Oesophageal stasis is a risk factor for chronic lung allograft dysfunction and allograft failure in lung transplant recipients

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Lung transplant recipients with oesophageal motility disorders are at an increased risk of chronic lung allograft dysfunction and failure. https://bit.ly/3PPKqaI

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Abstract

Background Morbidity and mortality in lung transplant recipients are often triggered by recurrent aspiration events, potentiated by oesophageal and gastric disorders. Previous small studies have shown conflicting associations between oesophageal function and the development of chronic lung allograft dysfunction (CLAD). Herein, we sought to investigate the relationship between oesophageal motility disorders and long-term outcomes in a large retrospective cohort of lung transplant recipients.

Methods All lung transplant recipients at the Toronto Lung Transplant Program from 2012 to 2018 with available oesophageal manometry testing within the first 7 months post-transplant were included in this study. Patients were categorised according to the Chicago Classification of oesophageal disorders (v3.0). Associations between oesophageal motility disorders with the development of CLAD and allograft failure (defined as death or re-transplantation) were assessed.

Results Of 487 patients, 57 (12%) had oesophagogastric junction outflow obstruction (OGJOO) and 47 (10%) had a disorder of peristalsis (eight major, 39 minor). In a multivariable analysis, OGJOO was associated with an increased risk of CLAD (HR 1.71, 95% CI 1.15–2.55, p=0.008) and allograft failure (HR 1.69, 95% CI 1.13–2.53, p=0.01). Major disorders of peristalsis were associated with an increased risk of CLAD (HR 1.55, 95% CI 1.01–2.37, p=0.04) and allograft failure (HR 3.33, 95% CI 1.53–7.25, p=0.002). Minor disorders of peristalsis were not significantly associated with CLAD or allograft failure.

Conclusion Lung transplant recipients with oesophageal stasis characterised by OGJOO or major disorders of peristalsis were at an increased risk of adverse long-term outcomes. These findings will help with risk stratification of lung transplant recipients and personalisation of treatment for aspiration prevention.

Introduction

Lung transplantation is the only therapeutic option for people with end-stage lung disease. However, allograft survival remains relatively poor with a median survival of approximately 6 years post-transplant [1]. Chronic lung allograft dysfunction (CLAD) is the leading cause of death among lung transplant recipients. Several subtypes of CLAD have been described: the more common phenotype of bronchiolitis obliterans syndrome (BOS), which primarily affects the airways, and a rarer but more severe phenotype with diffuse parenchymal fibrosis known as restrictive allograft syndrome (RAS) [2].

Several factors, including primary graft dysfunction, acute rejection and infection, have been identified as risk factors for CLAD [3]. Moreover, exposure of the airways to external stimuli can augment alloimmune responses, leading to dysregulated repair and fibrosis contributing to the development of CLAD. Along

these lines, recurrent aspiration of gastrointestinal contents into the tracheobronchial tree is associated with chronic airway inflammation and the development of CLAD [4–7]. Aspiration can be potentiated by several factors including gastric as well as oesophageal disorders. Lung transplant recipients are at a particularly increased risk of gastro-oesophageal disorders owing to transplant-associated iatrogenic vagus nerve injury, changes in their intra-thoracic and intra-abdominal pressures, and impaired gastric mobility related to immunosuppressive medications [8]. While gastro-oesophageal reflux disease (GORD), also referred to as gastro-esophageal reflux disease (GERD), has been extensively studied [9, 10], there is limited knowledge on the prevalence of oesophageal motility disorders in lung transplant recipients and their potential role in contributing to the development of CLAD.

We conducted a search in PubMed, from database inception to 22 January 2023, for reports in any language using the search terms ("lung transplant" OR "lung transplantation") AND ("chronic rejection" OR "chronic lung allograft dysfunction" OR "bronchiolitis obliterans syndrome" OR "CLAD" OR "BOS") AND ("esophagus" OR "esophageal" OR "manometry" OR "achalasia" OR "EGJOO" OR "esophagogastric junction outflow obstruction" OR "esophageal motility"), which yielded 53 articles. Of these, only five studies (with 50–93 patients) assessed the relationship between post-lung transplant oesophageal motility or function and any post-transplant outcomes [11–15]. Of these five, three only investigated symptomatic patients [11, 12, 14], one did not use CLAD as an outcome [13] and the fifth, while assessing CLAD as an outcome, did not correct for possible confounding variables [15]. We therefore concluded that a larger study was needed to evaluate the association between oesophageal disorders and CLAD in better powered multivariable models.

Oesophageal motor function is clinically assessed using high-resolution manometry (HRM), in which a transnasal catheter measures pressure topography of the oesophagus while the patient takes ten 5 mL liquid swallows. The Chicago Classification system is an international consensus document on interpreting HRM studies that can be used to identify patients with oesophageal disorders [16]. Herein, we conducted a retrospective study of 487 consecutive adult lung transplant recipients in the Toronto Lung Transplant Program, with transplant performed in 2012–2018, who had routine HRM testing within 7 months post-transplant. We hypothesised that oesophageal disorders among lung transplant recipients are significantly associated with shorter CLAD-free and overall allograft survival.

Methods

This study was approved by the Toronto University Health Network Research Ethics Board (REB# 15-9698). Prospectively collected patient information was deidentified and stored in the Toronto Lung Transplant Program Database (REB# 11-0170).

Study design

This was a single-centre retrospective cohort study. All first-time adult lung transplant recipients who received transplants between 2012 and 2018 at our programme and who underwent oesophageal HRM testing within 7 months of transplant were included in the study. Heart–lung transplant recipients, re-transplant recipients and those with an insufficient number of post-transplant pulmonary function tests ($\leqslant$4) for CLAD diagnosis were excluded from the study (figure 1).

HRM testing

Our programme's post-lung transplant monitoring protocol includes oesophageal HRM and 24 h pH impedance testing at around 3 months post-transplant. Topical analgesic was used to numb the throat followed by transnasal insertion of a HRM catheter. Pressure bands of both the upper oesophageal sphincter and lower oesophageal sphincter (LOS) were observed on the colour contour. Baseline pressures were obtained to identify the upper oesophageal sphincter and LOS followed by a series of wet swallows using 5 mL of room temperature normal saline to assess oesophageal motility and bolus transit. All testing was done at the University Health Network.

24-h pH impedance testing

A probe with pH and impedance sensors was positioned 5 cm above the proximal margin of the LOS in the patient's oesophagus with events below pH 4.0 recorded. Impedance sensors spanned the body of the oesophagus. The number of proximal and total reflux episodes within a 24-h time window were noted. Patients with $\geqslant$48 total reflux episodes within the 24-h time window were classified as having significant GORD, as per the laboratory cut-off.

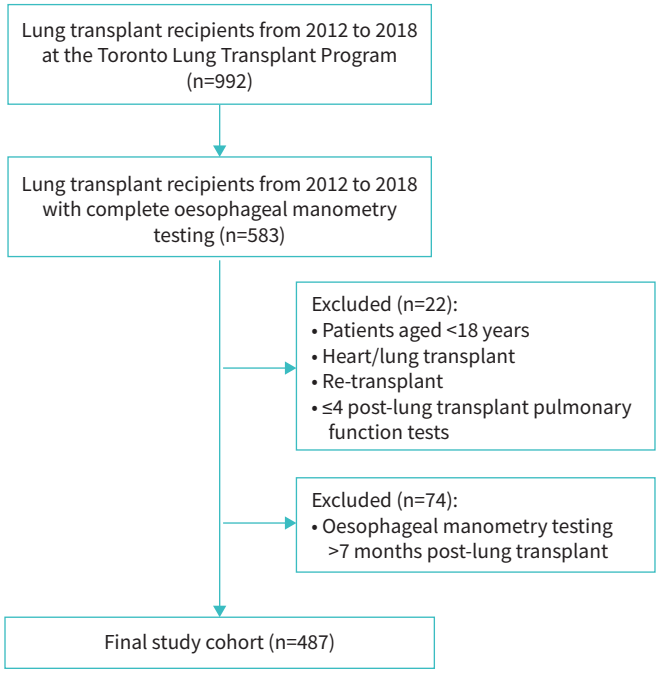

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) diagram of the study population.

Classification of oesophageal disorders

Because the study design included patients with HRM testing in 2012–2018, the 2017 Chicago Classification v3.0 was used at this time to identify oesophageal disorders [17]. Study participants were divided into cohorts based on their oesophageal function: 1) normal oesophageal function, 2) oesophagogastric junction outflow obstruction (OGJOO) as defined by LOS residual integrated relaxation pressure (IRP) >15 mmHg or 3) disorders of peristalsis as defined by LOS residual IRP <15 mmHg and normal peristaltic contractions. OGJOO was then further classified as 1) achalasia if 100% failed contractions were recorded or 2) non-achalasia OGJOO otherwise. Disorders of peristalsis were further classified as 1) major disorders of peristalsis if there were 0% peristaltic contractions recorded or 2) minor disorders of peristalsis otherwise.

Clinical treatment protocols and definitions

Post-transplant monitoring including bronchoscopy surveillance was performed as previously described by our group [5]. Definitions for primary graft dysfunction (PGD), pathological evaluation of surveillance bronchoscopies and baseline lung allograft dysfunction (BLAD) are described in the supplemental methods.

CLAD and allograft failure

CLAD was defined as per the International Society for Heart and Lung Transplantation (ISHLT) guidelines [18] based on available measurements of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC) and total lung capacity (TLC). Briefly, CLAD was defined as a sustained and irreversible decline in FEV_1 ⩽80% (based on two FEV_1 values separated by at least 3 weeks) of the post-transplant baseline (defined as the average of the two highest post-transplant FEV_1 values at least 3 weeks apart), in the absence of other confounding aetiologies. In accordance with the ISHLT guidelines, RAS was defined as TLC ⩽90% of the baseline at the time of CLAD onset, with computed tomography (CT) opacities and FEV_1/FVC ratio ⩾70%. Mixed CLAD phenotype was defined as TLC ⩽90% of the baseline at the time of CLAD onset, with CT opacities and FEV_1/FVC ratio <70% [18]. Time to allograft failure was defined as the time to death or re-transplantation.

Statistical analysis

R v4.1.3 (www.r-project.org) was used for statistical analysis. Patients with no oesophageal disorders, OGJOO and disorders of peristalsis were compared using Wilcoxon–Mann–Whitney and Fisher's exact tests for continuous and categorical variables, respectively. Univariable and multivariable Cox proportional

hazards models were used to assess the association between oesophageal disorders and CLAD-free survival (primary outcome) and overall allograft survival (secondary outcome). CLAD analyses were modeled as time from transplant to CLAD onset, censored at the time of last FEV_1 measurement or non-CLAD FEV_1 decline. Allograft survival analyses were modeled as time from transplant to death or retransplant, censored on 20 October 2021 (end of study). Multivariable Cox proportional hazards models included variables that were chosen based on either 1) their association with CLAD/allograft failure or 2) their association with oesophageal disorders in this study cohort: recipient age, recipient native lung disease (chronic obstructive pulmonary disease, cystic fibrosis, interstitial lung disease or other), transplant type (single *versus* bilateral), sex mismatch (no mismatch, donor male/recipient female or donor female/recipient male), cytomegalovirus (CMV) mismatch (donor seropositive/recipient seronegative *versus* all other), PGD grade 3 (PGD3) at 72 h post-transplant, BLAD and transplant year. A stepwise multivariable regression model showed similar results and as such only the multiple regression model is shown. Proportional hazards assumption was checked using the function cox.zph() in the *survival* package. The CLAD-free and overall allograft survival of patients were also estimated using Kaplan–Meier curves and compared using a log-rank test.

The association between oesophageal disorders and specific CLAD phenotypes was assessed using Cox proportional hazard models (cause-specific models) and competing risks regression (sub-distribution models) [19]. There were 29 RAS or mixed CLAD events in this study cohort. In keeping with the one-in-ten rule, multivariable models, for CLAD phenotype analysis only, were adjusted for two covariates based on variables that were associated with time to CLAD in this study cohort: CMV mismatch status (donor seropositive/recipient seronegative *versus* all other) and transplant year.

Results

Patient characteristics

A total of 487 adult, first-time lung transplant recipients were included in this study (figure 1). Based on the Chicago Classification v3.0, 383 patients (79%) had no oesophageal disorders, 57 patients (12%) had OGJOO and 47 patients (9%) had disorders of peristalsis. Among patients with OGJOO, six patients

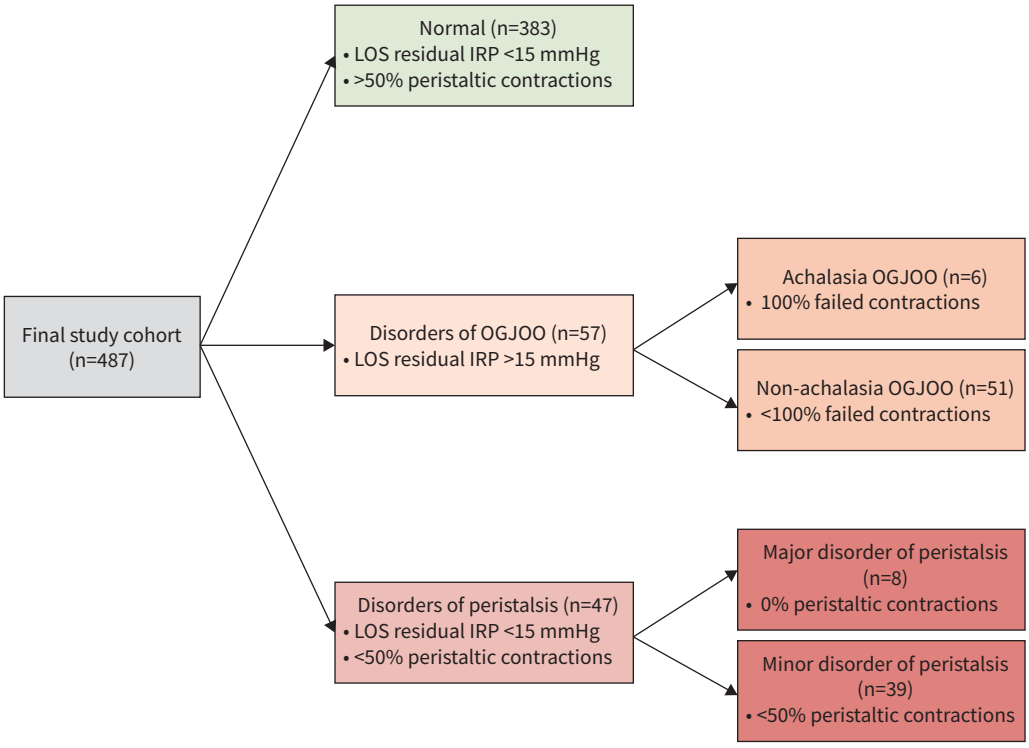

FIGURE 2 Study participants were categorised based on Chicago Classification v3.0 for oesophageal disorders. LOS: lower oesophageal sphincter; IRP: integrated relaxation pressure; OGJOO: oesophagogastric junction outflow obstruction. These terms are also referred to as lower esophageal sphincter (LES) and esophagogastric junction outflow obstruction (EGJOO) in US English.

(11%) had achalasia and 51 patients (89%) had non-achalasia OGJOO. Among patients with disorders of peristalsis, eight patients (17%) had major disorders of peristalsis and 39 patients (83%) had minor disorders of peristalsis (figure 2).

TABLE 1 Baseline and 24 h pH impedance-based patient characteristics

	Normal	Disorders of OGJOO	Disorders of peristalsis	p-value
Patients (n)	383	57	47	
Patient characteristics				
Recipient age (years)	59 (48–66)	62 (58–67)	65 (57–69)	0.001
Recipient sex (male)	251 (66)	29 (51)	29 (62)	0.10
Recipient BMI (kg·m^{-2})	24 (20–28)	25 (23–28)	23 (21–26)	0.28
Transplant type				
BLT	309 (81)	44 (77)	34 (72)	0.37
Native lung disease				0.07
COPD	85 (22)	14 (24)	13 (27)	
Cystic fibrosis	53 (14)	1 (2)	3 (6)	
Interstitial lung disease	166 (43)	33 (58)	24 (51)	
Other	79 (21)	9 (16)	7 (16)	
Scleroderma				0.46
Yes	7 (2)	2 (4)	2 (4)	
No	376 (98)	55 (96)	45 (96)	
Recipient urgency status at time of transplant[#]				0.88
1	99 (26)	12 (21)	13 (28)	
2	174 (45)	26 (46)	22 (47)	
3	110 (29)	19 (33)	12 (25)	
Transplant year	2016 (2015–2017)	2017 (2015–2018)	2016 (2014–2017)	0.35
Donor characteristics				
Age (years)	48 (33–61)	51 (40–62)	42 (29–58)	0.19
Male	234 (61)	26 (46)	36 (77)	0.005
DBD	299 (78)	45 (79)	41 (87)	0.35
Ever smoker	195 (51)	32 (56)	27 (57)	0.57
Sex mismatch				0.03
Donor male/recipient female	39 (10)	9 (16)	8 (17)	
Donor female/recipient male	56 (15)	12 (21)	1 (2)	
No mismatch	288 (75)	36 (63)	38 (81)	
CMV mismatch				0.77
D^+/R^-	94 (25)	12 (21)	9 (19)	
D^+/R^+ and D^-/R^+	202 (53)	29 (51)	28 (60)	
D^-/R^-	87 (22)	16 (28)	10 (21)	
Donor recipient pTLC ratio	1.05 (0.94–1.16)	1.01 (0.89–1.17)	1.08 (0.94–1.16)	0.29
24 h pH impedance testing-based characteristics				
Total reflux (n episodes)	15 (7–25)	11 (5–20)	19 (9–29)	0.07
Proximal reflux (n episodes)	2 (0–9)	1 (0–6)	3 (0–11)	0.22
GORD[¶]	17 (4)	3 (5)	4 (9)	0.47
Data unavailable	28 (7)	3 (5)	2 (4)	0.65
Days to oesophageal HRM testing	92 (86–97)	92 (87–96)	92 (89–97)	0.95

Continuous variables are described as median (interquartile range). Categorical variables are described as n (%). Continuous variables were compared using Mann–Whitney U test. Categorical variables were compared using Chi-squared test. Categorical variables for which any one category was less than five were compared using Fisher's exact test. OGJOO: oesophagogastric junction outflow obstruction; BMI: body mass index; BLT: bilateral lung transplantation; COPD: chronic obstructive pulmonary disease; DBD: donation after brainstem death; CMV: cytomegalovirus; pTLC: predicted total lung capacity; D^+: donor seropositive; R^-: recipient seronegative; R^+: recipient seropositive; D^-: donor seronegative; GORD: gastro-oesophageal reflux disease; HRM: high-resolution manometry. [#]: Canadian urgency status 1 is assigned to patients with lowest acuity, while 3 designates patients with highest severity of disease on the waiting list (patients bridged to transplant on extracorporeal membrane oxygenation were excluded (n=3)); [¶]: GORD classified as total reflux episodes ⩾48 within 24 h using pH/impedance testing.

Patients with oesophageal disorders were older and more likely to have interstitial lung disease. Of note, traditional risk factors for upper gastrointestinal issues in lung transplant recipients, such as scleroderma and body mass index and size mismatch, were not different between groups (supplementary table S1, table 1).

A total of 454 patients included in this study had concurrent 24 h pH impedance testing conducted to measure the number of reflux episodes. As expected, patients with OGJOO had fewer total reflux episodes (p=0.04). In contrast, the number of proximal reflux episodes and overall GORD status (⩾48 total reflux episodes in 24 h) were not different between groups (p=0.23 and p=0.47, respectively) (table 1).

Bronchoscopy-based characteristics and short-term outcomes

Patients with OGJOO tended to have a greater incidence of PGD3 at 72 h post-transplant and longer time to intensive care unit discharge; however, this was not statistically significant. Time to extubation, BLAD, cumulative A score, cumulative B score and cumulative infection score within 7 months post-transplant were not different between groups (table 2).

All lung transplant recipients with achalasia had interventional radiology-guided feeding tubes inserted post-lung transplantation

Because enteral feeding tubes can be inserted post-transplantation to prevent oesophageal dysmotility-associated aspiration, we investigated the use of this intervention within 7 months post-transplant in our patient groups. An interventional radiology (IR)-guided feeding tube was inserted for one patient with no oesophageal dysmotility disorder (0.3%), six patients with achalasia (100%), one patient with non-achalasia OGJOO (2%), two patients with major disorders of peristalsis (25%) and no patients with minor disorders of peristalsis (0%).

Non-oesophageal predictors of CLAD and allograft failure in this cohort

Among all study participant characteristics, CMV mismatch (donor seropositive/recipient seronegative) and transplant year were associated with increased risk of CLAD. CMV mismatch, transplant type, transplant

TABLE 2 Short-term recipient outcomes among study population

	Normal	Disorders of OGJOO	Disorders of peristalsis	p-value
Patients (n)	383	57	47	
PGD3 72 h post-transplant				0.09
Yes	76 (20)	16 (28)	5 (11)	
No	307 (80)	41 (72)	42 (89)	
Days to extubation	2 (1–4)	2 (1–5)	2 (1–4)	0.59
Days to ICU discharge	3 (2–8)	4 (3–12)	3 (2–5)	0.08
Cumulative A score[#]				0.37
0	162 (42)	29 (51)	23 (49)	
0.1+	221 (58)	28 (49)	24 (51)	
Cumulative B score[#]				0.19
0	358 (93)	57 (98)	46 (98)	
0.1+	25 (7)	1 (2)	1 (2)	
Cumulative infection score[¶]	0.17 (0–0.33)	0.13 (0–0.29)	0.14 (0–0.20)	0.43
BLAD[+]				0.83
Yes	220 (57)	32 (56)	29 (62)	
No	163 (43)	25 (44)	18 (38)	

Continuous variables are described as median (interquartile range). Categorical variables are described as n (%). Continuous variables were compared using Mann–Whitney U test. Categorical variables were compared using Chi-squared test. Categorical variables in which any one category was less than five were compared using Fisher's exact test. OGJOO: oesophagogastric junction outflow obstruction; PGD3: primary graft dysfunction grade 3; ICU: intensive care unit; BLAD: baseline lung allograft dysfunction. [#]: A-grades and B-grades obtained within 7 months post-transplant were added and divided by the number of evaluable biopsies (excluding AX and BX biopsies) to calculate a cumulative A score and cumulative B score, respectively; [¶]: bronchoalveolar lavage (BAL) microbiology specimens were classified as either "1=positive" or "0=negative" for containing significant pathogens and the cumulative infection score for the first 7 months post-transplant was generated by adding the number of positive BAL specimens and dividing by the total number of BAL specimens available within this time frame; [+]: BLAD within the first year post-transplant was defined by the baseline forced expiratory volume in 1 s (FEV_1) (defined as the average of the two highest FEV_1 values at least 3 weeks apart) remaining below 80% of the predicted value up to 13 months post-transplant.

year, PGD3 at 72 h post-transplant and BLAD were associated with increased risk of allograft failure (supplementary table S2).

Oesophageal stasis is associated with higher risk of CLAD

Patients with any oesophageal disorder tended to have an increased risk of CLAD (HR 1.39, 95% CI 0.99–1.95, p=0.06) (table 3).

OGJOO was significantly associated with increased risk of CLAD (HR 1.71, 95% CI 1.15–2.55, p=0.008). OGJOO with achalasia and without achalasia were both significantly associated with CLAD development (HR 3.99, 95% CI 1.58–10.08, p=0.003 and HR 1.55, 95% CI 1.01–2.37, p=0.04, respectively) (table 3, figure 3a).

Patients with any disorder of peristalsis were not significantly more likely to develop CLAD (HR 1.02, 95% CI 0.61–1.70, p=0.95). However, major disorders of peristalsis were significantly associated with CLAD development (HR 2.93, 95% CI 1.27–6.72, p=0.01) whereas minor disorders of peristalsis were not significantly associated with CLAD development (HR 0.74, 95% CI 0.39–1.38, p=0.35) (table 3, figure 3c).

Oesophageal stasis is associated with increased risk of allograft failure

Patients with any oesophageal disorder were at an increased risk of allograft failure (HR 1.45, 95% CI 1.03–2.04, p=0.03) (table 4).

OGJOO was associated with development of allograft failure (HR 1.69, 95% CI 1.13–2.53, p=0.01). OGJOO with achalasia and without achalasia were both associated with time to allograft failure (HR 3.82, 95% CI 1.51–9.63, p=0.004 and HR 1.52, 95% CI 0.99–2.34, p=0.058, respectively) (table 4, figure 3c).

Patients with any disorder of peristalsis were not at increased risk of allograft failure (HR 1.17, 95% CI 0.72–1.92, p=0.52). However, patients with major disorders of peristalsis specifically were at a significantly increased risk of allograft failure (HR 3.33, 95% CI 1.53–7.25, p=0.002). Minor disorders of peristalsis were not significantly associated with an increased risk of allograft failure (HR 0.85, 95% CI 0.47–1.54, p=0.59) (table 4, figure 3d).

Major peristaltic disorders were associated with an increased risk of RAS or mixed CLAD phenotype

Using multivariable analysis, adjusting for CMV mismatch and transplant year (confounders associated with time to CLAD in the cohort), we observed that major disorders of peristalsis, but not minor oesophageal disorders, were associated with an increased risk of RAS/mixed phenotype (table 5).

Discussion

In our single-centre retrospective cohort, we evaluated the utility of oesophageal HRM testing to predict adverse outcomes in lung transplant recipients. We found that lung transplant recipients with achalasia, non-achalasia OGJOO and major disorders of peristalsis were at a significantly increased risk of CLAD as

TABLE 3 Cox proportional hazard models assessing relationship between 2017 Chicago Classification and CLAD

	Univariable		Multivariable[#]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Any oesophageal disorder	1.35 (0.98–1.88)	0.07	1.39 (0.99–1.95)	0.06
Broad oesophageal disorder classification				
Disorders of OGJOO	1.63 (1.12–2.41)	0.01	1.71 (1.15–2.55)	0.008
Disorders of peristalsis	1.02 (0.62–1.69)	0.94	1.02 (0.61–1.70)	0.95
Narrow oesophageal disorder classification				
Achalasia	3.33 (1.36–8.17)	0.008	3.99 (1.58–10.08)	0.003
Non-achalasia OGJOO	1.49 (0.99–2.27)	0.06	1.55 (1.01–2.37)	0.04
Major disorders of peristalsis	2.93 (1.29–6.66)	0.01	2.93 (1.27–6.72)	0.01
Minor disorders of peristalsis	0.75 (0.41–1.39)	0.37	0.74 (0.39–1.38)	0.35

CLAD: chronic lung allograft dysfunction; OGJOO: oesophagogastric junction outflow obstruction. [#]: multivariable model adjusted for recipient age, recipient native lung disease, sex mismatch, cytomegalovirus mismatch, transplant type, primary graft dysfunction grade 3 at 72 h post-transplant, baseline lung allograft dysfunction at 13 months post-transplant and transplant year.

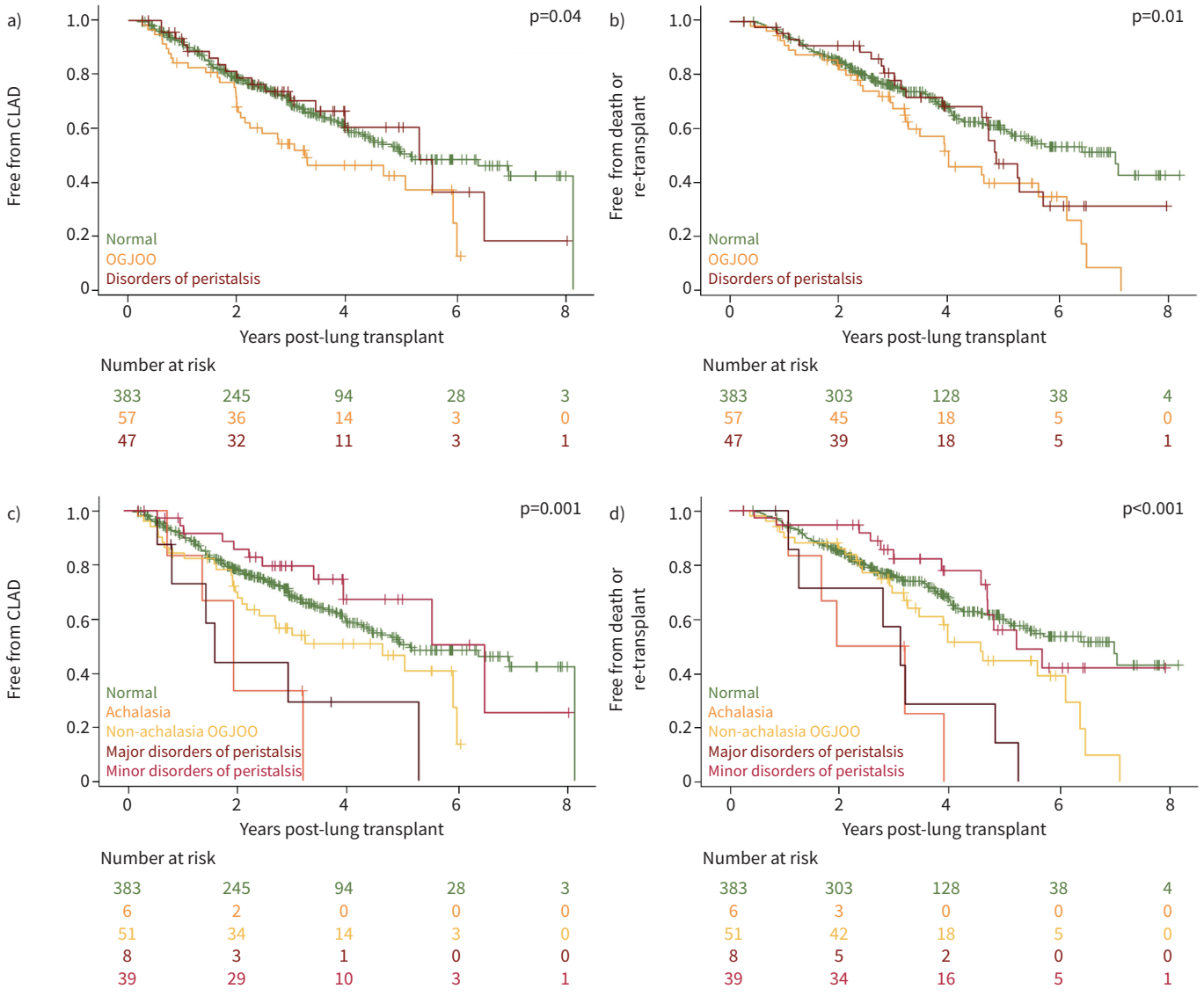

FIGURE 3 Kaplan–Meier curves assessing the relationship between oesophageal disorders and adverse post-lung transplant outcomes. a) Time to chronic lung allograft dysfunction (CLAD) analysis comparing lung transplant recipients with normal manometry testing (n=383; green), oesophagogastric junction outflow obstruction (OGJOO) (n=57; yellow) and disorders of peristalsis (n=47; red). b) Time to allograft failure analysis comparing lung transplant recipients with normal manometry testing (n=383; green), OGJOO (n=57; yellow) and disorders of peristalsis (n=47; red). c) Time to CLAD analysis comparing lung transplant recipients with normal manometry testing (n=383; green), achalasia (n=6; orange), non-achalasia OGJOO (n=51; yellow), major disorders of peristalsis (n=8; maroon) and minor disorders of peristalsis (n=39; red). d) Time to allograft failure analysis comparing lung transplant recipients with normal manometry testing (n=383; green), achalasia (n=6; orange), non-achalasia OGJOO (n=51; yellow), major disorders of peristalsis (n=8; maroon) and minor disorders of peristalsis (n=39; red). Log-rank analysis.

well as allograft failure. In contrast, minor disorders of peristalsis were not associated with adverse outcomes. Specifically, major disorders of peristalsis were associated with an increased risk of RAS and mixed CLAD phenotype.

We observed that 12% of our patients had OGJOO. In comparison, the only other study looking at OGJOO in lung transplant recipients found that 26% of their cohort (13 out of 50) had OGJOO [11]. The higher prevalence of OGJOO in that study was likely due to their investigation of only symptomatic individuals, while all lung transplant recipients were referred for testing in our current study. Although the prevalence of OGJOO in the general population is not known, 3–17% of people referred for HRM testing have been found to have OGJOO [20]. In this context, the 12% incidence in our lung transplant population

TABLE 4 Cox proportional hazard models assessing relationship between Chicago Classification v3.0 and time to death or re-transplant

	Univariable		Multivariable[#]	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Any oesophageal disorder	1.51 (1.09–2.09)	0.01	1.45 (1.03–2.04)	0.03
Broad oesophageal disorder classification				
Disorders of OGJOO	1.77 (1.20–2.62)	0.003	1.69 (1.13–2.53)	0.01
Disorders of peristalsis	1.22 (0.76–1.96)	0.40	1.17 (0.72–1.92)	0.52
Narrow oesophageal disorder classification				
Achalasia	4.05 (1.65–9.94)	0.002	3.82 (1.51–9.63)	0.004
Non-achalasia OGJOO	1.61 (1.06–2.44)	0.03	1.52 (0.99–2.34)	0.058
Major disorders of peristalsis	3.44 (1.60–7.37)	0.002	3.33 (1.53–7.25)	0.002
Minor disorders of peristalsis	0.91 (0.51–1.61)	0.74	0.85 (0.47–1.54)	0.59

OGJOO: oesophagogastric junction outflow obstruction. [#]: multivariable model adjusted for recipient age, recipient native lung disease, sex mismatch, cytomegalovirus mismatch, transplant type, primary graft dysfunction grade 3 at 72 h post-transplant, baseline lung allograft dysfunction at 13 months post-transplant and transplant year.

may be relatively high. This suggests that referring only symptomatic lung transplant recipients for manometry testing may miss patients with underlying OGJOO who are thus at increased risk of CLAD and allograft failure.

While some previous studies have investigated complete aperistalsis in lung transplant recipients, these were designed as case–control studies owing to the low prevalence of aperistalsis and could not comment on the prevalence of peristaltic disorders in lung transplant recipients overall [21, 22]. To our knowledge, this present study is the first to characterise the prevalence of peristaltic disorders in lung transplant recipients and the demographics of these patients. We found that 9% of patients had peristaltic disorders while only 2% had complete aperistalsis. Patients with peristaltic disorders in our cohort were older and had more total reflux episodes. This is in line with previous studies which found that the prevalence of peristaltic disorders increases with age and that inefficient peristalsis is associated with increased reflux in the general population [23, 24]. Patients with scleroderma are known to be at high risk for oesophageal dysmotility [25]. Our cohort only included 11 scleroderma patients, of whom seven had normal oesophageal testing. One scleroderma patient had achalasia OGJOO, one had non-achalasia OGJOO and two had major disorders of peristalsis. A future analysis focused on a larger cohort of scleroderma patients with HRM testing will be helpful. Interestingly, five patients in our study had achalasia OGJOO and six patients had complete aperistalsis with normal LOS pressure in the absence of a scleroderma diagnosis.

TABLE 5 Hazard ratios from cause-specific and sub-distribution models assessing relationship between Chicago Classification v3.0 and time to RAS/mixed CLAD phenotypes

	Multivariable[#]			
	Cause-specific HR (95% CI)	p-value	Sub-distribution HR (95% CI)	p-value
Any oesophageal disorder	1.44 (0.63–3.25)	0.39	1.34 (0.74–1.36)	0.42
Broad oesophageal disorder classification				
Disorders of OGJOO	1.29 (0.45–3.79)	0.63	1.29 (0.46–3.78)	0.62
Disorders of peristalsis	1.60 (0.55–4.70)	0.39	1.63 (0.69–3.92)	0.39
Narrow oesophageal disorder classification				
Achalasia	1.93×10^{-7} (0–infinity)	0.99	2.73 (0.41–6.03)	0.38
Non-achalasia OGJOO	1.41 (0.48–4.11)	0.53	1.43 (0.59–3.51)	0.52
Major disorders of peristalsis	7.36 (1.68–32.21)	0.008	6.81 (1.71–23.45)	0.009
Minor disorders of peristalsis	0.90 (0.21–3.86)	0.89	0.96 (0.27–3.45)	0.95

RAS: restrictive allograft syndrome; CLAD: chronic lung allograft dysfunction; OGJOO: oesophagogastric junction outflow obstruction. [#]: multivariable model adjusting for cytomegalovirus mismatch (donor seropositive/recipient seronegative *versus* all others) and transplant year.

To our knowledge, this is the first study using time-to-event analysis to evaluate the relationship between oesophageal motility disorders and adverse outcomes in lung transplant recipients. We observed that OGJOO as well as its subtypes, achalasia and non-achalasia OGJOO, are associated with increased risk of CLAD and allograft failure. These findings are in line with a previous smaller study that found a higher prevalence of OGJOO in lung transplant recipients with CLAD compared to those without CLAD [11].

Interestingly, while people with OGJOO have an increased risk of CLAD, they also have fewer reflux episodes. Traditionally, gastrointestinal disorders are believed to potentiate lung allograft dysfunction due to the reflux and aspiration of harmful substances like pepsin and bile acids from the distal foregut into the lung allograft [4, 5, 8, 26, 27]. However, OGJOO is a disorder in which the LOS fails to relax in response to a bolus. Thus, people with OGJOO are likely at an increased risk of aspirating their food before it reaches the stomach, rather than aspirating endogenous gastrointestinal contents. Our findings suggest that lung transplant recipients with OGJOO are a unique group of people at risk of CLAD due to aspiration of exogenous rather than endogenous compounds. Future translational studies should investigate whether the lung immunophenotype of people with OGJOO is different from those with GORD. Understanding the unique mechanisms of lung allograft dysfunction in recipients with OGJOO may help to better treat this population. Current interventions for people with OGJOO range from simple measures such as elevation of the head of the bed and avoiding meals before bedtime to botulinum toxin injection of the LOS and pneumatic dilation [28]. Further studies are needed to evaluate the utility of these interventions in prolonging allograft survival in lung transplant recipients with OGJOO. Of importance, these interventions need to avoid the possible complication of creating a hypotensive LOS, which can subsequently increase the risk of developing GORD.

Complete aperistalsis, but not minor disorders of peristalsis, was associated with increased risk of CLAD and allograft failure in our cohort of lung transplant recipients. Similarly, previous small case–control studies have identified that lung transplant recipients with complete aperistalsis have worse survival [21, 22]. There are limited interventions available for treating oesophageal aperistalsis. Some previous studies suggest a role for medical management with domperidone or nifedipine to improve oesophageal motility; however, this remains to be formally investigated in lung transplant recipients [29, 30].

RAS and mixed CLAD phenotypes have been shown to be more severe than other CLAD phenotypes, with a higher risk of death after CLAD onset [31]. In this study, using competing risks regression, we observed that lung transplant recipients with complete aperistalsis were at an increased risk of RAS/mixed phenotypes. Complete aperistalsis was also one of the disorders most strongly associated with CLAD and allograft failure. While no other oesophageal disorders were associated with an increased risk of RAS/mixed phenotypes in this study, this may have been due to smaller numbers of events in these analyses. Importantly, we observed that patients with interstitial lung diseases were more likely to have oesophageal disorders in this cohort. The relationship with oesophageal disorders and RAS/mixed phenotypes may be explained by the presence of immune complexities in certain interstitial lung diseases that predispose certain lung transplant recipients to RAS/mixed phenotypes over others. These findings place a greater emphasis on the need for early triage and treatment of complete aperistalsis among lung transplant recipients.

Feeding tubes can be inserted to prevent aspiration due to oesophageal dysmotility. In this study, although all patients with achalasia had an IR-guided feeding tube inserted, these sub-populations of patients remained at increased risk of CLAD. These findings question the efficacy of feeding tubes to prevent aspiration-induced lung injury in patients with achalasia. There was a limited number of patients in other subgroups with IR-guided feeding tubes and thus we were unable to assess the utility of this intervention in these groups. Of note, our analysis was limited because we did not have the data on patients with manually inserted feeding tubes without IR guidance.

We acknowledge that there is a more recent 2021 Chicago Classification (v4.0) [32]. This new guideline requires a second set of wet swallows in a secondary position. Because our retrospective cohort only included testing done before 2021, our patients did not have a secondary set of wet swallows completed. As a result, we opted to use Chicago Classification v3.0. This may complicate direct translatability of our findings into clinical practice and future studies should assess the utility of the new guidelines in lung transplant recipients. Moreover, our finding that minor disorders of peristalsis were not associated with CLAD may affect clinical decision-making in that more patients with this issue may be accepted for lung transplantation. This finding needs to be interpreted with caution because we had limited statistical power for this analysis owing to the relatively low incidence of minor disorders of peristalsis in the study population.

Overall, we found that classifying patients according to Chicago Classification v3.0 is useful in prognosticating CLAD and allograft survival in lung transplant recipients. Our findings suggest that oesophageal stasis, characterised as either 1) inability of the LOS to relax in response to a bolus (OGJOO) or 2) complete aperistalsis in response to a bolus (major disorders of peristalsis), is a significant risk factor for adverse outcomes in lung transplant recipients. While the efficacy of specific interventions still needs to be formally assessed and better strategies are needed, we would recommend routine post-transplant oesophageal HRM testing in all lung transplant recipients to allow for personalised management of specific oesophageal disorders, which may improve allograft survival in lung transplant recipients.

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