Esophageal Motility Disorders Associated With Death or Allograft Dysfunction After Lung Transplantation? Results of a Retrospective Monocentric Study

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OBJECTIVES: **Pathological gastroesophageal reflux (GER) is a known risk factor for bronchiolitis obliterans syndrome (BOS) after lung transplantation. This study aimed at determining whether functional esophageal evaluation might predict BOS occurrence and survival in this setting.**

METHODS: **Ninety-three patients who underwent esophageal high-resolution manometry and 24-hour pH-impedance monitoring within the first year after lung transplantation were retrospectively included. A univariable analysis was performed to evaluate the parameters associated with GER disease and BOS occurrence. The Cox regression model was used to identify the prognostic factors of death or retransplantation.**

RESULTS: **Thirteen percent of patients exhibited major esophageal motility disorders and 20% pathological GER. GER occurrence was associated with younger age, cystic fibrosis, and hypotensive esophagogastric junction. Within a median follow-up of 62 months, 10 patients (11%) developed BOS, and no predictive factors were identified. At the end of the follow-up, 10 patients died and 1 underwent retransplantation. The 5-year cumulative survival rate without retransplantation was lower in patients with major esophageal motility disorders compared with that in those without (75% vs 90%, $P = 0.01$) and in patients who developed BOS compared with that in those without (66% vs 91%; $P = 0.005$). However, in multivariable analysis, major esophageal motility disorders and BOS were no longer significant predictors of survival without retransplantation.**

DISCUSSION: **Major esophageal motility disorders and BOS were associated with allograft survival in lung transplantation in the univariable analysis. Although the causes of this association remain to be determined, this observation confirms that esophageal motor dysfunction should be evaluated in the context of lung transplantation.**

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INTRODUCTION

Lung transplantation is an effective treatment for end-stage lung diseases. The most common indications in adults are cystic fibrosis, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis (1). According to the 2016 report from the registry of the International Society for Heart and Lung Transplantation, adults who underwent primary lung transplantation between 1990 and 2014 had a median survival of 5.8 years (with an unadjusted survival of 80% at 1 year and 54% at 5 years) and those who survived up to 1 year after transplantation had a conditional median survival of 8.0 years (2).

Bronchiolitis obliterans syndrome (BOS) is a major concern in lung transplantation because it leads to chronic lung allograft dysfunction and death. Its prevalence is around 50% 5 years after transplantation (3). This syndrome is characterized by progressive shortness of breath associated with an irreversible obstructive spirometric progression (4). The histological hallmarks are obliteration of terminal bronchioles and evidence of aberrant remodeling in the airway epithelium, vasculature, stroma, and lymphoid system (5). The following risk factors have been associated with BOS: recurrent episodes of acute rejection, development of anti-human leukocyte antigen antibodies, bacterial or fungal colonization of the graft, community-

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acquired viral infection, cytomegalovirus pneumonitis, and gastroesophageal reflux disease (GERD).

GERD is prevalent after lung transplantation and may concern at least 50% of patients (6–10). GERD is more frequent and severe in lung-transplanted patients with BOS than in those without BOS (6,11,12). Laparoscopic fundoplication that aims at suppressing gastric content reflux into the esophagus has been proposed to reduce chronic damage to the graft and improve survival after lung transplantation (13). Because of the potential implication of GERD on the occurrence of BOS and graft survival, a systematic evaluation, based on esophageal high-resolution manometry (HRM) and reflux monitoring, is recommended because GERD may be asymptomatic in this population (14,15).

The role of esophageal motility disorders was recently evaluated in lung-transplanted patients using impedance-combined HRM (16). Esophagogastric junction (EGJ) outflow obstruction, incomplete bolus transit, and proximal reflux were risk factors of chronic lung dysfunction. Interestingly, patients with EGJ outflow obstruction exhibited less likely acid reflux than patients with normal esophageal motility, suggesting that motility disorders *per se* could be associated with graft dysfunction. Thus, we hypothesized that esophageal motility disorders could play a role on BOS, which is one of the causes for a graft dysfunction.

The aims of this study were to determine the prevalence of esophageal dysfunction with HRM and GERD with prolonged esophageal pH-impedance monitoring, in a single-center cohort of lung-transplanted patients and to evaluate whether esophageal dysfunction evaluated with HRM alone without impedance and GERD would be predictive of BOS, a cause for graft dysfunction, and survival after transplantation.

PATIENTS AND METHODS

Patients

Lung-transplanted patients referred to the digestive motility unit for esophageal testing between November 2007 (beginning of systematic esophageal evaluation in the unit) and July 2017 (to ensure a follow-up of at least 2 years in a large number of patients) were included in this retrospective study. Additional inclusion criteria were an esophageal evaluation with HRM and pH-impedance monitoring within 1 year after lung transplantation and absence of BOS at the time of evaluation. Exclusion criteria were a pH-impedance monitoring performed on proton pump inhibitors (PPIs) therapy and an incomplete HRM or pH-impedance monitoring. Immunosuppression therapy was induced with basiliximab and standard maintenance therapy consisted in combined administration of tacrolimus, mycophenolate mofetil, and prednisone. According to French Law, this retrospective analysis of data, obtained during the routine clinical evaluation of patients, does not require approval of an ethical review board. Patients were informed that their clinical data could be used for clinical research after anonymization. They were given the possibility to sign a document indicating their refusal to participate, in which case their files were not used for the study.

Esophageal evaluation

Esophageal functional testing was performed after an overnight fast. Patients were instructed to stop the PPI therapy at least 8 days before examination.

First, HRM (Medtronic, Minneapolis, MN) was performed to localize EGJ and to evaluate esophageal motility. Then, 24-h esophageal pH-impedance monitoring (Sandhill Scientific,

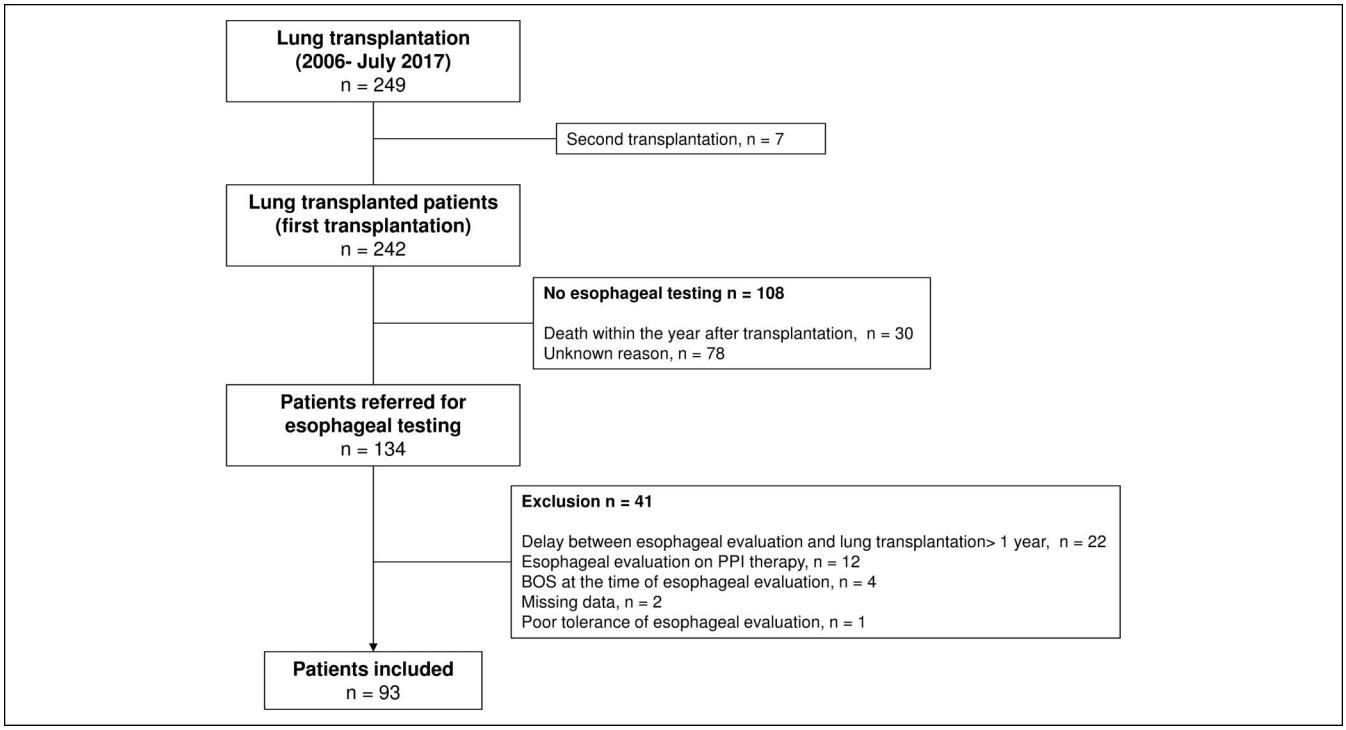


Figure 1. Patients' flow chart. Among the 249 lung transplantations performed between 2006 and July 2017, 134 patients were referred for esophageal testing. They were excluded of the study if the esophageal evaluation was performed more than 1 year after lung transplantation, on PPI therapy, at the time of BOS, or if the esophageal evaluation was not interpretable owing to poor tolerance. BOS, bronchiolitis obliterans syndrome; PPI, proton pump inhibitor.

Table 1. Patients' characteristics

Characteristics	
Mean age (range), yr	43.3 (17–65)
Gender, n (%)	
Male	56 (60.0)
Female	37 (40.0)
Transplantation type, n (%)	
Single	27 (29.0)
Bilateral	57 (61.3)
Cardiopulmonary transplantation	9 (9.7)
Underlying conditions, n (%)	
Cystic fibrosis	34 (36.5)
Emphysema	28 (30.1)
Pulmonary fibrosis	9 (9.7)
Pulmonary arterial hypertension	9 (9.7)
Bronchiectasis	4 (4.3)
Lymphangioleiomyomatosis	3 (3.2)
Systemic sclerosis	2 (2.2)
Other	4 (4.3)
Opiates treatment at the time of high-resolution manometry	
No opioid treatment	75 (80.6)
Tramadol	14 (15.1)
Dextropoxyphene	1 (1.1)
Fentanyl	1 (1.1)
Oxycodone	1 (1.1)
Data not available	1 (1.1)

Highlands Ranch, CO) was conducted to quantify gastroesophageal reflux.

Clinical and outcome data

Clinical and outcome data were collected retrospectively by searching the patients' charts. Causal disease, date of transplantation, type of transplantation (single, bilateral, or heart and lung transplantation), rejection episodes, reflux treatment, and treatment with opiates, PPI, and/or azithromycin were noted. The occurrence of BOS, which is defined as a persistent decline in forced expiratory volume in 1 second (≤90% of baseline) without other known or potentially reversible causes of post-transplant loss of lung function, was reported (17). Dates of the last follow-up visit in the lung transplantation center, dates of retransplantation, and/or dates of death were collected for all patients.

Data analysis

Esophageal HRM data were analyzed using ManoView software (Medtronic, Minneapolis, MN). EGJ baseline pressure was measured in the absence of swallowing, and hypotensive EGJ was defined as a baseline pressure < 5 mm Hg (18). Esophageal motility diagnosis was based on the Chicago Classification for esophageal motility disorders (19).

Table 2. Esophageal motility disorders categorized according to the Chicago Classification

	All patients (n = 93)	Patients with cystic fibrosis (n = 34)	Patients with other underlying conditions (n = 59)
Major motility disorders			
Esophagogastric junction outflow obstruction	2 (2.2%)	1 (2.9%)	1 (1.7%)
Absence of contractions	1 (1.1%)	0	1 (1.7%)
Distal esophageal spasm	2 (2.2%)	0	2 (3.4%)
Jackhammer esophagus	7 (7.5%)	0	7 (11.9%)
Minor motility disorders			
Ineffective esophageal motility	25 (26.8%)	15 (44.1%)[a]	10 (16.9%)
Normal	56 (60.2%)	18 (53.0%)	38 (64.4%)

[a] $P < 0.001$ vs other underlying conditions.

For gastroesophageal reflux events detection, pH-impedance recordings were analyzed using dedicated software (BioView Analysis, version 5.6.0.0, Sandhill Scientific, Highland ranch, CO). The Lyon Consensus criteria were applied to define GERD: an esophageal acid exposure time (AET, percentage of time with esophageal pH < 4) $> 6\%$ was considered as pathological, in addition to a total number of reflux events > 80/24 hours (20). An AET between 4% and 6% and/or a total number of reflux > 73/24 hours were considered as inconclusive or borderline for the diagnosis of GERD. An AET $< 4\%$ associated with a total number of reflux ≤ 73/24 hours was normal.

Statistical analysis

Data were expressed as median (range) unless otherwise mentioned. Continuous variables were compared using a nonparametric test (Mann-Whitney), whereas categorical data were compared using the Fisher exact test.

The survival rates were evaluated using the Kaplan–Meier method starting from the date of lung transplantation to that of death, retransplantation, or last clinical visit. The survival curves were compared using the log-rank test. Variables associated with a P value ≤ 0.05 using the log-rank test were introduced in a Cox regression model to determine independent prognostic factors for death or retransplantation.

RESULTS

Prevalence of esophageal motility disorders

Among the 242 patients who underwent lung transplantation for the first time between 2006 and July 2017, 134 were referred for esophageal testing and 93 included for retrospective analysis (Figure 1). The characteristics of the 93 patients are summarized in Table 1. Esophageal function was evaluated using HRM and pH-impedance monitoring off PPI within a median delay of 6 months (1–12 months) after lung transplantation.

The median EGJ resting pressure was 8 (0–32) mm Hg. EGJ was hypotensive in 26 patients (28.0%). Fifty-six patients (60.2%)

Table 3. Motility disorders according to the type of transplantation

	Single transplantation (n = 27)	Bilateral transplantation (n = 57)	Cardiopulmonary transplantation (n = 9)
Major motility disorders			
Esophagogastric junction outflow obstruction	0	2 (3.5%)	0
Absence of contractions	1 (3.7%)	0	0
Distal esophageal spasm	0	2 (3.5%)	0
Jackhammer esophagus	5 (18.5%)[a]	1 (1.8%)	1 (11.1%)
Minor motility disorders			
Ineffective esophageal motility	3 (11.1%)[b]	18 (31.6%)	4 (44.4%)
Normal	18 (66.7%)	34 (59.6%)	4 (44.4%)

[a] $P < 0.05$ vs bilateral transplantation.
[b] $P = 0.059$ vs bilateral transplantation.

showed normal esophageal motility (Table 2). The most frequent esophageal motility disorder encountered was ineffective esophageal motility (25 patients, 26.8%). The occurrence of esophageal motility disorder was associated with the underlying conditions. Patients with cystic fibrosis showed a significantly higher proportion of minor motility disorders ($P < 0.001$), whereas patients with other underlying conditions exhibited significantly more major motility disorders ($P = 0.03$). The distribution of motility disorders according to the type of transplantation is reported in Table 3. Jackhammer esophagus was more likely observed in patients with single transplantation compared with those with bilateral transplantation, whereas ineffective esophageal motility tended to be more frequently observed in patients with bilateral transplantation. Seventeen patients (18.3%) were on opiates at the time of HRM. EGJ outflow obstruction, jackhammer esophagus, and distal esophageal spasm (known to be induced by opiates) were observed in 1 (5.9%), 2 (11.8%), and 1 (5.9%) patients on opiates, respectively, vs 1 (1.3%), 5 (6.7%), and 1 (1.3%) patients without treatment, respectively ($P = 0.115$, Fisher exact test to compare opiates-induced motility disorders vs other disorders).

Prevalence of pathological gastroesophageal acid reflux

Applying the criteria of the Lyon Consensus to diagnose GERD, 19 patients (20.4%) presented pathological GERD (1 patient had both AET > 6% and an abnormal number of reflux events, 14 had only an AET > 6%, and 4 had only an abnormal number of reflux events), 9 patients (9.7%) had borderline AET, and 65 (69.9%) had normal AET. Factors associated with GERD were younger age (mean age 38.2 years vs 44.6, $P = 0.05$), cystic fibrosis (63.2% vs 29.7%, $P = 0.01$), and hypotensive EGJ (47.4% vs 22.9%, $P = 0.04$, Table 4). There was no significant difference in the distribution of esophageal motility disorders between patients with and without GERD ($P = 0.45$). In particular, ineffective esophageal motility was present in 5 patients with pathological GERD (26.3%) and in 20 without pathological GERD (27.0%) ($P = 1.00$, Fisher exact test).

Finally, the factors associated with GERD were similar when patients with pathological GERD were merged to those with borderline GERD and compared with patients with AET < 4% and number of reflux events ≤ 73/24 hours.

Outcome

The median (range) follow-up duration after lung transplantation was 62 (3–141) months. A follow-up shorter than 2 years was always because of an early death. Most patients received PPI

Table 4. Factors associated with GERD

	GERD (n = 19)	No GERD (n = 74)	*P*
Mean age (range), yr	38.2 (19–59)	44.6 (17–65)	0.05
Gender, n (%)			
Male	12 (63.2)	44 (59.5)	1.00
Median delay between lung transplantation and esophageal function evaluation (range), mo	5 (3–12)	6 (1–13)	0.63
Type of transplantation, n (%)			0.13
Single	2 (10.5)	25 (33.8)	
Bilateral	15 (79.0)	42 (56.7)	
Cardiopulmonary transplantation	2 (10.5)	7 (9.5)	
Underlying conditions, n (%)			0.01
Cystic fibrosis	12 (63.2)	22 (29.7)	
No cystic fibrosis	7 (36.8)	52 (70.3)	
Median EGJ resting pressure (range), mm Hg	5 (0–23)	9 (0–32)	0.15
Hypotensive EGJ, n (%)	9 (47.4)	17 (22.9)	0.04
Esophageal motility disorder, n (%)			0.45
Major motility disorder	1 (5.3)	11 (14.9)	
Minor motility disorder/No motility disorder	18 (94.7)	63 (85.1)	
Treatment with azithromycin, n (%)			0.80
Yes	8 (42.1)	28 (37.8)	
No	11 (57.9)	46 (62.2)	

EGJ, esophago-gastric junction; GERD, gastro-esophageal reflux disease.

Table 5. Factors associated with BOS

	BOS (n = 10)	No BOS (n = 83)	*P*
Mean age at transplantation (range), yr	46.6 (30–61)	42.9 (17–65)	0.49
Gender, n (%)			
Male	3 (30.0)	53 (63.9)	0.08
Median follow-up duration (range), mo	52.0 (15–121)	64.0 (3–141)	0.31
Type of transplantation, n (%)			0.71
Single	4 (40.0)	23 (27.7)	
Bilateral	5 (50.0)	52 (62.7)	
Cardiopulmonary transplantation	1 (10.0)	8 (9.6)	
Underlying conditions, n (%)			0.74
Cystic fibrosis	3 (30.0)	31 (37.3)	
No cystic fibrosis	7 (70.0)	52 (62.7)	
Hypotensive esophagogastric junction, n (%)	2 (20.0)	24 (28.9)	0.72
Esophageal motility disorder, n (%)			0.12
Major motility disorder	3 (30.0)	9 (10.8)	
Minor motility disorder or no motility disorder	7 (70.0)	74 (89.2)	
Esophageal pH-impedance monitoring, n (%)			
Pathological acid esophageal exposure	1 (10.0)	13 (15.7)	1.00
Abnormal number of reflux events	1 (10.0)	4 (4.8)	0.44
Pathological GERD	2 (20.0)	17 (20.5)	0.67
Pathological or borderline GERD	2 (20.0)	27 (32.5)	0.34
Treatment with azithromycin			0.18
Yes	6 (60.0)	30 (36.1)	
No	4 (40.0)	53 (63.9)	

BOS, bronchiolitis obliterans syndrome; GERD = gastroesophageal reflux disease

therapy during follow-up (80 patients, 86.0%) including 6 patients who underwent fundoplication. Only 13 patients (14.0%) did not receive any antireflux treatment. Furthermore, 37 patients (39.8%) received azithromycin in addition to PPI during the follow-up. Within the follow-up period, 10 patients (10.8%) developed BOS. No predictive factors of BOS were identified (Table 5).

At the end of the follow-up period, 82 patients were alive without retransplantation, 10 patients were dead, and 1 patient underwent retransplantation because of a bronchial stenosis. The causes of death were as follows: BOS (n = 3), sepsis (n = 2), pulmonary adenocarcinoma (n = 1), B-cell lymphoma (n = 1), glioblastoma (n = 1), myocardial rejection (n = 1), and tacrolimus-associated thrombotic thrombocytopenic purpura (n = 1). The 2- and 5-year cumulative survival rates without retransplantation were 94.7% and 86.7%, respectively. In the univariable analysis, the cumulative survival was lower in patients with BOS and in those with major esophageal motility disorders (Table 6; Figure 2). The cumulative survival at 5 years was not significantly different in patients with or without pathological GERD (100% vs 84.8%, $P = 0.29$). In the multivariable analysis, major esophageal motility disorders and BOS were no longer significantly associated with poor outcome (Table 6).

DISCUSSION

This study confirmed that esophageal motility disorders are frequent in lung-transplanted patients, with one-third of these motility disorders considered major. Based on the univariable analysis, major esophageal disorders and BOS were prognostic factors of decreased survival without retransplantation.

Different studies have already demonstrated the frequency of esophageal motility disorders after lung transplantation (up to 50% of patients) (21–24). Although these disorders were mainly hypotensive motility disorders, occurrences of EGJ outflow obstruction, distal esophageal spasm, and hypercontractility (major motility disorders) were also previously reported. In this study, esophageal motility disorders were related to the underlying conditions as previously reported (25). These motility disorders might exist before transplantation. Indeed, Basseri et al. (26) reported esophageal peristaltic dysfunction in 77% of lung transplant candidates. Among the 23 peristaltic dysfunctions observed, there were 2 cases of distal esophageal spasm and 1 case of EGJ outflow obstruction, whereas the other cases were with minor disorders. In their series, diagnosis of absence of contraction was more frequent in patients with idiopathic pulmonary fibrosis, which supports the relationship between esophageal motility disorders and underlying conditions. Recently, Ciriza de Los Ríos et al. (21) compared the frequency of esophageal motility disorders before and after lung transplantation. According to them and based on the Chicago Classification 3.0, the frequency of esophageal motor disorders was 33% before transplantation and 49% after transplantation. Other recent data are in favor of a significant increase of esophageal contractility after lung transplantation (27). The impact of major thoracic surgery, as well as the improvement of pulmonary function, might explain the differences observed before and after transplantation. Respiratory insufficiency by itself could impair the analysis of pretransplantation HRM and lead to a false-positive diagnosis of esophageal motility disorders. Sampath et al. (28) evaluated the effect of suspended breathing and hyperventilation on esophageal motility. They demonstrated that respiratory frequency and depth affected the waveform morphology of esophageal contractions. Thus, respiratory insufficiency, which is restored after lung transplantation, might explain that some pretransplantation esophageal motility disorders disappear. Finally, the use of opiates after transplantation could induce esophageal motility disorders (29). Thus, the major esophageal motility disorders potentially induced by opiates (EGJ outflow obstruction, jackhammer esophagus, and distal esophageal spasm) tended to be more frequent in patients on opiates at the time of HRM but the difference was not significant.

In the study herein, jackhammer esophagus was more frequently observed in patients with single transplantation than in those with other types of transplantation. The results regarding the type of transplantation and esophageal motility disorders are conflicting. Fisichella et al. (22) did not observe any association between the type of transplantation and the distribution of esophageal motility disorders. On contrary, Tangaroonsanti et al.

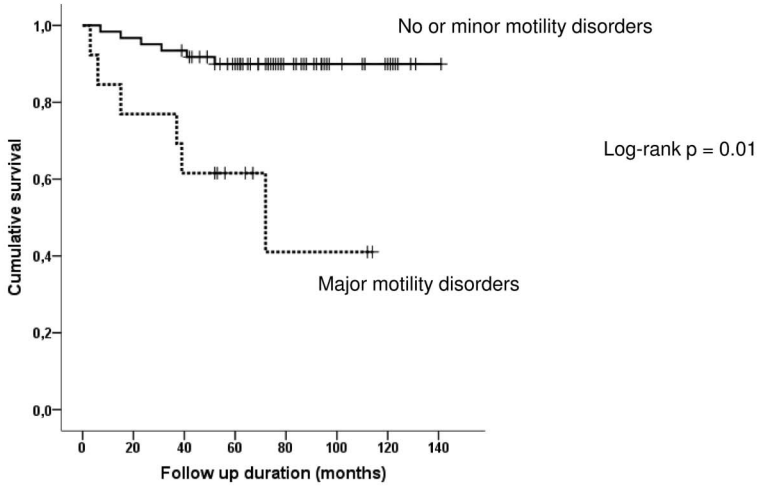
Table 6. Factors associated with death or retransplantation

		Univariable					Multivariable	
	n	2-yr survival (%)	3-yr survival (%)	4-yr survival (%)	5-yr survival (%)	*P*	HR (95% CI)	*P*
All patients		94.7	92.3	88.2	86.7			
Patients at risk		87	72	59	49			
Age at transplantation <45 yr	43	95.3	92.8	90.1	90.1	0.43		
Age at transplantation ≥45 yr	50	94.0	91.8	89.2	86.3			
Male	56	91.0	89.1	86.8	86.8	0.66		
Female	37	100	97.1	93.9	90.3			
Single lung transplantation	27	92.6	88.6	88.6	83.4	0.41		
Bilateral lung transplantation	57	94.7	92.7	90.4	90.4			
Cardiopulmonary transplantation	9	100.0	100.0	87.5	87.5			
Cystic fibrosis, yes	34	94.0	90.8	90.8	90.8	0.43		
Cystic fibrosis, no	59	94.9	93.1	88.7	86.1			
Bronchiolitis obliterans syndrome, yes	10	90.0	78.8	78.8	65.6	0.005	3.5 (0.9–13.3)	0.06
Bronchiolitis obliterans syndrome, no	83	95.1	93.8	90.8	90.8			
Hypotensive EGJ, yes	26	92.3	87.9	87.9	87.9	0.97		
Hypotensive EGJ, no	67	95.5	93.9	90.0	87.9			
Major motility disorders	12	83.3	83.3	75.0	75.0	0.01	1.7 (0.9–3.3)	0.12
Minor motility disorder or no motility disorder	81	96.3	93.5	91.9	90.0			
Pathological esophageal acid exposure, yes	14	100	100	100	100	0.50		
Pathological esophageal acid exposure, no	79	93.6	90.8	87.7	85.7			
Abnormal number of reflux events, yes	5	100	100	100	100	0.38		
Abnormal number of reflux events, no	88	94.3	91.7	88.9	87.2			
Pathological GER, yes	19	100	100	100	100	0.29		
Pathological GER, no	74	93.2	90.2	86.8	84.8			
Pathological or borderline GER, yes	29	93.1	89.1	89.1	89.1	0.75		
Pathological or borderline GER, no	64	95.3	93.6	89.6	87.1			
Treatment with azithromycin, yes	36	100.0	96.9	90.4	90.4	0.67		
Treatment with azithromycin, no	57	91.2	89.2	89.2	86.3			

CI, confidence interval; EGJ, esophagogastric junction; GER, gastroesophageal reflux; HR, hazard ratio.

(30) demonstrated that unilateral transplantation was more frequently associated with EGJ outflow obstruction and bilateral transplantation with hypocontractility. We confirmed this latter observation because, in our series, there was a trend of more ineffective esophageal motility in patients with bilateral transplantation. The type of transplantation is dependent of the underlying condition that may represent a confounding factor. The first cause of transplantation was cystic fibrosis in this study, and all patients with cystic fibrosis but one underwent bilateral transplantation; chronic obstructive pulmonary disease was the main cause of transplantation in the study by Fisichella et al. and idiopathic pulmonary fibrosis in the studies by Tangaroonsanti et al.

Interestingly, this study showed that major esophageal motility disorders diagnosed after transplantation were associated with a shorter survival without retransplantation in the univariable analysis. Previously, some authors observed a possible link between post-transplantation esophageal motility disorders and graft dysfunction. In a series of 57 patients, Ciriza de Los Ríos et al. (21) reported a higher frequency of esophageal motility disorders (distal esophageal spasm, hypercontractile esophagus, and EGJ outflow obstruction) in patients with rejection compared with those without rejection. Similarly Tangaroonsanti et al. (24) reported that 80% of patients with EGJ outflow obstruction developed obstructive chronic lung allograft dysfunction compared with 22% of those with normal motility ($P = 0.19$). Thus, esophageal dysmotility might be a risk factor for graft dysfunction. However, it is important to note that, when using the multivariable analysis, esophageal motility disorders were no longer significantly associated with poor outcome in this series, suggesting possible confounding factors. This differs from the study by Tangaroonsanti et al. (16). Different



		12 months	24 months	36 months	48 months	60 months
No or minor motility disorders	Survival (%)	98.8	96.3	93.5	91.9	90.0
	Patients at risk	80	76	61	52	44
Major motility disorders	Survival (%)	83.3	83.3	83.3	75.0	75.0
	Patients at risk	10	10	10	8	5

Figure 2. Cumulative survival in patients with major motility disorders (dashed line) and those with no or minor motility disorders (black line) according to the Kaplan–Meier method. At 36 months, the cumulative survival was 83.3% for patients with major motility disorders vs 93.5% for patients with no or minor motility disorders ($P = 0.01$, log-rank test).

hypotheses can be raised. The included population was older in the study by Tangaroonsanti et al. with diffuse parenchymal lung disease as the main cause of transplantation, whereas the main cause of transplantation was cystic fibrosis in our series. The median delay between lung transplantation and HRM was longer in our series (6 vs 3 months). Finally, all the patients of this series were explored off PPI contrary to the series by Tangaroonsanti et al. Esophageal acid exposure can play a role in the genesis of motility disorders (31,32).

There are several hypotheses to explain the relationship among esophageal dysmotility, graft dysfunction, and outcome. First, the post-transplantation respiratory status might be a confounding factor, and it is possible that patients with post-transplantation esophageal motility disorders exhibit a poorer lung function compared with those without. However, in this series, respiratory parameters (forced expiratory volume in 1 second, forced inspiratory volume 25%–75%, and vital capacity) were similar in patients with and without major esophageal motility disorders at the time of HRM. Second, esophageal dysmotility is a well-known determinant of GERD pathophysiology (33), and GERD can be associated with lung transplantation outcome (6,11,12). Thus, after lung transplantation, patients with esophageal dysmotility may exhibit pathological GERD more frequently than patients with normal motility (89% vs 33%, respectively, in the series by Tangaroonsanti et al., $P = 0.025$) (24). In this series, esophageal dysmotility (and ineffective esophageal motility in particular) was not significantly associated with GERD contrary to hypotensive EGJ. Furthermore, GERD was not associated with survival, contrary to esophageal motility disorders. The use of PPI in most patients of this series and performance of fundoplication in patients with uncontrolled GERD on PPI might have modified the impact of GERD on outcome. Esophageal motility disorders and hypotensive EGJ are not the only determinant of GERD occurrence. Delayed gastric emptying might also facilitate GERD. Azithromycin, which is frequently used in lung transplantation to prevent graft dysfunction, can accelerate gastric emptying and reduce GERD after lung transplantation (34). In this series, azithromycin treatment was not associated with GERD occurrence. Finally, impaired esophageal clearance induced by esophageal motility disorders might represent a risk for the development of obstructive chronic lung allograft dysfunction (16). A poor clearance of swallowed boluses might induce aspiration impairing graft function. Contrary to the study by Tangaroonsanti et al. (16), HRM was not combined with impedance in this study; therefore, it was not possible to confirm the role of incomplete bolus transit as a predictive factor of outcome.

This study has some limitations. Only patients referred for esophageal evaluation were included, whereas those who did not undergo esophageal evaluation within the first year after transplantation were systematically excluded. The reason for an absence of esophageal testing in 78 patients (32% of lung-transplanted patients) was unknown. Esophageal testing after lung transplantation is recommended but not mandatory. It could have been canceled in patients owing to poor condition, patient's refusal, or simply omitted. Thus, a recruitment bias is possible and might be responsible for the low number of patients with BOS and a relative better graft survival than that reported by the International Society for Lung and Heart transplantation (2). However, BOS was significantly associated with graft survival, as previously reported (12). The choice of inclusion and exclusion criteria also allowed for a better homogeneity of the current retrospective cohort. Furthermore, the delay between the transplantation and esophageal testing should be ideally within a narrower time frame than the time frame of this study. Because patients came frequently from

outside cities, esophageal testing was scheduled during one of the follow-up visits at the transplantation center. Depending on the patient's condition and other examinations, esophageal testing was postponed or even canceled. This heterogeneity of delay reflects the difficulty encountered in clinical practice to follow recommendations.

In conclusion, we confirmed that post-transplantation major esophageal motility disorders and BOS might impair survival after lung transplantation. The mechanism underlying the role of esophageal motility in the post-transplantation survival remains unclear. Additional studies are required to understand how esophageal dysmotility might facilitate graft dysfunction.

CONFLICTS OF INTEREST

Guarantor of the article: Sabine Roman.

Specific author contributions: Conception and design: F.P., F.M and S.R. Collection and assembly of data, data analysis, and drafting the manuscript: C.G., F.M. and S.R. Substantial contribution to the data acquisition and revision of the manuscript critically for important intellectual content: F.P., F.T., A.S., A.-M.R., and J.-F.M. All the authors approved the final manuscript.

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Study Highlights

WHAT IS KNOWN

- ✓ Gastroesophageal reflux disease is a risk factor for lung graft dysfunction.
- ✓ Esophageal manometry is used during GERD evaluation.
- ✓ Data regarding the impact of esophageal dysmotility on lung transplantation outcome are scarce.

WHAT IS NEW HERE

- ✓ Major esophageal dysmotility is associated with shorter survival after lung transplantation.

TRANSLATIONAL IMPACT

- ✓ Identification of esophageal motility disorders might be useful to predict survival after lung transplantation.

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