Functional esophageal testing at lung transplant candidates for connective tissue disorder: gastroesophageal reflux disease, esophageal motility, and short-term survival

PhD - Theses

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Theme:	**The investigation of pathological conditions of the circulation in *in vivo* surgical models and in-patients**

University of Pécs, Faculty of Medicine 2021.

Abbreviations

ACE – angiotenzin converting enzyme
AEM – absent esophageal motility
AL - abdominal length
BMI – body mass index
COPD – chronic obstructive pulmonary disease
CTD – connective tissue disease
DCI – distal contractility integral
DM – dermatomyositis
EGJ – esophagogastric junction
FEV-1 – first second of forced expiration
GERD – gastroesophageal reflux disease
HRM – high resolution manometry
IEM – ineffective esophageal motility
ILD – interstitial lung disease
IPF – idiopathic pulmonary fibrosis
IQR – inter-quartile range
IRP – integrated relaxation pressure
ISHLT – International Society of Heart and Lung Transplantation
LAS – lung allocation score
LESP – lower esophageal sphincter pressure
LTx – lung transplantation
MCTD – mixed connective tissue disease
OL – overall length
PAH – pulmonary arterial hypertension
PEM – preserved esophageal motility
PF – pulmonary fibrosis
PM – polymyositis
RA – rheumatoid arthritis
SLE – systemic lupus erythematosus
SS – Sjörgren's syndrome
SSc – scleroderma
TN - Tennessee
UCTD – unverified connective tissue disease
USA – United States of America

1. Introduction and set of goals

Due to the advancement of surgical technique and instrumentation, and the improvement of intensive care unit attendance, the number of lung transplantation has grown notably in the past decades. In 2017, only in the United States, 2478 lung transplants were performed, 66% of them were bilateral procedures [1]. From a ten-year perspective that was a 68.8% increase in the number of lung transplantation (1468 surgeries in 2007 vs. 2478 surgeries in 2017). Besides the continuously increasing number of available donor organs and number of surgeries, the appropriate choice of recipients has a crucial role to this day. That statement is proven by the data, that although in 2017, 326 patients died because they did not get an applicable organ donor, the 1-year survival of lung transplant recipients is over 80% in the United States of America [2].

The breakthrough in the short- and long-term post-transplant survival in the United States was possible in 2005, due to a newly introduced lung allocation system (lung allocation score – LAS), which redefined the appropriate allocation of the limited number of donor lungs. By determining the LAS in a scale from 1 to 100 using a complex algorithm, the advisory board can scale the recipients on the waiting list more effectively, and it can take account for both the urgency and the expected benefits (i.e., The survival without transplantation) of lung transplantation [3]. The introduction of the LAS has significantly increased the number of lung transplantation at formerly rejected patients with pulmonary fibrosis [PF], pulmonary arterial hypertension [PAH], and interstitial lung disease, over against the pre-LAS era dominant diseases such as chronic obstructive pulmonary disease (COPD). Recently, the most common indications for lung transplantations are idiopathic pulmonary fibrosis (IPF), COPD, PAH, and cystic fibrosis. The occasional, more rare indications are due to less common diseases, such as sarcoidosis, lymphangiomyelomatosis, and the pulmonary manifestations (ILD, PAH) of connective tissue diseases (CTD) [1;2].

Since the introduction of angiotensin-converting enzyme inhibitors, renal complications of CTDs have declined, and pulmonary complications are now the most common cause of morbidity and mortality [4]. In the past years, numerous studies were shown similar post-transplant survival results between patients who underwent lung transplantation due to connective tissue disease and patients receiving lung transplantation due to other disorders [5;6]. Because of the often-presented comorbidities, the proportion of all lung transplants due to connective tissue disease is less than 1% in the United States [1]. In this patient population, the pre-transplant workup is an especially complex procedure. In our institute, besides the guidelines of the International Society of Heart and Lung Transplantation (ISHLT), we perform numerous additional examinations on CTD patients to diagnose these pathological states [7]. From these comorbidities, the gastrointestinal complications should be highlighted, more specifically the decrease in esophageal motility, and the presence of the gastroesophageal reflux disease. These complications may not result from the immediate rejection of the candidate from lung transplantation, but it is proven that they can worsen survival after surgery [9]. Besides the upper endoscopic studies, high resolution manometry [HRM], timed barium swallow, and 24-hour pH study are mandatory for all lung transplant candidates.

In my study, my primary goal was to investigate the effects of these gastrointestinal comorbidities in connection with the short-term survival of CTD patients, moreover, my additional goal was to determine the change in the esophageal motility and gastroesophageal reflux disease after surgery.

Study goals:

1. Introduction and analysis of esophageal motility studies and 24-h pH studies at patients underwent lung transplantation due to connective tissue disease, and determine subgroups based on my findings.
2. Introduction of short-term survival results of lung transplant recipients due to connective tissue disease
    a. Comparison of the 1 and 3-year survival data using Kaplan-Meier analysis between the 33 CTD patients who underwent lung transplantation, and the 462 patients underwent lung transplantation due to other disorder
    b. Introduction of the 1 and 3-year survival data of 33 CTD patients who underwent lung transplantation correlation to esophageal motility using the Kaplan Meier analysis
    c. Introduction of the 1 and 3-year survival data of 33 CTD patients who underwent lung transplantation correlation to gastrointestinal reflux disease using the Kaplan Meier analysis
3. Analysis of the possible changes in esophageal motility before and after lung transplantation using Mann-Whitney U statistical analysis
4. Summary of the outcome and to formulate conclusions in connection with lung transplantation at connective tissue diseases.

2. Introduction and analysis of study results

2.1 Introduction

Systemic connective tissue disorders are a heterogeneous group of disorders characterized by abnormal connective tissue morphology and/or connective tissue function. CTDs can affect multiple organs concurrently. Since the introduction of angiotensin-converting enzyme inhibitors, renal complications of CTDs have declined, and pulmonary complications are now the most common cause of morbidity and mortality [4]. These patients' conditions may worsen over time, and when they reach end-stage lung disease, they may be candidates for lung transplantation (LTx).

There are some special considerations for LTx candidates. Gastrointestinal issues, such as esophageal dysmotility and gastroesophageal reflux, are known risk factors of allograft rejection and donor lung dysfunction [10]. To better understand how esophageal dysmotility and gastroesophageal reflux affect LTx outcomes, we assessed pre-and posttransplant foregut function tests and short-term survival in patients who underwent LTx.

2.2 Materials

All patients who undergo LTx at our institution are entered into a prospectively maintained database. After Institutional Review Board approval, we queried that database to identify patients who underwent LTx between January 2012 and December 2017. Of these, patients diagnosed with the following CTDs and associated lung disease were included for this study:

A. Pulmonary involvement from Systemic sclerosis (SSc)

B. Pulmonary involvement (ILD and/or PAH) from non-SSc CTDs

1. Rheumatoid arthritis (RA)
2. Dermatomyositis (DM) and/or polymyositis (PM)
3. Sjögren syndrome (SS)
4. Systemic lupus erythematosus (SLE)
5. Mixed connective tissue disease (MCTD)
6. Unverified connective tissue disease (UCTD)

Patients who had undergone previous LTx (i.e. redo transplants) were excluded. Demographic and anthropometric data (age, sex, body mass index (BMI), LAS, as well as pre-and post-LTx foregut function test results (e.g., high-resolution manometry [HRM], ambulatory pH testing, barium esophagography) were collected and re-analyzed. Short-term (i.e., 1 and 3-year) survival data were also collected.

2.3 Methods

2.3.1 Posttransplant Protocol and Data Collection

Our institution followed the current guidelines and protocols fully [7]. In summary, all patients who underwent lung transplantation got the standardized immunosuppression regimen independent of the underlying esophageal motility. Induction therapy with methylprednisolone before the lung allograft perfusion in addition with interleukin-2 receptor antagonist (basiliximab) or anti-CD20 monoclonal antibody (rituximab), in combination with intravenous immunoglobulin. After the transplantation, sustaining immunosuppression therapy in a

combination of three agents was applied, including steroid treatment, mycophenolic mofetil, and tacrolimus. A dual gastrojejunal tube was placed at the time of LTx in patients diagnosed with severe esophageal dysmotility or aperistalsis. Per-os feeding was suspended at these patients until the first foregut testing. Early (ie, 3 months) posttransplant foregut function testing was repeated in all CTD patients. We conducted pulmonary function surveillance with spirometry every 2 to 3 weeks in the first 6 months posttransplant, and monthly thereafter for the first 2 years posttransplant. When a patient's general state was deteriorating, further pulmonary examinations were scheduled.

2.3.2 High-resolution Manometry and Esophageal Motility before and after lung transplantation.

High-resolution manometry studies were performed with a 36-channel catheter with solid-state pressure transducers. The raw data were re-analyzed and interpreted by a single author (MCS) using ManoView ESO software version 3.3 (Given Imaging Yok. Israel).

The esophagogastric junction was assessed using the following HRM parameters: lower esophageal sphincter (LES) pressure, integrated relaxation pressure (IRP), overall LES length, and abdominal LES length. Esophageal body motility was measured based on ten 5-mL swallows of water. Using the Chicago Classification 3.0 [11], we sorted patients into the following groups based on esophageal motility findings:

1. Absent esophageal motility (**AEM**): Normal median IRP (≤15 mmHg), 100% failed peristalsis (distal contractile integral [DCI] for all swallows: <100 mmHg·s·cm^2),
2. Ineffective esophageal motility (**IEM**): Normal median IRP, > 50% ineffective swallows (ineffective swallows can be failed or weak; DCI >450 mmHg·s·cm^2), or
3. Preserved esophageal motility (**PEM**) including:

a. Normal esophageal motility: Normal median IRP, not fulfilling any of the above criteria
b. Hypercontractile esophageal motility: Normal median IRP with at least 2 swallows with DCI >8000 mmHg·s·cm^2.

Poor-quality studies were excluded from further analysis. Studies were considered being of poor quality if the catheter was mispositioned, for example, no gastric area was visible, the patient did not tolerate the examination and the minimal amount of 10 swallow was not registered, or if the swallows were affected by coughing, etc.

2.3.3 24-Hour pH monitoring before and after lung transplantation

Dual-channel ambulatory esophageal pH monitoring was conducted at the time that the HRM study was performed. A DeMeester score greater than 14.72 and total acid exposure time >4.2% signified pathological reflux. We recorded the reflux episodes longer than 5 minutes, the number of proximal episodes, and the duration of the longest reflux episode.

2.3.4 Data consumption and statistical analysis

We recorded all data in a REDCap database created specifically for this study. I performed statistical analysis using SPSS version 22.0.0.0 (IBM SPSS Statistics). Demographic data were calculated as median and interquartile range (IQR). McNemar's test was used to compare categorical variables, and Wilcoxon signed-rank test was used to compare continuous variables between pre- and post-LTx outcomes. Survival analysis was performed using the Kaplan-Meier analysis and log-rank test. To better understanding of the effect of the

absent esophageal motility, we used a propensity score matching (1:4) between the AEM patients, and a matched representative non-CTD population.

2.4 Results

2.4.1 Demographic data, introduction of the cohort

A total of 495 patients underwent bilateral LTx at our institution during the study period. Of these, 33 (6.9%) had been diagnosed with a systemic CTD. The remaining 33 patients formed the cohort of our study. The median age at the time of transplant was 62 years (IQR, 55.5–67.0 years), 24 of 33 patients (72.7%) were women, and the median body mass index was 24.7 kg/m^2 (IQR, 20.9–30.2 kg/m^2). Specific information on type of CTD can be found in **table 1**.

Table 1. *Diagnoses of 33 patients with connective tissue disorders who underwent bilateral lung transplant at our institution between January 2012 and December 2017.*

Connective Tissue Disorder	n (%)
Pulmonary involvement from SSc	**14**
Pulmonary involvement (ILD or PAH) from non-SSc CTDs	**19**
Rheumatoid arthritis (ILD or PAH)	13/19 (68.4)
Dermatomyositis/polymyositis (ILD or PAH)	3/19 (15.8)
Systemic lupus erythematosus (ILD or PAH)	2/19 (10.5)
MCTD (ILD or PAH)	1/19 (5.3)

Abbreviations: SSc, systemic scleroderma; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; CTD, connective tissue disorder; MCTD, mixed connective tissue disease

We performed the foregut function tests at a median of 2 months (range, 1–6 months) pre-LTx. Intraoperatively, the median ischemic time was 258 minutes (IQR, 224.5–283.5

minutes). Two patients (1 with scleroderma [AEM group] and one with rheumatoid arthritis [PEM group]) developed bronchiolitis obliterans syndrome within 6 months of transplant.

2.4.2 Pulmonary function tests after transplantation

We detected acute rejections at 6 patients (4 patients in the PEM group, 2 patients in the IEM group). Bronchiolitis obliterans syndrome (BOS) was detected at 2 patients in the 6 months post-LTx period (1 patient in the AEM group with SSc, and 1 patient in the PEM group presented with RA).

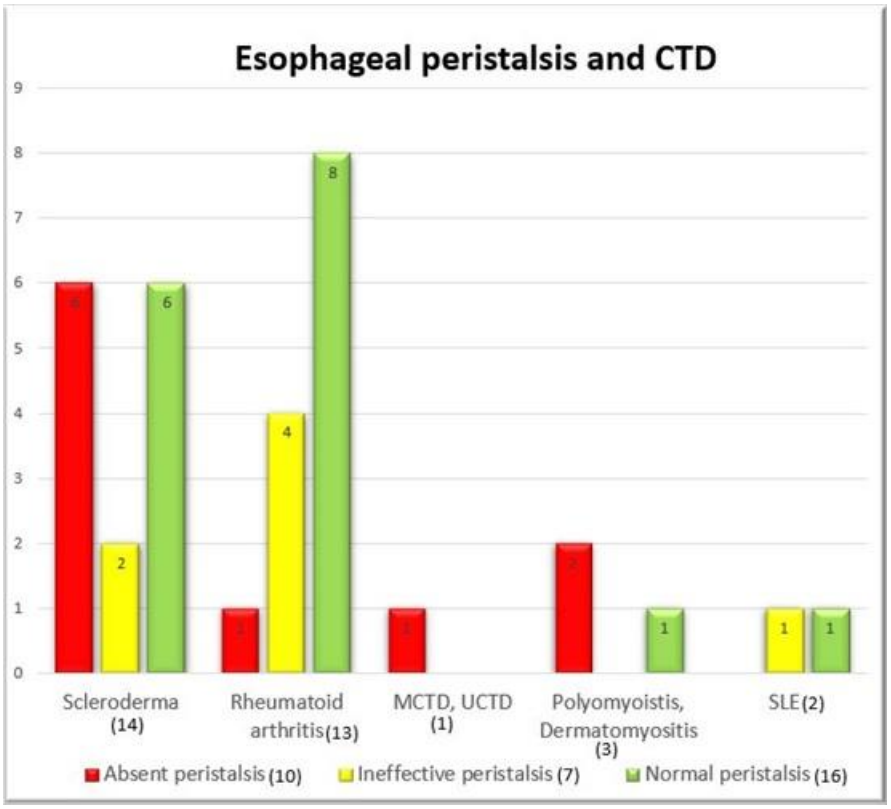
2.4.3. Lung allocation score (LAS)

The median LAS at the CTD group was 39.89 (38.0-49.5). Similar scores were noted in the PEM group 38.7 (37.1-45.9), and in the IEM group 38.7 (36.5-44.1), but the AEM group presented with a higher median score 43.9 (39.6-52.3). The difference between the groups was non-significant (p=0.63).

2.4.4 Changes of esophageal motility before and after transplantation

Pre-LTx motility data are visible at **figure 1.**

Figure 1. *Pre-transplant esophageal motility of connective tissue disease patients*



Source: Csucska M, Razia D, Masuda T, Omar A, Giulini L, Smith MA, Walia R, Bremner RM, Mittal SK. Bilateral Lung Transplant for a Connective Tissue Disorder: Esophageal Motility and 3-year Survival. Semin Thorac Cardiovasc Surg. 2021 Jun 15: S1043-0679(21)00285-9.

All 33 patients in this study underwent HRM pre-LTx. Overall, 10 patients (30.3%) presented with absent esophageal motility and formed the AEM group, 7 patients (21.2%) presented with ineffective esophageal motility and formed the IEM group, and 16 patients (48.5%) presented with preserved peristalsis and formed the PEM group. One patient in the PEM group met the manometric criteria for type III achalasia (ie, IRP exceeded 15 mmHg), but the patient underwent timed barium esophagography and esophagogastroduodenoscopy, neither of which showed any sign of LES dysfunction or delayed esophageal emptying. We therefore included this patient in the PEM group.

Post-transplant HRM studies were available in 29 of patients (87.9%). In the AEM group, 8 of 10 patients (80%) underwent post-LTx HRM. All 8 patients (100%) had persistent aperistalsis after lung transplantation. In the IEM group, 6 of 7 patients (85.7%) underwent

post-LTx HRM. Of these, 5 of 6 (83.3%) demonstrated recovery of normal peristaltic vigor, whereas 1 in 6 patients (16.7%) had persistent ineffective motility. In the PEM group, 15 of 16 (93.8%) underwent post-LTx HRM. Of these 15 patients, 1 (6.7%) had a decline in peristaltic vigor (ie, ineffective), but 14 of 15 patients (93.3%) had normal esophageal motility. None of the patients in either the PEM or the IEM group showed absent peristalsis post-LTx.

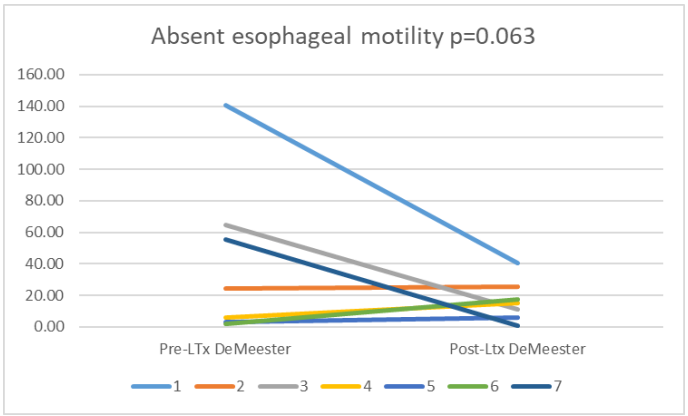
2.4.5 Lower esophageal sphincter function

Of the 33 patients in this study, 10 (30.3%) had a manometric hiatal hernia pre-LTx, and 6 of 29 patients (20.7%) had hiatal hernia post-LTx (p=0.05). No significant changes were noted in pre- and post-LTx measurements of median LES pressure (24.6 vs 28 mmHg; p=0.18) or abdominal LES length (2.5 vs 2.2 cm; p=0.7).

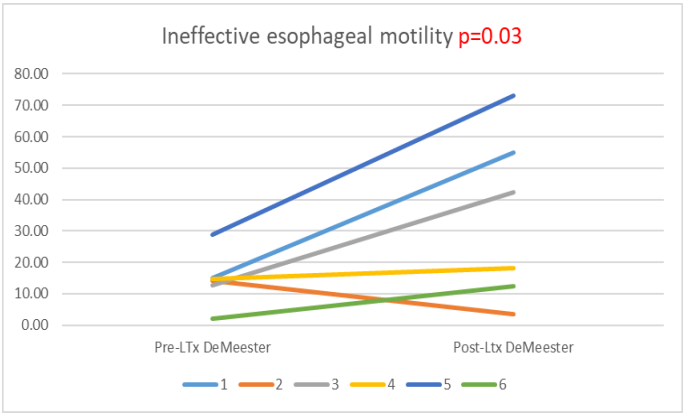
2.4.6 24-hour ambulatory-pH studies

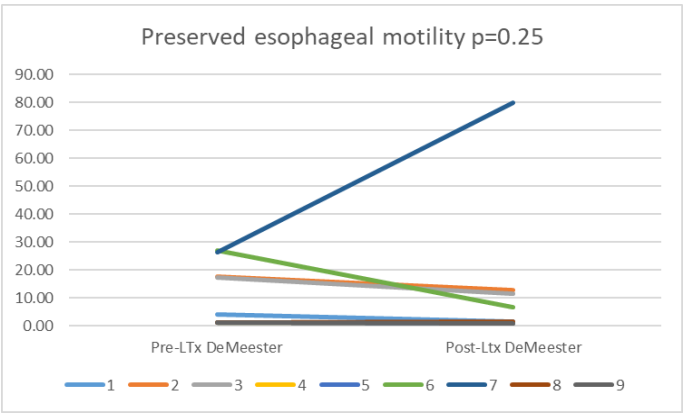
Of the 33 patients diagnosed with a systemic CTD-associated pulmonary disease, 30 (90.9%) had an available pre-transplant pH study, and 27 (81.8%) had an available post-transplant pH study. Fourteen of 30 patients (46.7%) had an abnormal DeMeester score pre-LTx, and 13 of

Figure 2. *Correlation of eosphageal motility and DeMeester score in context of lung transplantation*



27 patients (48.1%) had an abnormal DeMeester score post-LTx. Differences among motility groups were noted during the pre-LTx pH testing. The median proximal acid exposure episodes were 4 (IQR, 0–7) in the AEM group, 1 (IQR, 0–7) in the IEM group, and 0 (IQR, 0–1) in the PEM group. The median DeMeester score pre-LTx was 30.7 (IQR, 5.1–74.4) in the AEM group, 14.2 (IQR, 4.6–15.0) in the IEM group, and 6.4 (IQR, 1.3–18.6) in the PEM group; however, these differences were non-significant (p=0.16).





Twenty-two of the 33 patients (66.7%) in the study had both pre- and posttransplant pH studies available. **Figure 2.** shows the changes in DeMeester scores for each group. Patients in the PEM and AEM groups showed no-significant changes in the incidence of pathological reflux posttransplant (p=0.06 and p=0.25, respectively). Patients in the IEM group, however, showed a significant increase in DeMeester score (p=0.03) posttransplant.

2.4.7 Gastroduodenoscopy

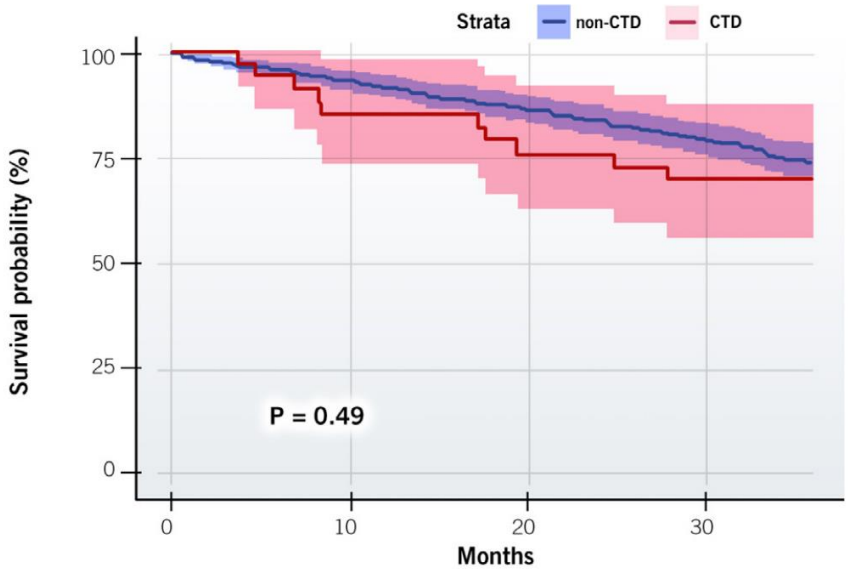
We performed an upper-endoscopic examination at all patients before lung transplantation. Endoscopic hiatal hernia (type I, over 2 cm) presented at 1 out of 16 patients (6.25%) at the PEM group, 1 out of 7 patients (14.3%) at the IEM, and 3 out of 10 patients (30%) at the AEM group. Barrett esophagus was also an uncommon finding: in the AEM group 1 out of 10 patients (10%), in the PEM group 3 out of 16 patients (18.75%) had a positive

endoscopic finding. 2 patients presented with Los Angeles Grade A esophagitis; we did not find more severe esophageal inflammation in our cohort.

2.4.8. Survival data

Kaplan-Meier analysis showed the overall 1-year survival of LTx recipients during the study period was 451 of 495 patients (91.1%). Patients without CTD showed an overall survival of 91.8% (424/462 patients) and 73.4% (339/462) after 1 and 3 years, respectively. In the CTD group, in the same intervals, the survival was 81.8% (27/33 patients) and 66.7% (22/33 patients). The mean survival was 67.7 months in the CTD and 60.3 months in the non-CTD group. Both the 1-year and 3-year data were both worse in the CTD group, the difference was non-significant (p=0.2 and p=0.5) **figure 3**.

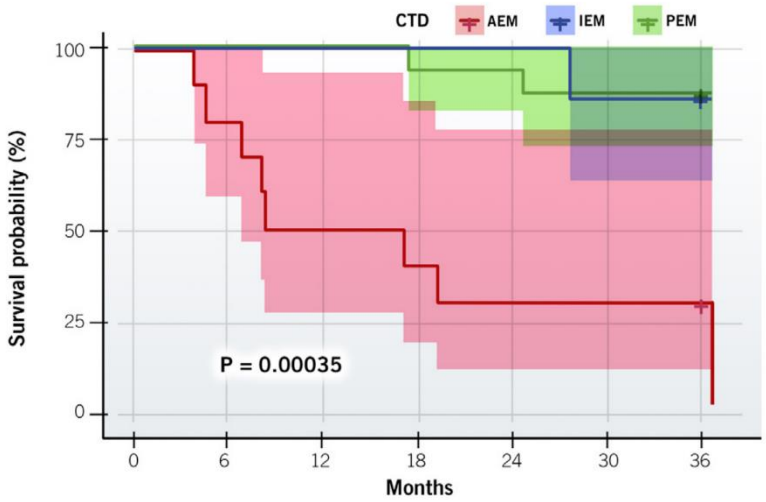
Figure 3: *Kaplan-Meier analysis of survival after bilateral lung transplantation in patients with or without a connective tissue disorder (CTD)*



Source: Csucska M, Razia D, Masuda T, Omar A, Giulini L, Smith MA, Walia R, Bremner RM, Mittal SK. Bilateral Lung Transplant for a Connective Tissue Disorder: Esophageal Motility and 3-year Survival. Semin Thorac Cardiovasc Surg. 2021 Jun 15 :S1043-0679(21)00285-9.

Patients with CTDs and pre-LTx PEM or IEM had a 1-year survival of 94.7% (15/16 patients) and 100% (7/7 patients), respectively, which is similar to the 1-year survival of the non-CTD group. Patients with AEM had a 1-year survival rate of 50% (5/10). The difference in survival in the groups was significant (p=0.001; **figure 4**). The 3-year survival in the PEM group was 87.5% (14/16), in the IEM group 85.7% (6/7), in the AEM group was significantly worse, only 20% (2/10), p<0.001. The overall mean survival was also significantly lower in the AEM group (21.7 months) than in the PEM (68.5 months) and in the IEM group (83.1 months), p<0.001 **figure 4**.

Figure 4. *Kaplan-Meier analysis of survival after bilateral lung transplantation in patients with a connective tissue disorder (CTD) grouped by pretransplant esophageal motility*



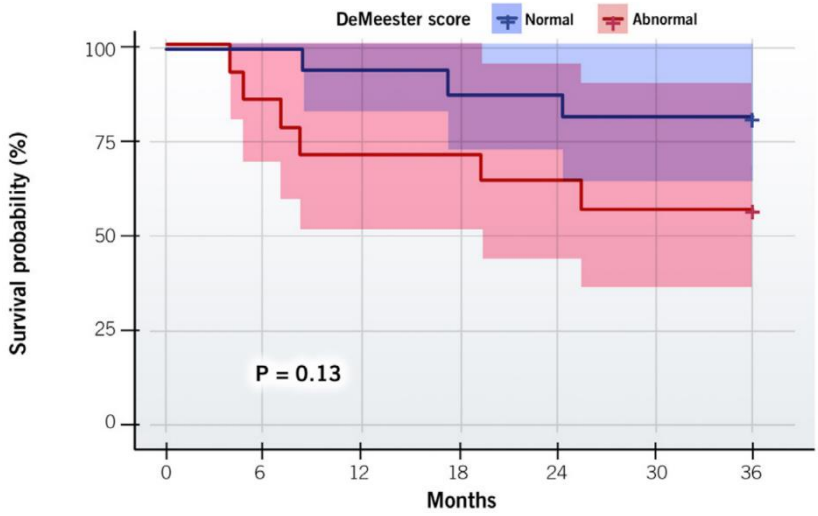
Source: Csucska M, Razia D, Masuda T, Omar A, Giulini L, Smith MA, Walia R, Bremner RM, Mittal SK. Bilateral Lung Transplant for a Connective Tissue Disorder: Esophageal Motility and 3-year Survival. Semin Thorac Cardiovasc Surg. 2021 Jun 15:S1043-0679(21)00285-9.

The most common cause of death in the AEM group was chronic allograft dysfunction (n=4), in 1 case we could not obtain any information (1 patient died at home). An additional 2 patients died because of antibody mediated reaction, and 1 patient died because of aortic dissection. In the PEM group the cause of death was malignant metastatic tumor (n=1), and unknown cause (n=1). In the IEM group, 1 patient deceased due to ischemic stroke (n=1). The

chronic allograft dysfunction free survival was significantly lower in the AEM group than in the PEM and IEM groups (40% vs. 56.3% and 71.3% p=0.013) respectively.

In connection of the gastroesophageal reflux disease, patients with the pre-LTx abnormal DeMeester score the 1-year survival was 71.4% (10/14 patients), 3-year survival was 57.1% (8/14 patients), which is inferior to the patients with normal DeMeester score (87.5% 1-year, and 81.3% 3-year survival), but the difference was non-significant (p=0.09, p=0.13) **figure 5**.

Figure 5. *Kaplan-Meier analysis of survival after bilateral lung transplantation in patients with a connective tissue disorder grouped by pretransplant DeMeester score*



Source: Csucska M, Razia D, Masuda T, Omar A, Giulini L, Smith MA, Walia R, Bremner RM, Mittal SK. Bilateral Lung Transplant for a Connective Tissue Disorder: Esophageal Motility and 3-year Survival. Semin Thorac Cardiovasc Surg. 2021 Jun 15:S1043-0679(21)00285-9.

We investigated the survival in the context of the lung allocation score. We used a propensity score matching method (1:4) pairing the pre-transplant AEM group, to a matched CTD cohort of patients. There was no difference based on the LAS score between the two groups (p=0.999) **table 2**.

The survival of the recipients of lung transplantation in the CTD group with AEM was significantly lower in both 1- and 3-year intervals than the matched CTD group (CTD-AEM:

50% and 20%, non-CTD 92.5% and 65%, p=0.001 and 0=0.012). The average survival in the CTD with AEM was 21.7 months, in the paired CTD group it was 67.9 months.

Table 2. *Baseline characteristics in the subgroups of propensity score matching*

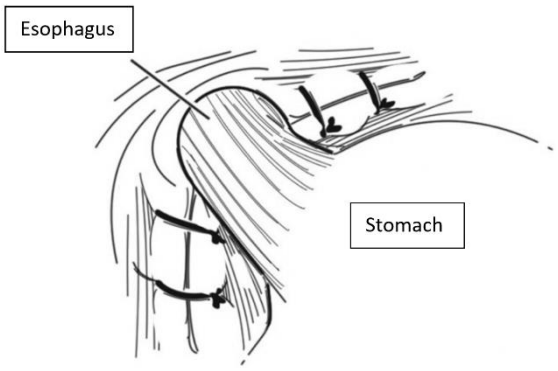
Variables	**Subgroups**		**Standardized mean difference**	**p value**
	CTD and AEM	Non-CTD		
LAS	43.5 ± 6.1	43.5 ± 6.1	0.00055	0.999

Abbreviations; CTD, connective tissue disease; AEM, absent esophageal motility; LAS, lung allocation score

2.4.9 Anti-reflux surgeries in our cohort

We performed anti-reflux surgeries in the CTD group at 4/33 (12%) patients in the post-transplant 3 months interval. 2/16 (12.5%) in the PEM group underwent Toupet fundoplication, 2 (20%) patients in the AEM group received a laparoscopic Roux-Y bypass surgery. We reconstructed the esophageal opening at all cases with sutures both among the transverse and the antero-posterior diameter of the hiatal defect (**figure 6.**). In the short (30 days) postoperative period we did not register any surgical complication.

Figure 6. *Schematic representation of the modified hiatal hernia repair*



Source: *Csucska M, Sumeet K M, Kovács B, Kremzer T, Ozorai L, Lóderer Z, Juhász Á. Tapasztalataink a rekeszsérvek laparoszkópos sebészetével [Our experience with the laparoscopic surgery of hiatal hernias]. Orv Hetil. 2021 May 9;162(19):754-759.*

3. Discussion, conclusion

Patients diagnosed with connective tissue disease experience dysfunction of multiple organ systems, including the pulmonary and gastrointestinal systems. Progressive decline in lung function can be an indication of lung transplantation in CTD patients. The recommendations of the International Heart and Lung Transplant Society emphasize that the concurring gastrointestinal complications can significantly decrease the post-transplant survival. In my study, I am presenting our short-term survival results after lung transplantation, particularly in connection with the esophageal motility disorders and gastroesophageal reflux disease.

In recent years, our institution was the busiest center according to lung transplantation, as the percentage of CTD patients underwent lung transplantation is higher than the national average (0.7% vs. 6.7%). Although the small sample size is a limitation of our study, we can safely assume that a study in a similar cohort size from a single-center is rare in the literature at the construct of this study.

In 1964, Stevens et a.l [12] and later in 2007, Gasper et al. [13] showed that esophageal dysmotility is common among LTx recipients with a CTD—both with scleroderma and non-scleroderma. Lock et al in 1998 [14] reported a significant association between esophageal dysmotility and reduced lung volume in patients diagnosed with SSc.

Masuda et al. [15] reported that esophageal dysmotility is frequent in patients undergoing LTx, though the severity differed between patients with obstructive and restrictive lung disease. In their study, an improvement in peristalsis was noted in most of patients after LTx, and they attributed this to restoration of pulmonary physiology.

Based on our result we can claim that ineffective esophageal motility can improve after lung transplantation at CTD patients. However, in the absent esophageal motility group no

recovery of peristaltic vigor was noted. We suspect that, in certain patients diagnosed with CTDs, esophageal motility can be affected not only by the underlying pathophysiology of end-stage lung disease, but also by the CTD itself. In these patients the underlying effect on esophageal motility due to the CTD is predominant and is not reversed when pulmonary physiology is restored post-LTx. CTD patients with ineffective motility, the noted decline in motility is because of the pulmonary dysfunction rather than a direct effect of the CTD on the esophagus, and can improve, as we noted.

Improvement of esophageal motility is important, especially if GERD is present post-LTx. Young et al. [16] reported that the incidence of pathological gastroesophageal reflux was higher after LTx than before LTx. Similarly, in this study, we found slight increase in the prevalence of GERD (from 46% to 48%). The high pre-LTx prevalence of GERD in our cohort (46.7%) is similar to the numbers reported in other studies.

Khan et al. [17] reported that the 1-year posttransplant survival in these patients varied between 59% and 93.4% at different LTx centers. Pradére et al. [6] also showed that scleroderma patients show comparable survival post-LTx to lung transplantation of another cause at European cohort. In our experience, however, patients with a CTD had lower short-term survival than other LTx recipients (1-year: 81.8% vs 91.8%, 3-year: 73.4% vs. 66.7%), the difference was non-significant $p=0.2$, $p=0.5$. However, when we further sub-categorized patients with a CTD based on esophageal dysmotility, it became apparent that patients with a CTD who have normal or ineffective esophageal motility pre-LTx have excellent survival (at 1-year 94.7% and 100%, at 3-year 87.5% and 85.7% $p<0.001$ respectively). However, the survival is poor in patients with absent esophageal motility (1-year 50.0%, 3-year 20%, $p<0.001$). Including a sizeable number of patients with aperistalsis in our cohort most likely explains the difference in survival compared with other series of LTx recipients diagnosed with CTDs.

Finally, I would like to mention the therapeutic options of esophageal motility disorders and gastroesophageal reflux disease, especially in the lights of the observation that the frequency of these disorders will likely rise after lung transplantation. Medical management and early anti-reflux surgeries can positively influence the FEV-1 decline and expected survival as well [18]. It should be highlighted, that although the early anti-reflux procedure is currently the gold standard in treating GERD, after the surgery the occasional recurrence is a documented phenomenon [19]. It is a challenge also, that laparoscopic fundoplication is not recommended at the absent esophageal motility patients with CTD, because of the frequent dysphagia after surgery [19]. At these patients, laparoscopic Roux-y bypass can be a viable surgical option, but it could be more stressful to the patients. In our opinion, besides the adequate patient selection, a modified surgical technique could be the answer to that problem.

Hiatal reconstruction is a crucial part of every anti-reflux procedure. In our institution, we introduced a modified reconstruction of the hiatal defect, in which we routinely used additional stitches at 2-3 o'clock orientation, in addition to the traditional anteroposterior closure [20]. The inspiration behind this modification is the documented observation, that the recurrence is most commonly developing at this anatomical week point [21]. Hopefully, this slight alteration could reduce the number of recurrences, can produce better long-term results. At the time of constructing this study, we don't have any follow-up results available, the validity of this method is still questionable. Because of the low number of surgeries, I could not make a statistical comparison between patients who underwent antireflux procedures and those who did not. My further goal is to prove the advantages of this surgical procedure over the more traditional approaches.

This study has limitations. Most importantly, it was a retrospective single-center cohort study. This limitation could be overcome with a multicenter study. In addition, the small sample size of the subgroups did not allow further statistical tests to show a more comprehensive set

of data. Finally, as we focused mainly on the survival data, the details of rehabilitation, length of stay, readmission, etc. were not collected in this study.

In conclusion, CTDs are not necessarily contraindications of LTx, patients who have both a CTD and pre-LTx esophageal aperistalsis were found to have significantly worse short-term survival compared with patients with ineffective or normal esophageal motility. Esophageal motility improved or remained normal after LTx in recipients with normal or ineffective preoperative esophageal motility, whereas no patient with absent esophageal motility showed an increase in contractile vigor. This suggests that pre-LTx esophageal aperistalsis may have an even more prominent impact on the overall survival of patients with a CTD, and CTDs must therefore be taken into serious consideration at the time of LTx selection. A multicenter cohort of LTx recipients with a CTD and complete preoperative esophageal evaluations should be analyzed to validate our results.

4. New statements of the dissertation

- In our study group, pre-transplant ineffective esophageal motility and preserved esophageal motility improves, or remains normal in almost all cases after lung transplantation.
- In opposition to that, aperistaltic esophageal vigor does not show any improvement after lung transplantation, the absent esophageal motility remains unchanged.
- In our institution, short-term survival of CTD patients is significantly lower than patients transplanted due to other cause
- Short-term post-transplant survival of patients with absent esophageal motility is significantly lower than patients with ineffective or preserved esophageal motility
- Short-term post-transplant survival of patients with gastroesophageal reflux disease is lower than patients without this pathological state but the difference is non-significant.

5. Bibliography

[1] Valapour M., Lehr C, Skeans M et al.: OPTN/SRTR 2017 Annual Data Report: Lung. *American Journal of Transplantation* 19 (2019) 404–84.

[2] Valapour M., Lehr C, Skeans M et al.: OPTN/SRTR 2018 Annual Data Report: Lung. *American Journal of Transplantation* 20 (2020) 427-508.

[3] Egan T, Murray R, Bustami T et al.: Development of the New Lung Allocation System in the United States. *American Journal of Transplantation* 5 (2006) 1212–27.

[4] Carmen-Pilar S, Armadans L, Fonollosa V et al.: Survival Prognostic Factors and Markers of Morbidity in Spanish Patients with Systemic Sclerosis. *Annals of the Rheumatic Diseases* 56, 12 (1997) 723–28.

[5] Miele C, Schwab K, Saggar R et al.: Lung Transplant Outcomes in Systemic Sclerosis with Significant Esophageal Dysfunction. A Comprehensive Single-Center Experience. *Annals of the American Thoracic Society* 13, 6 (2016) 793-802.

[6] Pradère P, Tudorache I, Magnusson J et al.: Lung Transplantation for Scleroderma Lung Disease: An International, Multicenter, Observational Cohort Study. *The Journal of Heart and Lung Transplantation* 37, 7 (2018) 903–11.

[7] Weill D, Benden C, Corris P et al.: A Consensus Document for the Selection of Lung Transplant Candidates: 2014—An Update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. *The Journal of Heart and Lung Transplantation* 34, 1 (2015) 1–15.

[8] Panchabhai T, Abdelrazek H, Bremner R: Lung Transplant in Patients with Connective Tissue Diseases. *Clinics in Chest Medicine* 40, 3 (2019) 637–54.

[9] King B, Iyer H, Leidi A et al.: Gastroesophageal Reflux in Bronchiolitis Obliterans Syndrome: A New Perspective. *The Journal of Heart and Lung Transplantation* 28, 9 (2009) 870–75.

[10] Lee J., Collard H, Raghu G et al. Does Chronic Microaspiration Cause Idiopathic Pulmonary Fibrosis? *The American Journal of Medicine* 123, 4 (2010) 304–11.

[11] Kahrilas P, Bredenoord J, Fox M et al.: The Chicago Classification of Esophageal Motility Disorders, v3.0. *Neurogastroenterology & Motility* 27, 2 (2015) 160–74.

[12] Stevens M, Hookman P, Siegel C et al.: Aperistalsis of the Esophagus in Patients with Connective-Tissue Disorders and Raynaud's Phenomenon. *New England Journal of Medicine*, 270 (1964) 1218-22.

[13] Gasper W, Sweet M, Golden J et al.: Lung Transplantation in Patients with Connective Tissue Disorders and Esophageal Dysmotility. *Diseases of the Esophagus* 21, 7 (2008) 650–55.

[14] Lock G, Straub R, Zeuner M et al.: Association of Esophageal Dysfunction and Pulmonary Function Impairment in Systemic Sclerosis. *The American Journal of Gastroenterology* 93, 3 (1998) 341–45.

[15] Masuda T, Mittal S, Csucska M et al.: Esophageal Aperistalsis and Lung Transplant: Recovery of Peristalsis after Transplant Is Associated with Improved Long-Term Outcomes'. *The Journal of Thoracic and Cardiovascular Surgery* 160, 6 (2020)1613–26.

[16] Young L, Hadjiliadis D, Duane Davis R et al.: Lung Transplantation Exacerbates Gastroesophageal Reflux Disease. *CHEST* 124, 5 (2003) 1689–93.

[17] Khan I, Singer L, Perrot M et al.: Survival after Lung Transplantation in Systemic Sclerosis. A Systematic Review. *Respiratory Medicine* 107, 12 (2013) 2081–87.

[18] Davidson JR, Franklin D, Kumar S, et al.: Fundoplication to preserve allograft function after lung transplant: Systematic review and meta-analysis. *J Thorac Cardiovasc Surg*. 160 (3) (2018) 858-866.

[19] Bakhos CT, Petrov RV, Parkman HP, Malik Z, Abbas AE. Role and safety of fundoplication in esophageal disease and dysmotility syndromes. *J Thorac Dis*. 2019;11(Suppl 12):S1610-S1617. doi:10.21037/jtd.2019.06.62

[20] Csucska M, Sumeet K M, Kovács B, et al.: Tapasztalataink a rekeszsérvek laparoszkópos sebészetével [Our experience with the laparoscopic surgery of hiatal hernias]. *Orv Hetil.* 162(19) (2021) 754-759.

[21] Suppiah AP, Sirimanna S, Vivian J, et al. Temporal patterns of hiatus hernia recurrence and hiatal failure: quality of life and recurrence after revision surgery. *Dis Esophagus* 2017; 30: 1–8.

6. Publications in connection with this manuscript

6.1 First author publications

- **Csucska M**, Masuda T, Bremner RM, Mittal SK. Esophagogastric Junction Outflow Obstruction: Are We Missing Anything? [published online ahead of print, 2020 Apr 14]. *J Clin Gastroenterol*.
- **Csucska M**, Masuda T, Bremner RM, Mittal SK. Clinical Symptom Presentation of Hypercontractile Peristalsis in the Era of High-Resolution Manometry: A Single-Center Experience *Dig Dis*. 2020;1-9.
- **Csucska M**, Kovács B, Masuda T, Razia D, Bremner RM, Mittal SK. Progression of Hiatal Hernias. *J Gastrointest Surg*. 2020 Sep 28.
- **Csucska M**, Mittal SK, Kovács B, Kremzer T, Ozorai L, Lóderer Z, Juhász Á. Tapasztalataink a rekeszsérvek laparoszkópos sebészetével. Orvosi hetilap 2021. Accepted publication ahead of print

- **Csucska M**, Razia D, Masuda T, Omar A, Giulini L, Smith MA, Walia R, Bremner RM, Mittal SK. Bilateral Lung Transplant for a Connective Tissue Disorder: Esophageal Motility and 3-year Survival. Semin Thorac Cardiovasc Surg. 2021 Jun 15: S1043-0679(21)00285-9.

6.2 Co-author publications

- Masuda T, Kovacs B, **Csucska M**, Bremner RM, Mittal SK. Pathological Implications of Swallow-Associated Transient Lower Esophageal Sphincter Elevation [published online ahead of print, 2019 Dec 2]. *J Gastrointest Surg*. 2019;10.1007/s11605-019-04452-1.
- Masuda T, Mittal SK, Kovacs B, **Csucska M**, Bremner RM. Simple Manometric Index for Comprehensive Esophagogastric Junction Barrier Competency Against Gastroesophageal Reflux. *J Am Coll Surg*. 2020;230(5):744-755.e3.
- Masuda T, Mittal SK, **Csucska M**, et al. Esophageal aperistalsis and lung transplant: Recovery of peristalsis after transplant is associated with improved long-term outcomes [published online ahead of print, 2020 Feb 19]. *J Thorac Cardiovasc Surg*. 2020; S0022-5223(20)30452-9.
- Kovács B, Orosz M, **Csucska M**, Singhal S, Juhász Á, Lóderer Z. Autologous Dermis Graft Implantation: A Novel Approach to Reinforcement in Giant Hiatal Hernias. *Case Rep Surg*. 2018; 2018:9069430. Published 2018 May 8.
- Giulini L, Mittal S, Masuda T, Razia D, **Csucska M**, Walia R, Smith M, Bremner R, Factors associated with Esophageal Motility Improvement After

Bilateral Lung Transplant in Patients with an Aperistaltic Esophagus. *J Thorac Cardiovasc Surg*. 2021, January 09.

Cummulative impact faktor: 25.6

First-author impact faktor: 10.98

7. Acknowledgements

I would like to thank to

- **Árpád Juhász MD,** who showed me the interesting opportunities in the field of esophageal surgery. I would like to thank him all the valuable practical and theoretical advice which were essential to make this dissertation,
- **Professor Sumeet K. Mittal MD**, for showing exceptional support during my one-year fellowship in the United States,
- **Professor Ross M. Bremner MD** and the whole **Norton Thoracic Institute**, for accepting me as a co-worker, for supporting my research ideas at every level, and for expanding the framework of this dissertation with constructive criticism,
- **Zoltán Lóderer MD, László Jáger MD**, for giving me opportunities to perform esophageal motility studies and let me take an active role in anti-reflux surgeries in their department
- **Professor Béla Márkus MD**, for improving the quality of this manuscript with critical notions,
- **All my Hungarian and American co-workers**, for showing active and helpful support during the examinations.