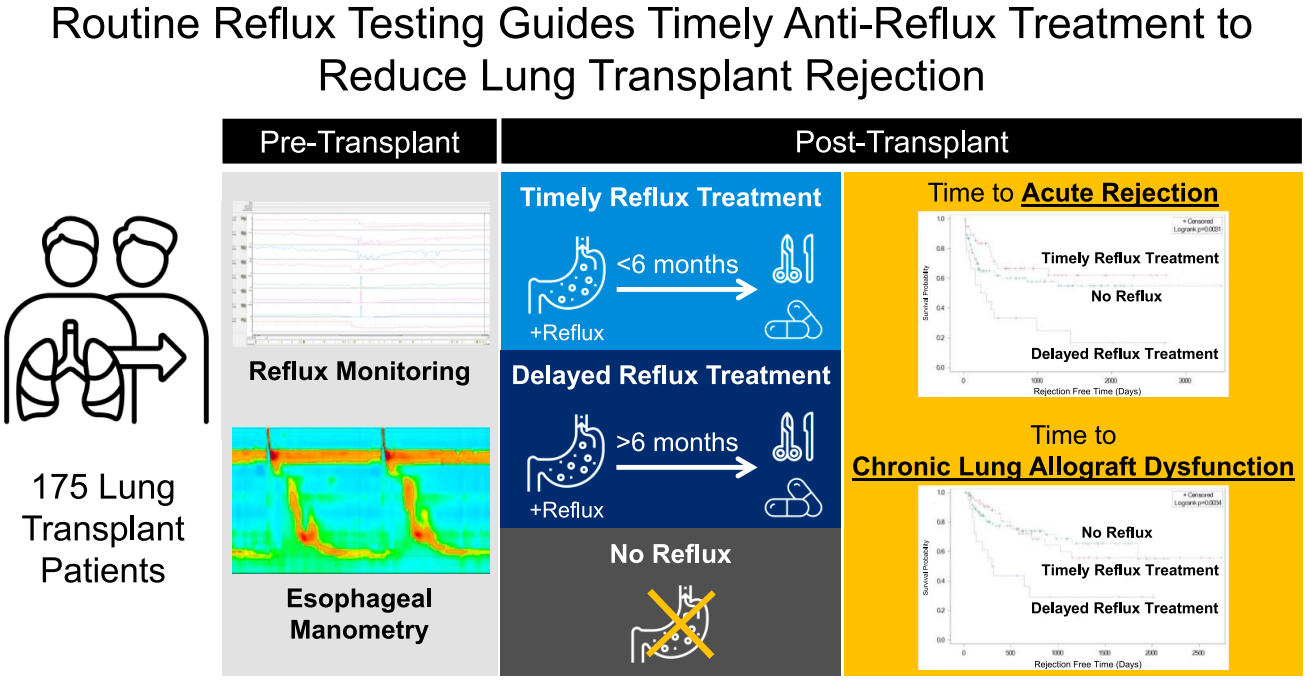
Routine Reflux Testing Guides Timely Antireflux Treatment to Reduce Acute and Chronic Rejection After Lung Transplantation

Wai-Kit Lo, MD, MPH[1,2,3], Hilary J. Goldberg, MD, MPH[3,4], Nirmal Sharma, MD[3,4], Jon O. Wee, MD[3,5] and Walter W. Chan, MD, MPH[1,3]

INTRODUCTION: **Gastroesophageal reflux has been associated with poorer lung transplantation outcomes, although no standard approach to evaluation/management has been adopted. We aimed to evaluate the effect of timely antireflux treatment as guided by routine reflux testing on postlung transplant rejection outcomes.**

METHODS: **This was a retrospective cohort study of lung transplant recipients at a tertiary center. All patients underwent pretransplant ambulatory pH monitoring. Timely antireflux treatment was defined as proton pump inhibitor initiation or antireflux surgery within 6 months of transplantation. Patients were separated into 3 groups: normal pH monitoring (−pH), increased reflux (+pH) with timely treatment, and +pH with delayed treatment. Rejection outcomes included acute rejection, bronchiolitis obliterans syndrome, and chronic lung allograft dysfunction per International Society for Heart and Lung Transplantation criteria. Time-to-event analyses using Cox proportional hazard models were applied. Patients not meeting outcomes were censored at death or last clinic visit.**



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[1]Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Boston, Massachusetts, USA; [2]Division of Gastroenterology, Boston VA Healthcare System, Boston, Massachusetts, USA; [3]Harvard Medical School, Boston, Massachusetts, USA; [4]Division of Pulmonary and Critical Care Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA; [5]Division of Thoracic Surgery, Brigham and Women's Hospital, Boston, Massachusetts, USA.
Correspondence: Walter W. Chan, MD, MPH. Email: wwchan@bwh.harvard.edu.
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RESULTS: **One hundred seventy-five patients (59% men/mean 56.3 yr/follow-up: 496 person-years) were included. On multivariable analyses, +pH/delayed treatment patients had higher risks of acute rejection (adjust hazard ratio [aHR]:3.81 [95% confidence interval [CI]: 1.90–7.64], $P = 0.0002$), bronchiolitis obliterans syndrome (aHR: 2.22 [95% CI: 1.07–4.58], $P = 0.03$), and chronic lung allograft dysfunction (aHR: 2.97 [95% CI: 1.40–6.32], $P = 0.005$) than +pH/timely treatment patients. Similarly, rejection risks were increased among +pH/delayed treatment patients vs −pH patients (all $P < 0.05$). No significant differences in rejection risks were noted between +pH/timely treatment patients and −pH patients. Failure/complications of antireflux treatment were rare and similar among groups.**

DISCUSSION: **Timely antireflux treatment, as directed by pretransplant reflux testing, was associated with reduced allograft rejection risks and demonstrated noninferiority to patients without reflux. A standardized peri-transplant test-and-treat algorithm may guide timely reflux management to improve lung transplant outcomes.**

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INTRODUCTION

Lung transplantation is associated with a high risk of morbidity and mortality, especially in comparison with other solid organ transplants (1). Gastroesophageal reflux disease (GERD) may contribute to this risk by increasing post-transplant aspiration, which could induce an inflammatory cascade in the lung allograft, resulting in acute rejection (AR). Recurrent episodes of AR and allograft injury may then contribute to chronic rejection, culminating in graft failure.

Prior research has demonstrated that objective measures of reflux on pretransplant ambulatory reflux monitoring predict poorer outcomes after transplantation, including early allograft injury (2), early rehospitalization (3), and chronic rejection (4). Antireflux interventions have also been evaluated. Medical acid suppression, particularly proton pump inhibition (PPI), was associated with improved post-transplant outcomes, while histamine-2-receptor antagonist use was not statistically significant (5). Other studies have shown that antireflux surgery (ARS) may be associated with preservation of lung function post-transplantation in patients with GERD (6), improvement in immunologic biomarkers associated with aspiration and reflux (7), and reduction in bronchiolitis obliterans syndrome (BOS) and mortality (8). The timing of ARS is important to consider, with pretransplant or early post-transplant ARS within 6 months of transplantation demonstrating greater protection against rejection than ARS after 6 months post-transplant (9), though not all patients may be suitable candidates for pretransplant ARS, given the higher operative risk.

Despite the evidence for potential deleterious effects of GERD and benefits of antireflux therapy, a standard approach to esophageal evaluation and management has not been established in lung transplantation. More specifically, the effect of timely medical and surgical antireflux treatment, as applied within the framework of a pretransplant reflux testing protocol, has not been assessed. In this study, we aimed to evaluate the effect of such an approach on short-term and long-term rejection outcomes after lung transplantation. We hypothesized that timely antireflux therapy would be associated with a reduced risk of acute and chronic rejection, underscoring the importance of standardized prompt reflux evaluation and management in lung transplant recipients.

METHODS

This was a retrospective cohort study of lung transplant recipients (aged older than 18 years) who underwent pretransplant reflux testing with 24-hour pH monitoring or multichannel intraluminal impedance and pH study (MII-pH) off acid suppression at a tertiary care center in 2007–2016. Patients with a history of ARS before reflux monitoring and those who completed their study on acid suppression therapy were excluded. Patients who did not survive the initial transplant hospitalization were also excluded, as such early mortality often reflects postoperative complications or hyperacute rejection unrelated to the present model of reflux-related allograft injury under study. Similarly, patients who required extended tube feeding due to persistent oropharyngeal dysphagia were also excluded because it represents a distinct risk factor for aspiration unrelated to reflux.

Baseline characteristics (age at transplantation, sex, race, body mass index [BMI]), pulmonary diagnosis, and results of standard pretransplant cardiopulmonary testing, including echocardiogram, right heart catheterization, and spirometry, were recorded. ABO compatibility was assured for all donors and recipients before transplantation.

Pretransplant ambulatory reflux monitoring

All patients included in the study underwent reflux monitoring with either pH only or MII-pH testing (Sandhill Scientific, Highland Ranch, CO) before transplantation, after an overnight fast and off acid suppression for at least 7 days. The reflux monitoring systems included a portable electronic datalogger and a catheter with 1 or 2 pH sensor(s). The catheter was passed into the esophagus transnasally and positioned with the distal pH sensor localized to 5 cm above the lower esophageal sphincter. During the 24-hour study, patients were asked to remain upright during the day and recumbent at night, maintaining their normal scheduled activities. Meal periods were documented by the patients through the datalogger and 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). Parameters of interest included acid exposure time (percentage of total study time with pH < 4 at the distal pH sensor) and the DeMeester score, a composite measure of acid reflux severity (10). Standard normative cutoffs were used in determining increased reflux, including 4% for acid exposure time and 14.72 for DeMeester score (11,12). All reflux monitoring tracings were reviewed by 2 dedicated expert readers.

Post-transplant care and outcomes

After transplantation, patients received standard immunosuppressive therapy with azathioprine or mycophenolate, a calcineurin

inhibitor, and methylprednisolone per established protocol (13). Routine surveillance bronchoscopy and pulmonary function testing (PFT) were performed at regular intervals in asymptomatic individuals according to institutional protocol and reflexively in symptomatic patients to evaluate for complications. Primary outcomes assessed included AR, BOS, and chronic lung allograft dysfunction (CLAD), as defined by PFT and histologic findings per International Society of Heart and Lung Transplantation guidelines (14,15). Secondary outcomes included any adverse events resulting from medical or surgical antireflux therapies during the follow-up period.

Antireflux interventions

Post-transplant PPI use was not routinely recommended; however, the threshold to initiate such medication was low with any reflux-associated symptoms or based on evidence of objective reflux on pretransplant testing. Nevertheless, not all included patients received PPI therapy during the study period because this was not within established clinical protocol.

Patients were offered surgical fundoplication based on objective evidence of reflux. In some cases, clinical decline in pulmonary function spurred more aggressive antireflux management, including medical acid suppression; however, ARS was only offered when objective reflux had been established on pretransplant testing. A cutoff of 6 months was used to distinguish "early" post-transplant fundoplication procedures from "late" procedures (9).

Exposure categories

Based on pretransplant reflux monitoring results and application of antireflux therapies, patients were classified into 3 groups for comparison (i): objective reflux on monitoring and "timely" antireflux treatment (PPI or ARS before 6 months post-transplant) (ii), objective reflux on monitoring and "absent/delayed" antireflux treatment (no PPI and ARS after 6 months post-transplant or no ARS), and (iii) no objective reflux on pretransplant reflux monitoring.

Statistical analyses

Separate statistical analyses were performed for each outcome of interest including AR, BOS, and CLAD. Time-to-event models using Cox proportional hazards were constructed to assess the relationship between exposures of interest and development of rejection outcomes. Patients not meeting the rejection outcome were censored during last clinic visit or death, whichever was earliest. The Kaplan-Meier method was used to construct time-to-event curves, with log-rank testing to quantify differences. The Fisher exact test for binary variables and the Student *t* test for continuous variables were performed to assess for differences between exposure groups. Multivariable analyses with Cox regression models were performed for the association between exposures and transplant outcome, controlling for age at transplant, sex, BMI, and number of lungs transplanted. All statistical analyses were performed using SAS 9.3 statistical package (SAS Institute, Cary, NC). The study was approved by the Partners Healthcare Institutional Review Board (2011P001563) before inception.

RESULTS

Study cohort

One hundred seventy-five patients met inclusion criteria during the study period. The mean age at transplantation for the cohort was 56.3 ± 12.6 years, and 104 (59.4%) patients were male. The mean follow-up time for the cohort was 2.7 ± 2.2 years for a total of 496 person-years. The most common pulmonary diagnosis was idiopathic pulmonary fibrosis (IPF, 84 patients, 48%). The outcome of AR was reached in 72 patients (41.1%), while BOS and CLAD were reached in the same 48 patients (27.4%), although some patients developed CLAD earlier through a restrictive rather than obstructive phenotype.

Overall, 74 (42.3%) had positive parameters for acid reflux by pretransplant testing. Of them, 34 patients were treated with PPI medication only, with a median time to PPI initiation of 0 days (but no later than 68 days). Twenty-two patients underwent pretransplant or early post-transplant ARS, with a median time of 3.8 months, and 18 underwent late post-transplant ARS, with a median time of 9.9 months. Of the remaining 101 patients with negative pretransplant parameters of reflux, none developed reflux after transplant requiring surgical management. In total, 56 patients received timely medical or surgical antireflux treatment, and 18 patients received delayed surgical antireflux treatment (Figure 1).

IPF as an underlying pulmonary diagnosis was more common among both cohorts of patients with increased reflux (+pH/timely treatment and +pH/delayed treatment) compared with those with normal reflux monitoring. This was consistent with previous publications showing increased reflux among patients with restrictive vs obstructive lung diseases (16,17). No other significant differences in patient demographics and clinical characteristics were noted among the 3 reflux/treatment cohorts, including sex, age, BMI, baseline cardiopulmonary function, and lung(s) transplanted (Table 1).

Rejection outcomes

Compared with patients receiving timely treatment, those receiving delayed treatment had an increased risk of AR (hazard ratio [HR] 3.42 [95% confidence interval [CI] 1.77–6.59], $P = 0.0002$), BOS (HR 2.27 [1.11–4.65], $P = 0.02$), and CLAD (HR 2.86 [1.36–6.03], $P = 0.006$) on both Cox univariate and Kaplan-Meier analyses (Figure 2). Moreover, compared with patients without objective

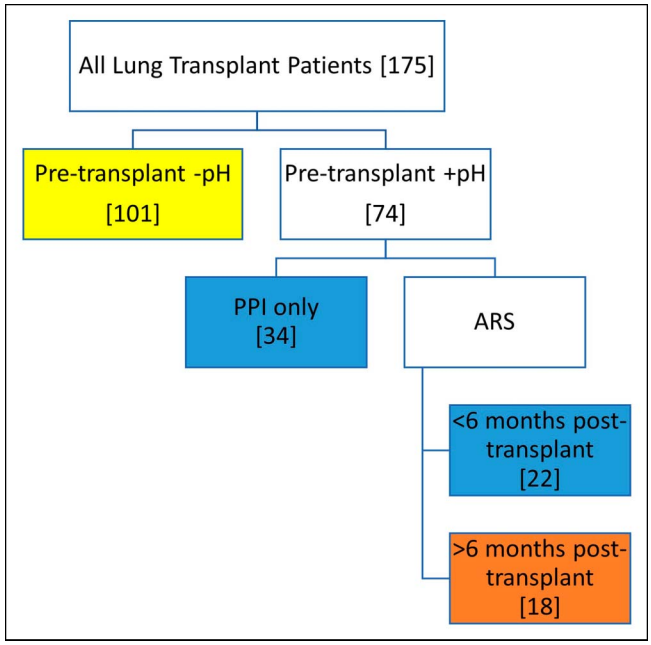

Figure 1. Schema of included lung transplant patient cohort. ARS, antireflux surgery; PPI, proton pump inhibitor.

Table 1. Baseline demographics and clinical characteristics

	Total (n = 175)	Normal reflux monitoring (n = 101)	Increased reflux with timely treatment (n = 56)	Increased reflux with delayed treatment (n = 18)
Follow-up (p-y)	477 (SD 376)	248 (SD 208)	149 (SD 112)	80 (SD 43)
Male sex	104 (59.4%)	60 (59.4%)	33 (58.9%)	11 (61.1%)
BMI	26.0 (SD 4.50)	26.3 (SD 4.60)	25.4 (SD 4.32)	26.8 (SD 4.85)
Age at transplant (yr), mean	56.3 (SD 12.6)	56.2 (SD 13.0)	56.9 (SD 12.5)	54.8 (SD 11.2)
White race	163 (93.1%)	96 (95.0%)	49 (87.5%)	18 (100%)
Pulmonary diagnosis				
ILD	113 (64.6%)	59 (58.4%)	41 (73.2%)	13 (72.2%)
IPF	84 (48.0%)	38 (37.6%)[a,b]	34 (60.7%)	12 (66.7%)
COPD	37 (21.1%)	23 (22.8%)	9 (16.1%)	5 (27.8%)
CF	19 (10.9%)	10 (9.9%)	7 (12.5%)	2 (11.1%)
Cardiac function				
LVEF, mean (%)	0.60 (SD 0.05)	0.60 (SD 0.06)	0.60 (SD 0.06)	0.61 (SD 0.05)
PaP, mean (mm Hg)	27.5 (SD 11.6)	29.4 (SD 12.9)	25.2 (SD 9.51)	24.7 (SD 8.71)
PCWP, mean (mm Hg)	10.2 (SD 4.95)	10.7 (SD 5.23)	9.27 (SD 4.44)	10.0 (SD 3.54)
PVR, mean (dynes/s/cm^{-5})	238.7 (SD 154)	251.2 (SD 167.8)	229.6 (SD 132.0)	228.9 (SD 155.4)
Pulmonary function, baseline				
FVC	1.78 (SD 0.75)	1.79 (SD 0.71)	1.74 (SD 0.82)	1.61 (SD 0.78)
FVC, %-pred	0.44 (SD 0.16)	0.45 (SD 0.15)	0.43 (SD 0.19)	0.38 (SD 0.16)
FEV1	1.26 (SD 0.64)	1.22 (SD 0.59)	1.33 (SD 0.71)	1.30 (SD 0.69)
FEV1, %-pred	0.39 (SD 0.19)	0.39 (SD 0.18)	0.41 (SD 0.21)	0.39 (SD 0.20)
FEV1/FVC	0.71 (SD 0.22)	0.69 (SD 0.23)	0.75 (SD 0.20)	0.78 (SD 0.17)
Lungs transplanted				
Unilateral	80 (45.7%)	46 (45.5%)	27 (48.2%)	7 (38.9%)
Bilateral	95 (54.3%)	55 (54.5%)	29 (51.8%)	11 (61.1%)
CMV mismatch	49 (28.0%)	25 (24.7%)	17 (30.4%)	7 (38.9%)
Reflux monitoring				
pH metrics				
AET	3.25 (SD 4.65)	1.19 (SD 1.12)	10.47 (SD 6.18)	6.77 (SD 4.04)
Demeester	12.1 (SD 14.8)	5.08 (SD 3.96)	35.06 (SD 15.9)	27.5 (SD 20.2)
Impedance metrics (N = 73)		n = 56	n = 13	n = 4
BET	2.85 (SD 2.94)	2.11 (SD 1.65)	4.73 (SD 3.87)	7.90 (SD 6.60)
Distal episodes	59.5 (SD 38.3)	51.8 (SD 28.6)	81.3 (SD 51.2)	106 (SD 64.1)
Proximal episodes	27.8 (SD 18.9)	25.2 (SD 17.3)	34.9 (SD 20.9)	43 (SD 32.3)
HREM				
Normal	113 (64.6%)	65 (64.4%)	35 (62.5%)	13 (72.2%)
IEM	57 (32.6%)	34 (33.7%)	18 (32.1%)	5 (27.8%)
DES	2 (1.14%)	0 (0.99%)	2 (3.57%)	0
EGJOO	3 (1.71%)	2 (1.98%)	1 (1.79%)	0

AET, acid exposure time; BET, bolus exposure time; BMI, body mass index; CF, cystic fibrosis; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; DES, distal esophageal spasm; EGJOO, esophagogastric junction outflow obstruction; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HREM, high-resolution esophageal manometry; IEM, ineffective esophageal motility; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LVEF, left ventricular ejection fraction; PaP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

[a] $P < 0.05$ vs +pH, timely tx.

[b] $P < 0.05$ vs +pH, delayed tx.

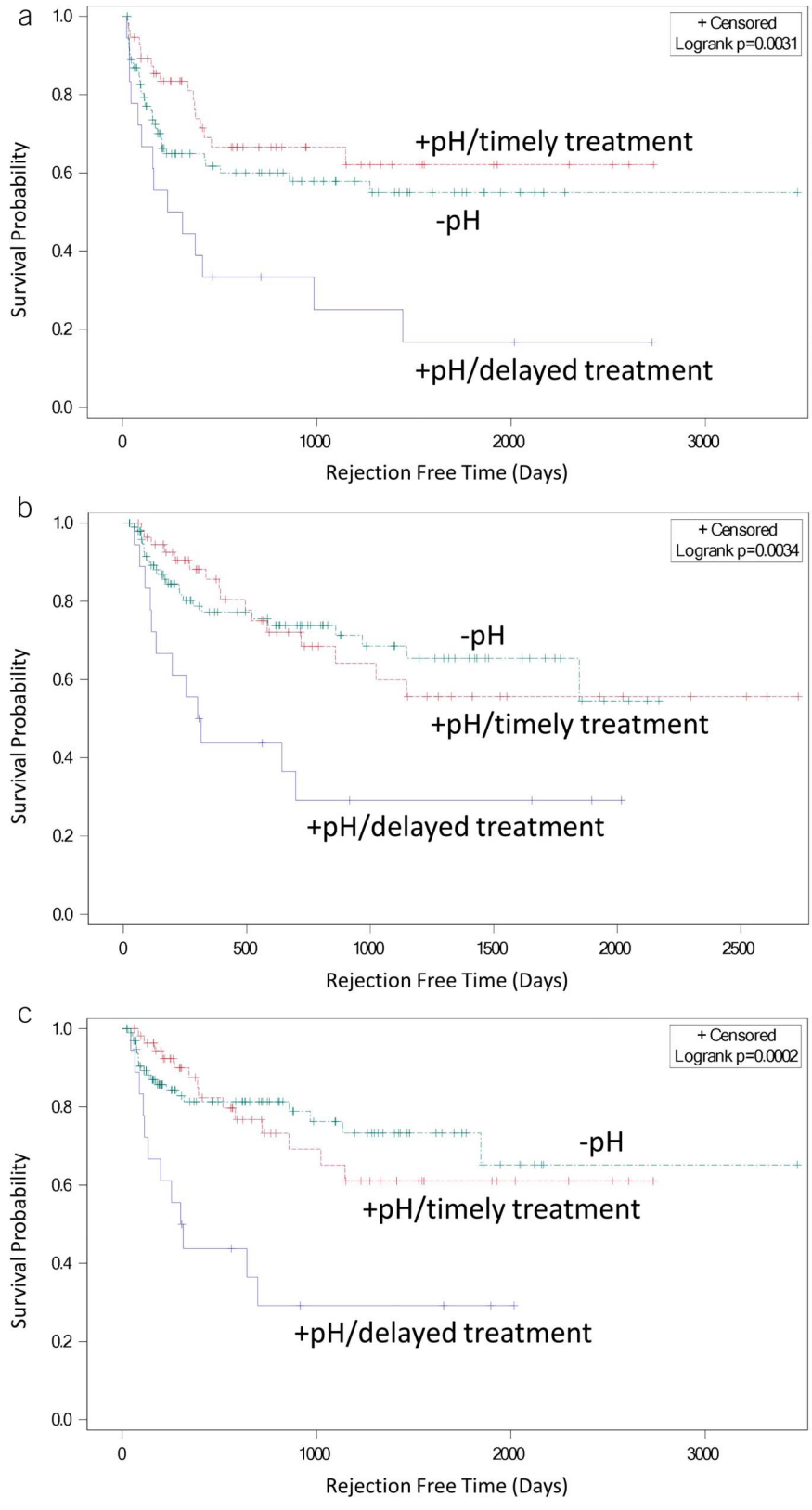

Figure 2. Kaplan-Meier analyses comparing patients with (i) normal reflux monitoring (−pH), (ii) objective GERD and timely antireflux therapy (+pH/timely treatment), and (iii) objective GERD and delayed therapy (+pH/delayed treatment) for rejection outcomes of (**a**) AR, (**b**) BOS, and (**c**) CLAD. AR, acute rejection; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; GERD, gastroesophageal reflux disease.

pretransplant reflux, those receiving delayed treatment also had an increased risk of AR (HR 2.19 [1.26–3.81], $P = 0.006$), BOS (HR 2.25 [1.17–4.33], $P = 0.01$), and CLAD (HR 3.04 [1.53–6.05], $P = 0.001$). No statistically significant difference in risks of rejection outcomes (AR, BOS, and CLAD) were detected between patients receiving timely treatment and those without objective evidence of reflux on ambulatory reflux monitoring. Results from Kaplan-Meier analyses are shown in Figure 2.

Univariate analyses performed on other baseline demographic and clinical characteristics revealed that male sex was associated with AR (HR 1.69 [1.02–2.81], $P = 0.04$), BMI was associated with BOS (HR 1.96 [1.09–3.50], $P = 0.02$), and both BMI and single lung transplant (HR 2.17 [1.14–4.10], $P = 0.02$ and HR 1.89 [1.06–3.36], $P = 0.03$, respectively) were associated with CLAD (Table 2). These variables were included in the logistic regression models for multivariable analyses to address possible confounding.

On multivariable analyses, patients receiving delayed treatment had an increased risk of AR (HR 3.81 [95% CI 1.90–7.64], $P = 0.0002$), BOS (HR 2.22 [95% CI 1.07–4.58], $P = 0.03$), and CLAD (HR 2.97 [1.40–6.32], $P = 0.005$) compared with patients receiving timely treatment and an increased risk of AR (HR 2.26 [1.29–3.96], $P = 0.004$), BOS (HR 2.40 [1.24–4.63], $P = 0.009$), and CLAD (HR 3.21 [1.61–6.41], $P = 0.0009$) compared with patients without objective pretransplant reflux.

On subgroup analyses separating those receiving early antireflux therapy to PPI treatment only or pretransplant/early post-transplant ARS, the risk of AR, BOS, and CLAD were not significantly different between either group and those without objective signs of reflux. In addition, each subgroup had a significantly lower risk of both acute and chronic rejection compared with the late post-transplant therapy group (Figure 3).

Overall, the effect of delayed therapy compared against timely therapy or the absence of objective reflex was HR 2.50 (1.39–4.51, $P = 0.002$) for AR, HR 2.88 (1.51–5.49, $P = 0.001$) for BOS, and HR 3.63 (1.87–7.01, $P = 0.001$) for CLAD. On multivariable analyses, the overall effect of delayed therapy compared with timely therapy or the absence of objective reflux was HR 2.59 (1.43–4.69, $P = 0.002$) for AR, HR 3.04 (1.58–5.84, $P = 0.0009$) for BOS, and HR 3.86 (1.97–7.56, $P < 0.0001$) for CLAD, after controlling for confounders.

Table 2. Univariate Cox analyses of baseline characteristics for rejection outcomes

	Univariate hazard ratio for AR (95% CI)	Univariate hazard ratio for BOS (95% CI)	Univariate hazard ratio for CLAD (95% CI)
Male sex	**1.69 (1.02–2.81), $P = 0.04$**	1.28 (0.73–2.25), $P = 0.39$	1.38 (0.75–2.55), $P = 0.30$
BMI	1.58 (0.97–2.57), $P = 0.07$	**1.96 (1.09–3.50), $P = 0.02$**	**2.17 (1.14–4.10), $P = 0.02$**
Age at transplant (yr), mean	1.01 (0.99–1.03), $P = 0.38$	1.01 (0.99–1.03), $P = 0.35$	1.01 (0.99–1.04), $P = 0.41$
White race	0.74 (0.32–1.70), $P = 0.47$	4.77 (0.66–34.5), $P = 0.12$	3.95 (0.54–28.6), $P = 0.17$
Pulmonary diagnosis			
ILD	1.22 (0.75–1.98), $P = 0.41$	1.36 (0.77–2.42), $P = 0.29$	1.33 (0.72–2.45), $P = 0.36$
IPF	1.29 (0.81–2.04), $P = 0.28$	1.67 (0.97–2.88), $P = 0.06$	1.73 (0.96–3.10), $P = 0.07$
COPD	0.76 (0.42–1.40), $P = 0.38$	1.29 (0.69–2.42), $P = 0.42$	1.22 (0.62–2.40), $P = 0.56$
CF	0.44 (0.18–1.09), $P = 0.08$	0.94 (0.40–2.19), $P = 0.88$	0.86 (0.34–2.17), $P = 0.75$
Cardiac function			
LVEF, mean	0.60 (0.01–36.1), $P = 0.81$	0.22 (0.002–29.3), $P = 0.54$	0.12 (0.001–22.7), $P = 0.43$
PaP, mean	1.01 (0.99–1.02), $P = 0.41$	0.99 (0.97–1.02), $P = 0.52$	0.99 (0.96–1.02), $P = 0.59$
PCWP, mean	0.98 (0.94–1.03), $P = 0.47$	0.99 (0.94–1.05), $P = 0.80$	0.98 (0.92–1.04), $P = 0.50$
PVR, mean	1.00 (1.00–1.00), $P = 0.54$	1.00 (1.00–1.00), $P = 0.97$	1.00 (1.00–1.00), $P = 0.86$
Pulmonary function, baseline			
FVC	1.08 (0.81–1.44), $P = 0.59$	0.96 (0.69–1.34), $P = 0.82$	0.97 (0.68–1.38), $P = 0.86$
FVC, %-pred	0.74 (0.18–2.96), $P = 0.67$	0.59 (0.12–2.93), $P = 0.52$	0.62 (0.11–3.49), $P = 0.58$
FEV1	1.19 (0.85–1.66), $P = 0.32$	1.11 (0.75–1.63), $P = 0.61$	1.07 (0.70–1.61), $P = 0.77$
FEV1, %-pred	1.23 (0.39–3.92), $P = 0.72$	1.14 (0.30–4.28), $P = 0.85$	1.02 (0.24–4.28), $P = 0.97$
FEV1/FVC	1.68 (0.57–4.92), $P = 0.34$	1.57 (0.47–5.26), $P = 0.46$	1.37 (0.38–4.93), $P = 0.62$
Lungs transplanted			
Unilateral	1.35 (0.85–2.14), $P = 0.20$	1.29 (0.82–2.36), $P = 0.23$	**1.89 (1.06-3.36), $P = 0.03$**
Bilateral	Ref	Ref	Ref
CMV mismatch	0.87 (0.51–1.48), $P = 0.61$	1.64 (0.93–2.89), $P = 0.09$	1.47 (0.79–2.70), $P = 0.22$

AR, acute rejection; BMI, body mass index; BOS, bronchiolitis obliterans syndrome; CF, cystic fibrosis; CI, confidence interval; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LVEF, left ventricular ejection fraction; PaP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.
Bold entries represent characteristics with statistically significant ($P < 0.05$) association with rejection outcomes.

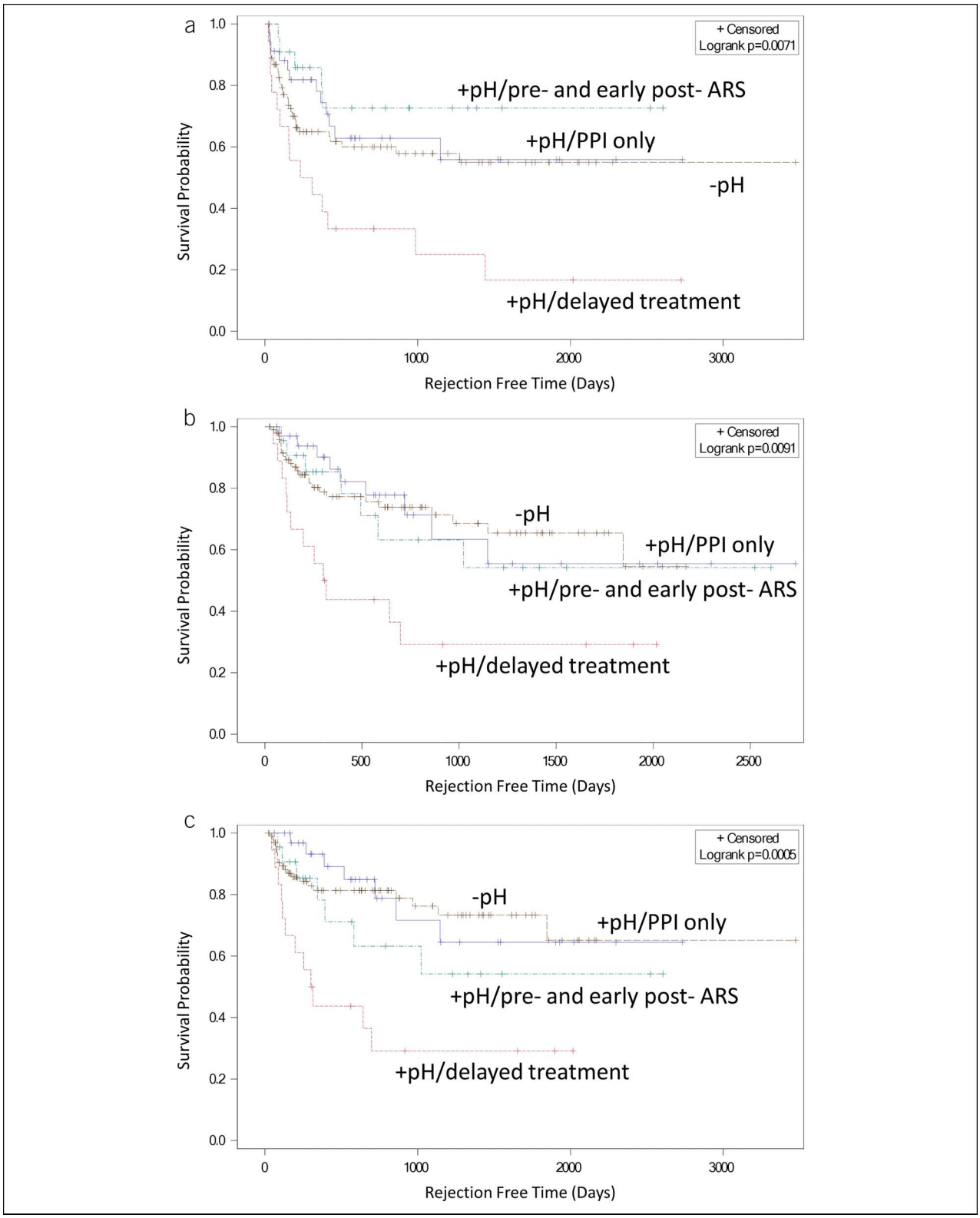

Figure 3. Kaplan-Meier analyses comparing patients with (i) normal reflux monitoring (−pH), (ii) objective GERD and timely medical antireflux therapy (+pH/PPI only), (iii) objective GERD and timely surgical anti-reflux therapy (+pH/pre- or early post-ARS), and (iv) objective GERD and delayed therapy (+pH/delayed treatment) for rejection outcomes of (**a**) AR, (**b**) BOS, and (**c**) CLAD. AR, acute rejection; ARS, antireflux surgery; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; GERD, gastroesophageal reflux disease; PPI, proton pump inhibitor.

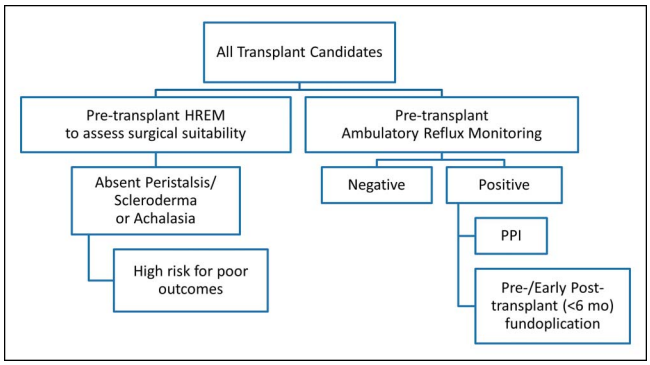

Figure 4. Rational clinical approach to reflux evaluation and management in lung transplant patients. All transplant candidates should undergo esophageal function testing for risk assessment and planning of antireflux therapy if needed. Those with positive reflux monitoring results should be initiated on medical treatment for reflux with PPI and considered for antireflux surgery to be performed within 6 months post-transplant. HREM, high-resolution esophageal manometry; PPI, proton pump inhibitor

Adverse events

A review of individual cases revealed that PPI and ARS treatments were well-tolerated overall. No reported complications requiring discontinuation of treatment were noted among patient receiving PPI therapy. Among those who underwent pretransplant or early post-transplant ARS, 1 patient required surgical revision for slipped wrap and paraesophageal herniation (who had undergone pre-transplant ARS). Among patients receiving late post-transplant ARS, 3 patients had complications: 1 required surgical revision for wrap laxity, 1 needed surgical conversion to Toupet fundoplication due to persistent postoperative dysphagia, and 1 died of aspiration pneumonia 2 weeks after ARS in the setting of active BOS diagnosis.

DISCUSSION

Previous studies have demonstrated the potential role of reflux and aspiration to increase allograft injury and rejection after lung transplantation (2,4,18,19). Furthermore, both medical and surgical antireflux interventions have been linked to more favorable outcomes, including improved allograft function (5,6,20–23), particularly when provided early in the clinical course (5,9,21–24). Despite these observations, esophageal evaluation and management remains variable among transplant centers, with no standardized approach. Our study demonstrated that routine pretransplant evaluation with ambulatory reflux monitoring identifies lung transplant patients at potentially increased risk for GERD-related allograft injury and timely medical or surgical antireflux therapy as directed by reflux monitoring outcomes significantly reduces the risks of acute and chronic rejections post-transplantation. Of importance, patients with increased reflux burden receiving timely therapy had rejection risks that were noninferior to those without objective evidence of GERD. In addition, we established the critical period within 6 months of transplantation as the optimal window for antireflux intervention, with delayed treatment resulting in >2-fold increase in allograft rejection risk compared with those with timely reflux therapy or no GERD. Given the established association between rejection and mortality, reducing rejection risk may help preserve allograft function and improve survival of these high-risk patients.

The correlation between reflux and lung transplant outcomes has been suggested previously, including studies of pepsin and bile acids in the bronchoalveolar lavage fluid of transplant recipients with allograft rejection (18,19). While such biochemical testing awaits further development and standardization, ambulatory reflux monitoring as an objective measure of GERD may help guide management of this population. Indeed, studies by our group and other groups have associated measures of reflux on ambulatory reflux monitoring with increased rejection (2,4,18,19), early rehospitalization (3), pulmonary dysfunction, and survival (25). Of importance, typical esophageal reflux symptoms are often absent among lung transplantation and chronic lung disease patients with GERD (26,27), which further supports a standardized rather than symptom-based approach to reflux evaluation.

On subgroup analyses of the timely reflux treatment cohort, the patients receiving PPI therapy only and undergoing early ARS had similar rejection outcomes, which were significantly better than those with late or no GERD treatment and similar to those without objective evidence of reflux. This finding is interesting and deserves further investigation because previous studies have suggested the prevalence and potential importance of nonacidic bolus reflux on transplant outcomes (23,28,29). However, in this select group of patients with objective evidence of increased acid reflux burden, the acidic component of the refluxate may predominate in GERD-related allograft injury, thereby explaining the efficacy of acid suppression. Because not all patients in our cohort underwent impedance-based testing, we were unable to analyze the relative effect of acid (pH $<$ 4) vs weakly or nonacidic (pH $>$ 4) reflux or their association with antireflux measures and outcomes. This would certainly deserve further investigation–to better define the optimal modalities for reflux testing and management and to determine whether selection of treatment modalities may be tailored according to reflux testing outcomes. Nevertheless, given the significant benefits demonstrated in this study, alongside previous evidence of the role of bolus reflux, ARS should remain the mainstay of reflux therapy in lung transplantation, with PPI serving mainly as an adjunctive treatment or bridge to ARS after transplant.

All patients in our cohort underwent ambulatory reflux monitoring during the pretransplant, rather than post-transplant period, as in some previous studies (30,31). As demonstrated by our results, timely intervention of pathologic reflux seems to be a critical factor to improve transplant outcomes. Therefore, earlier identification of patients at risk of GERD-related allograft injury would help increase the likelihood of completing antireflux intervention within the suggested time frame of 6 months post-transplant. In previous studies correlating post-transplant reflux monitoring with outcomes, reflux testing was performed at least 3 months after transplantation, partly due to the often complicated and prolonged post-operative hospital course (30–33). This would greatly shorten the time frame for completion of ARS if indicated and could result in ARS performed outside the 6-month period altogether. In addition, in our cohort of patients with normal reflux monitoring, none developed symptoms or clinical decline that later required antireflux intervention. Nevertheless, a standard protocol that would both capture patients who need antireflux intervention and allow timely intervention within 6 months of transplantation is most important—whether the reflux monitoring is completed before or soon after transplant. This distinction may be dependent on local volume, expertise, testing capacity, and, if needed, surgical wait time.

Limitations of the study include the retrospective design, although all patients underwent standard reflux testing and peri-transplant care, including immunosuppressant regimens and routine bronchoscopy/PFT. Prospective randomized trials for

ARS would also likely not be possible in this high-risk population, given the established association between reflux and worse transplant outcomes. Initiation of PPI was not standardized in our study because there was a low threshold to start acid suppression regardless of reflux monitoring results. Often, PPI use was based more on any report of esophageal or other abdominal symptoms, and there were patients who were started on PPI despite normal acid exposure time. However, this would likely have biased our results toward null. Our cohort also has a high proportion of patients with IPF, although a variety of pulmonary diagnoses was still represented, with similar distributions in both the early and delayed antireflux treatment groups. Finally, our cohort was moderate in size, although it is consistent with other studies in this area and nearly all included patients had a routine clinic follow-up, with only a few being censored due to inadequate follow-up data. There are also several areas of interest that may drive future investigations in this area. Application of the Lyon consensus criteria for reflux monitoring, the role and normative values of reflux testing performed on PPI, comparative analyses of the optimal antireflux treatment timeline, and the potential values of advanced MII metrics all deserve further evaluation. Moreover, delayed gastric emptying, which is not routinely assessed at our center, has been suggested to correlate with adverse lung transplantation outcome through a reflux-microaspiration pathway, although data regarding its treatment remain limited (34,35). Therefore, the role of routine evaluation and intervention for gastric dysmotility in the management algorithm of lung transplant patients deserves further evaluation.

Based on findings from this and other studies, we propose a rational standardized approach to peri-transplant esophageal testing and management to optimize outcomes (Figure 4). In this algorithm, esophageal function testing including manometry and ambulatory reflux monitoring should be part of routine assessment of lung transplant patients. Esophageal manometry is a crucial component of this protocol for several reasons. First, proper placement of reflux monitoring catheters requires manometric localization of the lower esophageal sphincter and other anatomic landmarks. Second, given the potential need for ARS, high-risk conditions for fundoplication, such as absent contractility, can be identified. Moreover, major motility disorders such as achalasia may increase the risk of aspiration and post-transplant complications. Manometry findings may, therefore, contribute to the risk assessment of lung transplant candidates for planning of perioperative care, determining candidacy at particular centers, and consideration for referral to centers highly specialized in high-risk populations. Finally, outside of major diagnoses such as absent contractility and achalasia, certain manometric findings have also been associated with CLAD, although causality remains unclear (32,33). How to use this information obtained from pretransplant manometry may be dependent on local transplant volume and experience/expertise with higher-risk populations. For patients with increased reflux on ambulatory reflux monitoring, aggressive antireflux interventions including initiation of acid suppression with PPI and performance of ARS within 6 months of transplantation should be used to improve outcomes.

In summary, timely medical or surgical intervention of reflux within 6 months of lung transplantation, as directed by pretransplant ambulatory reflux monitoring results, was associated with significantly reduced risk of allograft rejection, including AR, BOS, and CLAD, compared with those who received no or delayed treatment. Of importance, the rejection risk for patients receiving timely reflux therapy was similar to those without evidence of increased reflux on pretransplant ambulatory reflux monitoring, supporting the effectiveness of antireflux measures in modulating the risk of reflux-induced allograft injury. A standardized peri-transplant testing and treatment algorithm may help guide timely evaluation and management of GERD among lung transplant recipients, with associated reduction in rejection outcomes, and should be established across transplant centers to improve outcomes.

CONFLICTS OF INTEREST

Guarantors of the article: Walter W. Chan, MD, MPH.
Specific author contributions: W.W.C. and W.K.L.: initiated study concepts and design; W.K.L., H.J.G., J.O.W., and W.W.C.: contributed to acquisition of data; W.W.C., W.K.L., H.J.G., and N.S.: performed analysis and interpretation of data; W.W.C. and W.K.L.: drafted the manuscript; W.W.C., W.K.L., H.J.G., N.S., and J.O.W.: contributed to critical revision of manuscript for important intellectual content; W.W.C. and W.K.L.: performed statistical analyses; W.W.C.: provided administrative support and overall study supervision.
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Study Highlights

WHAT IS KNOWN

- ✓ Gastroesophageal reflux disease has been associated with worse lung transplant outcomes.
- ✓ There is no current standard approach to reflux evaluation and management among transplant centers.

WHAT IS NEW HERE

- ✓ Routine standardized reflux testing identifies lung transplant patients at increased risks for reflux-related allograft injury.
- ✓ Early antireflux treatment within 6 months of transplantation as guided by standardized reflux testing is safe and significantly reduces acute and chronic allograft rejection.
- ✓ A standard management algorithm that includes routine reflux assessment of lung transplant patients may help improve outcome.

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