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## Retrospective Cohort Study

# Pre-Lung transplant reflux testing demonstrates high prevalence of gastroesophageal reflux in cystic fibrosis and reduces chronic rejection risk

Wai-Kit Lo, Ryan Flanagan, Nirmal Sharma, Hilary J Goldberg, Walter W Chan

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## Abstract

### BACKGROUND

Gastroesophageal reflux (GER) has been associated with poor outcomes after lung transplantation for chronic lung disease, including increased risk of chronic rejection. GER is common in cystic fibrosis (CF), but factors influencing the likelihood of pre-transplant pH testing, and the impact of testing on clinical management and transplant outcomes in patients with CF are unknown.

### AIM

To evaluate the role of pre-transplant reflux testing in the evaluation of lung transplant candidates with CF.

### METHODS

This was a retrospective study from 2007-2019 at a tertiary medical center that included all patients with CF undergoing lung transplant. Patients with pre-transplant anti-reflux surgery were excluded. Baseline characteristics (age at transplantation, gender, race, body mass index), self-reported GER symptoms prior to transplantation, and pre-transplant cardiopulmonary testing results, were recorded. Reflux testing consisted of either 24-h pH- or combined multichannel intraluminal impedance and pH monitoring. Post-transplant care included a standard immunosuppressive regimen, and regular surveillance bronchoscopy and pulmonary spirometry in accordance with institutional practice as well as in symptomatic patients. The primary outcome of chronic lung allograft dysfunction (CLAD) was defined clinically and histologically per International Society of

Heart and Lung Transplantation criteria. Statistical analysis was performed with Fisher's exact test to assess differences between cohorts, and time-to-event Cox proportional hazards modeling.

## RESULTS

After applying inclusion and exclusion criteria, a total of 60 patients were included in the study. Among all CF patients, 41 (68.3%) completed reflux monitoring as part of pre-lung transplant evaluation. Objective evidence of pathologic reflux, defined as acid exposure time > 4%, was found in 24 subjects, representing 58% of the tested group. CF patients with pre-transplant reflux testing were older (35.8 vs 30.1 years,  $P = 0.01$ ) and more commonly reported typical esophageal reflux symptoms (53.7% vs 26.3%,  $P = 0.06$ ) compared to those without reflux testing. Other patient demographics and baseline cardiopulmonary function did not significantly differ between CF subjects with and without pre-transplant reflux testing. Patients with CF were less likely to undergo pre-transplant reflux testing compared to other pulmonary diagnoses (68% vs 85%,  $P = 0.003$ ). There was a decreased risk of CLAD in patients with CF who underwent reflux testing compared to those who did not, after controlling for confounders (Cox Hazard Ratio 0.26; 95% CI: 0.08-0.92).

## CONCLUSION

Pre-transplant reflux testing revealed high prevalence of pathologic reflux in CF patients and was associated with decreased risk of CLAD. Systematic reflux testing may enhance outcomes in this patient population.

**Key Words:** Cystic fibrosis; Gastroesophageal reflux; Lung transplantation; pH monitoring

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**Core Tip:** This study found that objective evidence of gastroesophageal reflux disease was present in > 50% of lung transplant candidates with cystic fibrosis (CF). However, CF patients were less likely than those with other pulmonary diagnoses to undergo pre-transplantation reflux testing. CF patients who underwent objective reflux testing were less likely to develop chronic lung allograft dysfunction, as those tested positive were more likely to undergo anti-reflux surgery. Our findings provided evidence for the association of routine peri-transplant reflux testing with improved lung transplant outcomes in CF patients, and the importance of timely identification of reflux to allow early intervention.

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## INTRODUCTION

Gastroesophageal reflux (GER) has been associated with poor outcomes after lung transplantation including early rehospitalization[1], early allograft injury[2], and chronic allograft rejection[3]. The proposed mechanism for this involves the increased risk of post-transplant aspiration, which may lead to an inflammatory cascade resulting in recurrent allograft injury and ultimately rejection. GER has been recognized as a common condition associated with cystic fibrosis (CF), with a reported prevalence of 67%-90% in adult CF patients[4-8]. Since CF is a common indication for lung transplantation, the detection and treatment of GER in this population may potentially reduce multiple preventable post-lung transplant complications[9].

Unfortunately, despite the high prevalence of GER in CF patients and the association between GER and worse lung transplant outcomes, the testing and management of GER in these patients remain inconsistent across lung transplant centers. For instance, some centers have selectively pursued objective GER testing and treatment in patients with restrictive lung disorders such as idiopathic pulmonary fibrosis (IPF) rather than all chronic lung diseases, likely due to a correlation between GER and IPF in several early studies[10-13]. However, the factors that influence whether patients with CF undergo testing for GER prior to lung transplant are unknown. Additionally, the long-term outcomes and effects of pre-lung transplant GER testing and management for patients with CF have not been evaluated.

In this study, we aimed to assess the differences between CF patients with and without GER on reflux testing during pre-lung transplant assessment, as well as the relationship between reflux test performance and chronic rejection in this cohort. We hypothesized that GER symptoms and demographic factors would influence the likelihood of undergoing pre-transplant reflux testing, and that performance of pre-transplant reflux testing to identify candidates for reflux interventions would decrease the risk of post-transplant allograft rejection in this patient population.

## MATERIALS AND METHODS

This was a retrospective cohort study of lung transplant recipients at a tertiary care center from 2007-2019. All patients above the age of 18 who underwent lung transplant for a primary indication of CF were included in the primary analysis; all transplant recipients of any indication were included to calculate differences in the rates of reflux test performance between CF and non-CF patients. Patients with pre-transplant anti-reflux surgery were excluded. Baseline characteristics [age at transplantation, gender, race, body mass index (BMI)], self-reported GER symptoms prior to transplantation, and pre-transplant cardiopulmonary testing results, including echocardiogram, right heart catheterization, and spirometry, were recorded. ABO compatibility was assured for all donors and recipients prior to transplantation.

Reflux testing consisted of either 24-h pH- or combined multichannel intraluminal impedance and pH monitoring (Sandhill Scientific Inc, Highland Ranch, CO, United States) performed off acid suppression medications prior to transplantation. The reflux monitoring systems included a catheter with one or two pH sensor(s) which was introduced transnasally and positioned in the esophagus with the distal sensor localized to 5 cm above the lower esophageal sphincter, as well as a portable electronic datalogger. During the 24-h study, subjects remained upright during the day and recumbent at night, maintaining their normal scheduled activities. Meal periods, as documented by the patients using the datalogger, were excluded from analysis. Reflux monitoring results were analyzed with the assistance of a dedicated software package (Bioview Analysis, version 5.6.3.0, Sandhill Scientific Inc, Highland Ranch, CO, United States). Parameters of interest included acid exposure time [(AET) percentage of total study time with pH < 4 at the distal pH sensor] and the DeMeester score, a composite measure of acid reflux severity[14]. Standard normative cutoffs were employed in determining abnormal reflux[15,16].

Following transplantation, patients were prescribed a standard immunosuppressive regimen with azathioprine or mycophenolate, a calcineurin inhibitor, and methylprednisolone[17]. Routine surveillance bronchoscopy and pulmonary spirometry were performed at regular intervals according to institutional practice, and reflexively in symptomatic patients to evaluate for complications. The primary outcome was chronic rejection manifesting as chronic lung allograft dysfunction (CLAD), which was defined clinically and histologically per International Society of Heart and Lung Transplantation criteria[18].

Of note, post-transplant proton pump inhibitor (PPI) use was not part of the established clinical protocol. However, the threshold to initiate such medication was low with any reflux-associated symptoms or based on evidence of objective reflux on pre-transplant testing.

Statistical analyses were performed using  $\chi^2$  test or student's *t*-test for comparison of baseline characteristics between patient groups. Time-to-event analysis was performed for chronic rejection outcome using Cox proportional hazards model. Subjects not meeting the outcome were censored at time of post-transplant anti-reflux surgery, last clinic visit, or death, whichever was earliest. Potential confounders adjusted for in the multivariable Cox regression model were selected based on univariate analyses, and included presence of typical GER symptoms pre-transplant, forced expiratory volume in 1 s on pulmonary function testing prior to transplant, BMI, and age at transplant. All statistical analysis was performed using SAS 9.4 statistical package (SAS Institute Inc., Cary, NC, United States).

The study was approved by the Mass General Brigham Healthcare Institutional Review Board (2011P001563) prior to inception.

## RESULTS

Of the 368 patients who underwent lung transplant during the study period, 60 subjects with CF met inclusion criteria for the study, with 50% male, a mean age of 34 years, and a total follow-up of 254 person-years. Among all CF patients, 41 (68.3%) completed reflux monitoring as part of pre-lung transplant assessment. Overall, objective evidence of increased acid reflux, defined as AET > 4%, was found in 24 (58.4%) subjects. Of the subgroup of 22 (53.7%) patients reporting typical esophageal symptoms of GER, including heartburn, regurgitation, and chest pain, 14 (63.4%) demonstrated increased acid reflux on pH-monitoring.

Patients with CF were less likely to undergo reflux testing during pre-lung transplant assessment compared to those with other pulmonary diagnoses (68% *vs* 85%, *P* = 0.003). CF patients with pre-transplant reflux testing were older (35.8 years *vs* 30.1 years, *P* = 0.01) and more commonly reported

typical esophageal symptoms of GER (53.7% *vs* 26.3%,  $P = 0.06$ ) compared to those without reflux testing. Conditions that may affect reflux, including major esophageal motility disorders (achalasia, absent contractility) and gastroparesis, were not noted in our study cohort during the pre-transplant period, likely because many patients with known history of these conditions were not transplanted. Other patient demographics and baseline cardiopulmonary function did not significantly differ between CF subjects with and without pre-transplant reflux testing. All CF patients underwent bilateral lung transplant, and none received lung allografts from donors with risk factors for blood-borne disease transmission. Post-transplant infection rates were similar between subjects who did and did not undergo pre-transplant reflux testing, and were relatively high across both groups as is commonly seen in this patient population (Table 1).

A significantly lower proportion of patients in the pre-transplant reflux testing group developed CLAD compared to the no reflux testing group (21.9% *vs* 63.1%,  $P = 0.02$ ). The risk of acute rejection did not differ significantly between groups. Both all-cause and pulmonary mortality were higher among those who did not undergo pre-transplant reflux testing, although statistical significance was not reached (42.1% *vs* 19.5%,  $P = 0.11$  and 31.6% *vs* 12.2%,  $P = 0.09$ , respectively). Post-transplant PPI use was very common in both groups, including 83.9% in the pre-transplant testing group compared with 89.5% in the no testing group ( $P = 0.70$ ), and higher than pre-transplant PPI use in both groups. One third (8/24) of patients who were found to have objective evidence of acid reflux on pre-transplant testing proceeded to anti-reflux surgery in the post-transplant follow-up period, while none of the patients in the no reflux testing group underwent anti-reflux surgery.

Multivariable time-to-event analysis, summarized in Table 2, similarly demonstrated a decreased risk of CLAD in patients with CF who underwent reflux testing during pre-lung transplant assessment compared to those who did not, even after controlling for confounders [Cox Hazard Ratio (HR) 0.26; 95%CI: 0.08-0.92,  $P = 0.03$ ]. In the Cox multivariable regression model, reports of typical reflux symptoms also significantly predicted development of CLAD (HR 3.13; 95%CI: 1.03-9.54,  $P = 0.04$ ). On subgroup analysis of patients who underwent pre-transplant reflux testing, those with abnormal reflux had a trend of increased risk of CLAD compared to those with normal reflux burden, although statistical significance was not reached (HR 4.09; 95%CI: 0.74-35.2,  $P = 0.20$ ).

## DISCUSSION

GER has been suggested to represent a potentially modifiable risk-factor for the development of chronic allograft rejection in lung transplant patients, given the potential role of reflux and aspiration in the risk of allograft injury[2,3,19,20]. Moreover, both medical and surgical anti-reflux therapies have been associated with improved allograft function and transplantation outcome among those with GER[21-26]. The prevalence of GER in CF patients is particularly high as reported in prior studies as well as in our cohort, where 58.4% of patients tested showed objective acid reflux on pH testing. Despite these findings, reflux testing remains non-standardized in the evaluation of lung transplant candidates across transplant centers and in the management of chronic lung diseases including CF. Traditionally, objective reflux testing is more commonly obtained for patients with restrictive lung diseases, particularly those with IPF, as prior evidence suggests a higher prevalence of and more severe reflux among those with restrictive *vs* obstructive lung disease[27,28]. Data for lung transplant candidates with CF, characterized by both restrictive and obstructive features, remains more limited. Our study demonstrated that transplant patients with CF less likely underwent reflux testing as part of pre-transplant assessment. However, completing pre-transplant reflux testing was an independent predictor for lower risk of developing CLAD, after adjusting for severity of lung disease, possibly due to more timely GER treatment. Among the subgroup who underwent reflux testing, abnormal reflux was associated with a trend for increased risk for CLAD.

In addition to poor standardization of reflux evaluation and management in lung transplantation, there are several other reasons why CF patients may undergo reflux testing less frequently than patients with other chronic lung diseases. While GER can be present at any age, the risk of GER increases as one gets older[29]. Since most CF patients present for clinical evaluation at a younger age, clinicians may be less likely to consider GER as a contributor to clinical symptoms and pulmonary function decline. This may, in part, explain the finding in our data that CF patients without reflux testing were significantly younger than those who did undergo reflux testing.

Another possible explanation for why some CF patients were less likely to undergo reflux testing was that these patients may have had more severe clinical disease, requiring urgent transplantation without time for additional evaluation. In this scenario, these non-testing patients may have more severe pulmonary disease before transplant and may be at higher risk for complications and poor outcomes following transplant regardless of gastroesophageal reflux disease. Reassuringly, the pre-transplant pulmonary function test measures were similar between CF patients who did and did not undergo pre-transplant reflux testing, suggesting similar baseline lung function prior to transplantation between both groups, although this may not fully reflect the speed of pulmonary decline or clinical severity that may occasionally drive the urgency of lung transplantation.

**Table 1 Differences in demographics, transplant risk, reflux parameters, and post-transplant management between cystic fibrosis subjects receiving and not receiving pre-transplant gastroesophageal reflux evaluation, *n* (%)**

Covariate	CF patients with pre-transplant reflux testing ( <i>n</i> = 41)	CF patients without pre-transplant reflux testing ( <i>n</i> = 19)	<i>P</i> value
Male gender	21 (51.2)	9 (47.4)	1.00
Age at lung transplant	35.8 ± 8.21	30.1 ± 7.89	0.01
Body mass index	20.4 ± 2.51	19.4 ± 1.97	0.11
Caucasian race	41 (100)	19 (100)	1.00
FEV1 before transplant	0.84 ± 0.36)	0.75 ± 0.22	0.24
LVEF before transplant	0.60 ± 0.05	0.59 ± 0.05	0.52
Bilateral lung transplant	41 (100)	19 (100)	1.00
CMV mismatch	15 (36.6)	6 (31.6)	0.78
High-risk donor	0	0	1.00
GER symptoms before transplant	22 (53.7)	5 (26.3)	0.06
Pre-transplant PPI use	27 (65.8)	16 (84.2)	0.22
Abnormal testing/ Acid reflux	24 (58.4)	-	
Post-transplant PPI use	34 (82.9)	17 (89.5)	0.70
Post-transplant Nissen fundoplication	8 (19.5)	0 (0)	<b>0.05</b>
Any infection	35 (85.4)	17 (89.5)	1.00
Acute rejection	12 (29.3)	7 (36.8)	0.56
Chronic rejection/CLAD	9 (21.9)	12 (63.1)	<b>0.02</b>
Death (All-cause)	8 (19.5)	8 (42.1)	0.11
Death (Pulmonary)	5 (12.2)	6 (31.6)	0.09

CF: Cystic fibrosis; FEV1: Forced expiratory volume in 1 second; LVEF: Left ventricular cardiac ejection volume; CMV: Cytomegalovirus; GER: Gastroesophageal reflux; PPI: Proton pump inhibitor; CLAD: Chronic lung allograft dysfunction.

**Table 2 Cox multivariate time-to-event analysis demonstrating the association between pre-transplant reflux testing and reduction in chronic rejection (chronic lung allograft dysfunction) in cystic fibrosis patients, after controlling for confounders, suggesting that reflux testing and timely treatment may reduce rejection in this patient cohort**

Covariate	Cox multivariate analysis hazard ratios for chronic lung allograft dysfunction	<i>P</i>
Pre-transplant reflux testing	0.26 (0.08-0.92)	0.03
Gastroesophageal reflux symptoms before transplant	3.13 (1.03-9.54)	0.04
Forced expiratory volume in 1 second before transplant	3.17 (0.61-16.4)	0.17
Body mass index	0.98 (0.75-1.28)	0.88
Age at transplant	0.98 (0.90-1.05)	0.54

In our study, reflux testing was also associated with a significantly reduced risk of chronic rejection, independent of baseline pulmonary function and patient-reported GER symptoms. This is notable as symptomatic patients may be more likely to get tested and our multivariable model also found GER symptoms to be associated with increased risk for CLAD, thereby potentially biasing the pre-transplant reflux testing group towards development of CLAD. Our observation that completing reflux testing correlated with lower risk of CLAD despite this potential selection bias further strengthens our results. The possible mechanism by which reflux testing reduced risk of CLAD was likely related to the increased early detection of pathologic acid reflux leading to consideration of anti-reflux therapy. In our cohort, one-third of patients with pre-transplant reflux testing eventually underwent anti-reflux surgery, compared to none in the no reflux testing group. Since most patients in both groups received

PPI therapy post-transplant, anti-reflux surgery represented the major difference in clinical anti-reflux management between patient cohorts. Thus, the difference in CLAD risk between groups could be due, in part, to increased and earlier diagnosis of GER with more timely and aggressive management, through appropriate application of anti-reflux surgery when indicated.

Despite prior evidence demonstrating the potential deleterious effect of GER on lung allografts[2,3,19,20,30,31] and the protective effect of both medical and surgical anti-reflux therapy[21,22,24-26,32-35], the value and optimal strategy for reflux assessment among lung transplant patients remain debated and inconsistent across centers. In particular, timely or early anti-reflux therapy, often defined in prior studies as within 6 mo of transplantation, has been associated with improved outcomes compared to late or no reflux treatment among lung transplant patients with GER[23,36]. Therefore, accurate and prompt detection of abnormal reflux among lung transplant patients may play a role in reducing allograft dysfunction and improving outcomes. Currently, testing strategies employed by lung transplant centers may include: No esophageal assessment; selective testing based on presence of esophageal symptoms; selective testing based on underlying lung disease diagnosis; routine testing for all patients. Furthermore, the testing modality obtained may include barium esophagram, upper endoscopy, or objective reflux testing such as pH-monitoring. However, prior studies have found that esophageal symptoms are often absent among chronic lung disease patients with abnormal reflux and may not be adequate in guiding reflux testing, and that barium esophagram may not be sufficiently sensitive for detection of abnormal reflux[37]. As discussed above, some centers routinely perform reflux testing for patients with restrictive lung disease due to the higher reflux burden often observed in this population. However, our study provides evidence that routine reflux testing should also be advocated for CF patients undergoing lung transplant, especially given the high prevalence of reflux and mixed restrictive and obstructive property of the condition.

The limitations of our study include its retrospective nature, which makes it difficult to assign causality. Another limitation is the modest sample size, which reduces the statistical power, particularly in subgroup analyses such as that of patients with reflux testing showing abnormal reflux. Additionally, the sample size and retrospective design also limit the ability to perform more comprehensive analyses of other potential factors that may be associated with performance of reflux testing. Despite these limitations, our study would add to the current scarce data on the impact of objective reflux testing on post-transplant outcomes in patients with CF.

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## CONCLUSION

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Given that patients with CF have favorable outcomes compared to the general lung transplant population, the judicious use of pre-transplant pH testing and appropriate management of GER is crucial to reducing CLAD[38]. Our findings suggest that while lung transplant patients with CF are less likely to undergo reflux testing compared to patients with other chronic lung diseases, they would likely benefit from more routine use of reflux testing to inform prompt and effective management of GER, including anti-reflux surgery when indicated. Thus, standardized reflux testing followed by timely reflux management should be adopted systematically in the care of patients undergoing lung transplant to improve post-transplant outcomes, especially among patients with CF.

## ARTICLE HIGHLIGHTS

### **Research background**

Gastroesophageal reflux is prevalent in chronic lung disease and can negatively impact lung transplant outcomes. However, the impact of pre-transplant reflux testing is not established in the cystic fibrosis (CF) population.

### **Research motivation**

Routine reflux evaluation remains poorly standardized in lung transplantation, and this work contributes to the growing literature on the utility of reflux testing and timely management in lung transplant patients, especially those with CF.

### **Research objectives**

To evaluate the impact of pre-transplant reflux testing on transplant outcomes in CF, as well as determining the prevalence of reflux in this patient population.

### **Research methods**

This was a retrospective cohort study of CF patients that underwent lung transplantation at a tertiary referral center.

### Research results

Lung transplant candidates with CF were less likely than those with other chronic lung diseases to undergo reflux testing. Pre-transplant reflux testing identified high prevalence of pathologic reflux in CF. Reflux testing was associated with decreased risk of chronic rejection.

### Research conclusions

Pre-transplant reflux testing revealed high prevalence of pathologic reflux in CF patients and was associated with decreased risk of chronic lung allograft dysfunction.

### Research perspectives

Systemic reflux testing may improve lung transplant outcomes in the CF population. Future research should focus on the implementation of standardized reflux evaluation and timely reflux management in lung transplantation, and its impact on transplant outcomes, particularly in patients with CF.

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## FOOTNOTES

**Author contributions:** Chan WW and Lo WK initiated study concepts and design; Lo WK, Goldberg HJ, and Chan WW contributed to acquisition of data; Chan WW, Lo WK, Flanagan R, Goldberg HJ, and Sharma N performed analysis and interpretation of data; Lo WK, Flanagan R, and Chan WW drafted the manuscript; Chan WW, Lo WK, Flanagan R, Goldberg HJ, and Sharma N contributed to critical revision of manuscript for important intellectual content; Chan WW and Lo WK performed statistical analyses; and Chan WW provided administrative support and overall study supervision.

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