionally, the high doses of immunosuppression and the frequent use of broad spectrum antibiotics can significantly alter the gastrointestinal microbiome [34–37]. All of these might have a significant impact on the integrity of the gastrointestinal mucosa. This is highlighted by the fact that most surgeries, both in our cohort and in similar studies, tend to happen earlier in the post-transplant period, when recipients are exposed to higher rates of these various insults [38,39]. This, combined with other genetic and environmental risk factors, might put certain patients at higher risk for *de novo* and more rapidly progressive diverticular disease particularly in the early post-transplant period.

Two such genetic conditions commonly associated with gastrointestinal derangements and frequently leading to the need for lung transplantation are A1AT and CF. In fact, we found that transplantation for both A1AT and CF was associated with the need for diverticular surgery following lung transplantation. Although prior investigations evaluating the need for early surgical intervention following lung transplantation had noted an increased incidence among people transplanted for A1AT, they were not able to correlate this with a difference in survival [40,41]. The present investigation not only linked A1AT to increased incidence of complicated diverticular disease requiring surgery, but also demonstrated a significant difference in subsequent survival. Outside of the lung transplant population, this finding is consistent with investigations from both the National Heart, Lung and Blood Institute's (NHLBI) registry and the Swedish National A1AT registry which found an increased risk of death because of diverticulitis in patients with severe A1AT deficiency compared to age- and sex-matched controls in the general population [42,43]. Although the exact mechanism is unclear, A1AT has been linked to inflammation in the colon. Preclinical models have shown that A1AT can attenuate inflammation in the small and large bowel through reduction of pro-

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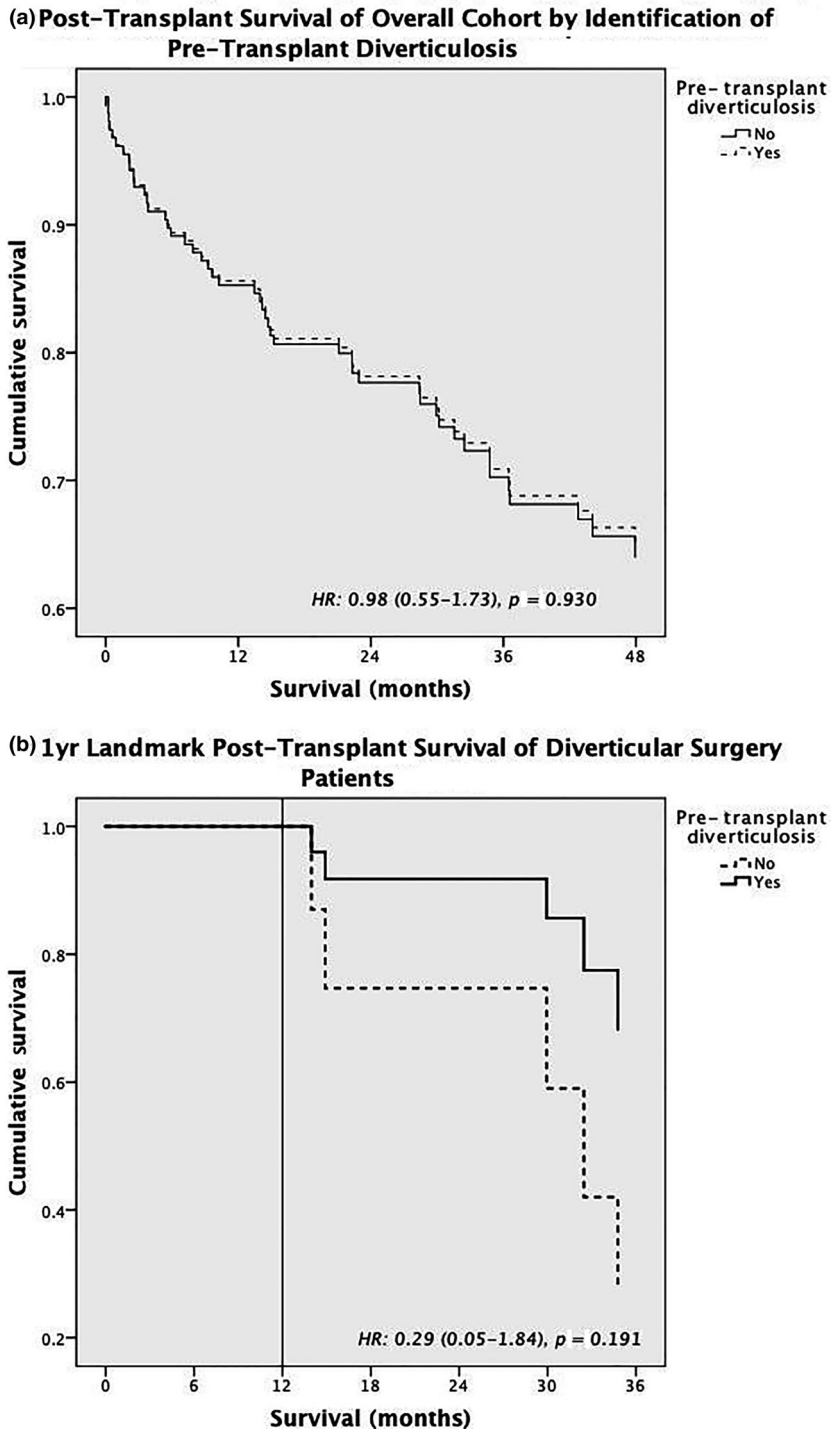

Figure 3 (a) Overall post-transplant univariable Cox regression survival analysis of entire cohort by identification of pretransplant diverticulosis and (b) 1-year landmark univariable Cox Regression survival analysis of patients undergoing diverticular surgery within the first post-transplant year. Vertical line indicates landmark timepoint.

inflammatory cytokines [44]. Additionally, A1AT is known to have anti-inflammatory activity, and levels are associated with other markers of inflammation in patients with inflammatory bowel disease [45,46]. A1AT deficiency is likely to be exacerbated in the setting of immunosuppression after transplantation. It is important for transplant pulmonologists to be aware of the increased risk of complicated diverticular disease

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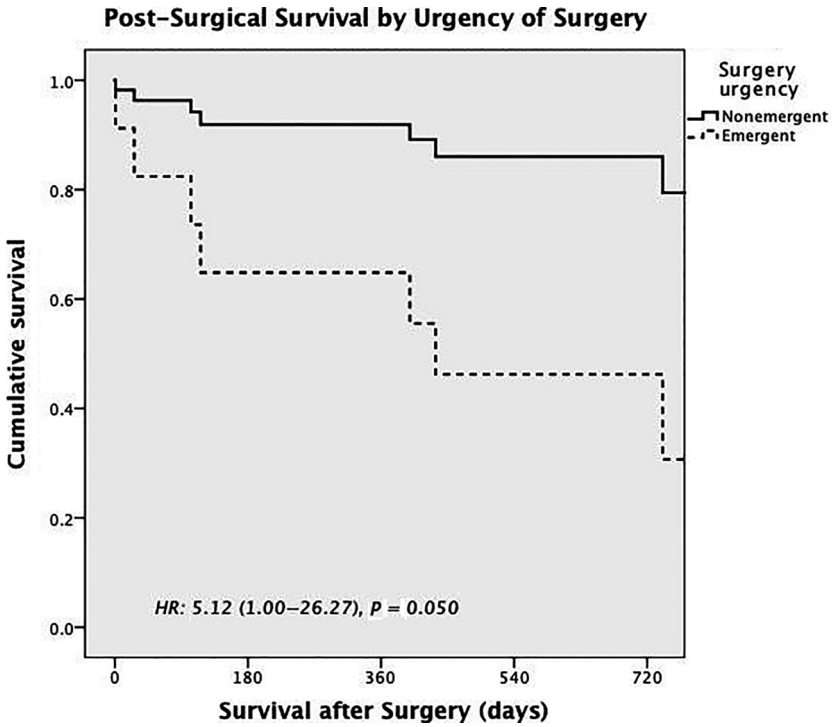

Figure 4 Univariable Cox regression analysis of impact of surgery urgency on postsurgical survival. Time 0 on the *x*-axis signifies the time of surgery, not time of transplant.

requiring surgical intervention following lung transplant in these patients.

An important factor potentially contributing to the increased mortality associated with diverticular surgery after transplant is the timing of the surgery and whether it is elective or emergent. Of the 17 patients in our cohort who required diverticular-related surgery post-transplant, 10 underwent emergent surgery because of perforation or concern for impending perforation. Despite our small cohort, we were able to see a nearly significant trend for poorer survival in lung transplant patients requiring emergent surgery. The finding of poorer survival following emergent procedures is consistent with previously reported findings. Studies in both the general and transplant populations evaluating the timing of surgical intervention and impact on mortality have shown a trend towards improved survival in patients undergoing earlier, elective surgical treatment [47–49]. Reshef *et al.* performed a case–control study of solid organ transplant recipients and found worse post-operative outcomes for urgent surgery when compared to elective surgery [50]. Similarly, in a cohort of lung transplant patients with severe diverticulitis requiring surgery, Timrott *et al.* found that an emergency surgical intervention was associated with a 28% higher mortality rate compared to patients not requiring surgery, while elective surgical interventions had no influence on mortality [51]. These studies suggest that transplant pulmonologists and care team members caring for lung transplant recipients should be vigilant about the development of diverticular-related complications. Given the favourable outcomes with nonemergent surgery among solid organ transplant recipients, an earlier surgical intervention for severe diverticular disease might lead to more favourable long-term outcomes compared to more conservative approaches. Indeed the American Society of Colon and Rectal Surgeons acknowledges this with their recommendation to consider earlier surgical intervention for solid organ transplant recipients [52]. It remains to be determined if any screening is warranted in patients with known diverticular disease who are considered high risk because of their immunosuppressed status.

At the end, conclusively, transplant patients are at higher risk for developing complications from diverticular disease post-transplant than the general population. Those who develop complicated diverticular disease have an increased mortality. The current method of screening with a colonoscopy pretransplant does not reliably identify those patients at increased risk for developing complications from diverticular disease post-transplant. Those with a diagnosis of A1AT or CF seem

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to have a significantly higher risk of developing complicated diverticular disease post-transplant. This investigation was unable to identify any other pretransplant or perioperative risk factors predictive of diverticular disease requiring surgery. Post-transplant surveillance of high-risk patients is an area that needs further investigation. In those recipients in whom high-risk diverticular disease is identified, an aggressive approach with early surgery as opposed to waiting until an emergent situation occurs is beneficial.

Authorship

LKT participated in research design, performance of the research, data analysis and writing the manuscript. WA participated in research design and data analysis. KAY participated in performance of the research and data analysis. OJK participated in performance of the research and data analysis. EM participated in performance of the research and writing the manuscript. EL participated in research design, performance of the research, data analysis and writing the manuscript. All authors reviewed and offered feedback and approval of the final manuscript.

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Conflict of interest

The authors have no relevant financial conflicts of interest to disclose.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. 1-year landmark analysis of time to CLAD development by diverticular surgery status.

Table S1. Site and surgery outcomes for patients undergoing diverticular surgery.

Table S2. 1-year landmark Cox regression analysis for predictors of chronic lung allograft dysfunction.

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