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WORD COUNT 3258
TIME SUBMITTED 18-APR-2023 03:50PM
PAPER ID 98836639

Name of Journal: *World Journal of Gastroenterology*

Manuscript NO: 82319

Manuscript Type: ORIGINAL ARTICLE

Retrospective Cohort Study

Ineffective Esophageal Motility is Associated with Acute Rejection After Lung Transplantation Independent of Gastroesophageal Reflux

Esophageal Hypomotility Predicts Lung Transplant Rejection

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Abstract

BACKGROUND

Gastroesophageal reflux (GER) is associated with poorer outcomes after lung transplant, likely through recurrent aspiration and allograft injury. Although prior studies have demonstrated a relationship between impedance-pH results and transplant outcomes, the role of esophageal manometry in the assessment of lung transplant patients remains debated, and the impact of esophageal dysmotility on transplant outcomes is unclear. Of particular interest is ineffective esophageal motility (IEM) and its associated impact on esophageal clearance.

AIM

To assess the relationship between pre-transplant IEM diagnosis and acute rejection after lung transplantation.

METHODS

This was a retrospective cohort study of lung transplant recipients at a tertiary care center between 2007 and 2018. Patients with pre-transplant anti-reflux surgery were excluded. Manometric and reflux diagnoses were recorded from pre-transplant esophageal function testing. Time-to-event analysis using Cox proportional hazards model was applied to evaluate outcome of first episode of acute cellular rejection, defined histologically per ISHLT guidelines. Subjects not meeting this endpoint were censored at time of post-transplant anti-reflux surgery, last clinic visit, or death. Fisher's exact test for binary variables and student's t-test for continuous variables were performed to assess for differences between groups.

RESULTS

184 subjects (54% men, mean age: 58, follow-up: 443 person-years) met criteria for inclusion. Interstitial pulmonary fibrosis represented the predominant pulmonary diagnosis (41%). During the follow-up period, 60 subjects (33.5%) developed acute

rejection. The all-cause mortality was 16.3%. Time-to-event univariate analyses demonstrated significant association between IEM and acute rejection (HR 1.984, 95%CI 1.03-3.30, P = 0.04), confirmed on Kaplan-Meier curve. On multivariable analysis, IEM remained independently associated with acute rejection, even after controlling for potential confounders such as the presence of acid and nonacid reflux (HR 2.20, 95%CI 1.18-4.11, P = 0.01). Nonacid reflux was also independently associated with acute rejection on both univariate (HR 2.16, 95%CI 1.26-3.72, P = 0.005) and multivariable analyses (HR 2.10, 95%CI 1.21-3.64, P = 0.009), adjusting for the presence of IEM.

CONCLUSION

Pre-transplant IEM was associated with acute rejection after transplantation, even after controlling for acid and nonacid reflux. Esophageal motility testing may be considered in lung transplant to predict outcomes.

Key Words: Ineffective esophageal motility; Esophageal hypomotility; Esophageal manometry; Gastroesophageal reflux disease; Lung transplantation; Acute rejection

Lo WK, Hiramoto B, Goldberg HJ, Sharma N, Chan WW. Ineffective Esophageal Motility is Associated with Acute Rejection After Lung Transplantation Independent of Gastroesophageal Reflux. *World J Gastroenterol* 2023; In press

Core Tip: While gastroesophageal reflux (GER) has been associated with poorer outcomes after lung transplant, the impact of esophageal dysmotility remains unclear. Our study found that ineffective esophageal motility (IEM) identified on pre-transplant esophageal manometry was independently associated with increased acute allograft rejection, even after adjusting for GER. This suggests that esophageal hypomotility may increase the risk of poor lung transplant outcome independent of GER. Routine esophageal function assessment should be considered in the peri-transplant evaluation

of lung transplant patients to identify, risk stratify, and more effectively manage esophageal dysfunction in such patients at risk of poorer outcomes.

INTRODUCTION

Lung transplantation survival remains the lowest among solid organ transplants despite small gains over the past decade. Current 5-year survival rates are estimated at 59.2%[1]. Gastroesophageal reflux disease (GERD) and esophageal dysmotility are commonly found in patients undergoing lung transplant evaluation and have been associated with worsened transplant outcomes. For example, GERD has been implicated in the development of acute rejection and chronic lung allograft dysfunction (CLAD). Acute rejection is an early risk factor for CLAD, an important mediator of mortality after the first year post-transplant[2,3]. While esophageal dysmotility may be associated with worsened severity of GERD due to aberrant peristaltic clearance of refluxed gastroduodenal contents, less is known regarding its independent effects on lung transplant outcomes[4-6].

Acute lung rejection is common within the first year post-transplant with rates as high as >50%[7]. Prior work from our group demonstrated an association between pre-transplant impedance measures of reflux and early allograft injury post-transplant as well as early hospital readmission[8,9]. These measures included prolonged bolus clearance, and increased total proximal and distal reflux episodes[10]. Studies in humans and mouse models have demonstrated that markers of refluxate such as pepsin and bile acids are also associated with allograft dysfunction, and result in impaired innate immune responses[11-14].

Despite the established connection between esophageal motility and reflux clearance, few studies have analyzed transplant outcomes in patients with esophageal dysmotility. Notably, the International Society of Heart and Lung Transplantation (ISHLT) guidelines consider severe esophageal dysmotility to be a risk factor associated with a substantially increased risk of a poor outcome[15]. A few single center studies to date have demonstrated disorders of esophageal motility impacting lung transplant

outcomes like CLAD in esophagogastric junction outflow obstruction (EGJOO), as well as 1-, 3-, and 5- year survival in the more severe phenotype of esophageal aperistalsis[16,17]. Thus far, limited data has impeded our understanding of less severe phenotypes of impaired peristalsis on lung transplant outcomes. The goal of our study is to determine the impact of pre-transplant esophageal dysmotility on lung transplant outcomes of acute rejection, specifically subjects with weak or impaired, but not fully absent, contractility, characterized as ineffective esophageal motility (IEM). We hypothesized that measures of esophageal dysmotility such as IEM are associated with increased rates of acute rejection in lung transplant patients.

MATERIALS AND METHODS

This was a retrospective cohort study of adult patients age >18 who underwent lung transplantation between 2007 and 2018 at a tertiary care referral center. Patients with pre-transplant high-resolution manometry (HRM) and multichannel intraluminal impedance and pH (MII-pH) testing were included, and patients with a history of pre-transplant antireflux surgery were excluded. Study subjects meeting inclusion and exclusion criteria were reviewed for collection of baseline characteristics and outcomes data.

Baseline demographics included age at time of transplantation, sex, body mass index (BMI), primary pulmonary diagnosis, and pre-transplant cardiac ejection fraction. Covariates of interest included ineffective esophageal motility (IEM) on HRM, and presence of acid reflux and non-acid reflux on MII-pH study. The primary outcome of interest was development of first episode of acute cellular rejection. This was defined by clinical and histologic criteria per ISHLT guidelines[18]. Other measured outcomes included all-cause mortality during the study period, use of proton pump inhibitor (PPI) medication post-transplant, and development of pulmonary infection.

Pre-transplant HRM:

All patients included in the study underwent HRM (Diversatek Healthcare, Milwaukee, WI, USA) prior to transplant. This system utilized a solid-state catheter with 32 circumferential pressure sensors spaced 1 cm apart. Transnasal catheter placement was performed with distal sensor placement directed into the proximal stomach, ensuring that the catheter is properly positioned across the lower esophageal sphincter (LES). After a brief accommodation period, patients were asked to perform ten 5-mL liquid swallows in the supine position. Results were analyzed utilizing a dedicated software package (BioView 5.6.3.0; Diversatek Healthcare, Milwaukee, WI, USA). IEM was defined by ≥50% weak or failed swallows using Chicago Classification v3.0 criteria[19]. Presence of IEM was classified as a dichotomous variable for data analysis.

Pre-transplant MII-pH Monitoring:

All patients included in the study also MII-pH monitoring (Diversatek Healthcare, Milwaukee, WI, USA) off PPI prior to transplant. This system includes a portable data collection device, as well as the MII-pH catheter with two pH sensors (0, 15 cm) and eight impedance electrodes (-3, -1, 1, 3, 5, 9, 11, 13 cm). Transnasal catheter placement was performed and positioned with the distal pH sensor localized to 5 cm above the LES. Patients were asked to continue their normal daily activities during the 24-hour study and to record meal periods, which were excluded from the analysis. MII-pH tracings were manually reviewed and analyzed utilizing a dedicated software package (BioView 5.6.3.0; Diversatek Healthcare, Milwaukee, WI, USA). Increased acid reflux was defined by acid exposure time (AET) >4%, while increased non-acid reflux was defined as >27 weakly acidic or alkaline (pH>4) episodes per prior publications[20].

Post-transplant Management and Diagnosis of Early Allograft Injury:

Patients were placed on a standard immunosuppressive regimen consisting of azathioprine or mycophenolate, tacrolimus, and methylprednisolone. Surveillance bronchoscopy and biopsies were obtained according to standardized post-transplant

protocol at 1, 3, 6, and 12 mo. Additional diagnostic bronchoscopies were triggered by development of clinical symptoms concerning for infection or rejection. Acute rejection was categorized according to ISHLT criteria. Minimal rejection grades of A1B0 were counted as acute rejection if the patient presented with suggestive clinical symptoms and received treatment with pulsed steroids, or had persistent grade A rejection on repeat bronchoscopy.

Statistical analysis:

All statistical analyses were performed utilizing SAS 9.3 statistical package (SAS Institute Inc., Cary, NC, USA). Baseline characteristics were compared using student's t-test for continuous variables and Fisher's exact test for dichotomous variables. Time-to-event analysis using Cox proportional hazards model was utilized to analyze the primary outcome of first episode of acute rejection. Cox proportional hazards regression was used to adjust for baseline covariates in the final analysis.

RESULTS

181 patients met inclusion criteria for the study with a total of 439 person-years of follow-up. The mean age of the cohort was 58 with a slight male predominance (54%), and the most common pulmonary diagnosis was idiopathic pulmonary fibrosis (IPF) which accounted for 41% of patients. Acute rejection was demonstrated in 59 patients (33.5% of those receiving at least one bronchoscopy with biopsy) during the follow-up period for this study. There were 30 deaths during the study period reflecting an all-cause mortality rate of 16.6%.

Pre-transplant HRM revealed normal esophageal motility in 130 patients (71.8%) and IEM in 31 patients (17.1%). The remaining 20 patients had abnormal manometry of other causes (7 DES, 7 Jackhammer, 6 EGJOO). No patients had achalasia or absent contractility. The IEM group had slightly fewer Caucasian patients, but the remaining demographics were statistically similar compared to the normal group (Table 1). For the primary outcome on univariate analysis, IEM was associated with a decreased time to

acute rejection [Hazard Ratio (HR) 1.984, 95%CI 1.03-3.30, P = 0.04). The Kaplan-Meier survival curve trended toward significance with 40% of the IEM cohort developing acute rejection within approximately 250 days, compared to 500 days for the normal esophageal motility group (Figure 1). On multivariable analysis after adjusting for potential confounders including the presence of acid and nonacid reflux, IEM remained independently associated with acute rejection (HR 2.20, 95%CI 1.18-4.11, P = 0.01) (Table 2).

The presence of pathologic acid or nonacid reflux per MII-pH testing was also analyzed. Notably, pathologic acid reflux defined by AET >4.2% was not associated with acute rejection on univariate (HR 1.06, 95%CI 0.63-1.76, P = 0.83) or multivariable analyses (HR 0.92, 95%CI 0.53-1.61, P = 0.77). On the other hand, increased non-acid reflux was associated with decreased time to acute rejection in the IEM group on univariate analysis (HR 2.16, 95%CI 1.26-3.72, P = 0.005) and multivariable analysis (HR 2.10, 95%CI 1.21-3.64, P = 0.009) (Table 2). This relationship occurred independent of the presence of IEM.

DISCUSSION

GERD and esophageal dysmotility are frequent comorbid conditions in patients with end-stage lung disease. There is increasing recognition of the role these esophageal dysfunctions play in the pathogenesis and clinical progression of specific etiologies of end-stage lung disease, as well as their role in the clinical outcomes of lung transplantation. Our study sought to determine the impact of esophageal hypomotility in the development of acute rejection after lung transplantation. We found that IEM demonstrated on pre-transplant testing was associated with increased risk of acute rejection after lung transplantation. This relationship remained after controlling for covariates including pre-transplant measures of acid and non-acid reflux. The magnitude of association was increased after controlling for these baseline factors on multivariate analysis. This suggests that esophageal motility may play a role in lung transplant outcomes that is independent of reflux-related allograft injury and rejection.

Acute rejection was demonstrated in 33.5% of the cohort in the study follow up. This is consistent with prior estimates which have ranged from 28% in the ISHLT registry to 53.3%[7,21]. Baseline demographics did not differ significantly between the IEM and control groups. Amongst the other covariates of interest, non-acid reflux was independently associated with decreased time to the development of acute rejection, and did not substantially alter the association between IEM and acute rejection.

Abnormal esophageal motility was found in 29.3% of our cohort. Of those with abnormal esophageal motility, 59% of these patients were classified as having IEM (or 17% of the total cohort). Prior studies have demonstrated esophageal dysmotility in as high as 78% of patients undergoing lung transplant evaluation, though it is important to note significant heterogeneity in how esophageal dysmotility has been categorized[22-25]. The prevalence in our cohort was consistent with another study that also categorized HRM diagnoses based on Chicago Classification v3.0, which found IEM in 32.7% of patients undergoing lung transplant evaluation[25], supporting the generalizability of our findings.

Recent studies have begun to characterize the impact of esophageal dysmotility on lung transplant outcomes. In a single center study of 31 patients with pre-transplant esophageal aperistalsis, defined as ≥90% failed swallows without any effective peristalsis on HRM, the 1-, 3-, and 5-year post-lung transplant survivals were lower than that of the control group with normal esophageal motility[17]. This study also demonstrated that recovery of peristaltic function post-transplant was associated with improved transplant survival outcomes matching that of the control group. Another study from the same group noted HRM diagnoses of esophageal dysmotility frequently changed post-lung transplant (51.4%) and that peristaltic vigor tends to increase, implicating a dynamic relationship between esophageal motility and pulmonary function[25]. These studies suggest that chronic lung diseases and the resultant altered respiratory mechanics may impact esophageal motility, most commonly associated with hypomotility that may improve with recovery of pulmonary function after transplantation. Two other single center studies utilizing post-lung transplant HRM

also demonstrated associations between esophageal dysmotility and outcomes of acute and chronic rejection[16,26].

The mechanism through which esophageal dysmotility may impact lung transplantation outcomes is not completely clear, although it is speculated to largely be related to increased risk of microaspiration due to reduced esophageal clearance. Esophageal hypomotility may result in decreased clearance and increased proximal migration of gastric refluxate, thereby leading to higher risk for exposure to the airway. Reduced esophageal bolus transit and clearance may also be associated with elevated risk of esophago-pharyngeal reflux, with potential resultant injury to the lung allograft. On the other hand, abnormal reflux, which has already been previously linked with worse lung transplant outcomes, may also lead to esophageal hypomotility. However, our results suggested that esophageal hypomotility may be associated with higher risk of allograft rejection independent of reflux burden.

There remains significant heterogeneity in reflux and esophageal motility testing in the pre- and post-lung transplant settings. HRM is standardized within the pre-transplant evaluation at our institution. The results of this study indicate that results of pre-transplant HRM are informative for risk stratification and prognostication for lung transplant outcomes. This information, in turn, may also guide post-transplant care and monitoring for acute rejection.

There are several notable strengths to our study. Pre-transplant evaluation of esophageal motility on HRM and reflux measurements on MII-pH were standardized across all lung transplant candidates. Ascertainment bias for determination of acute rejection was minimized by surveillance bronchoscopy per standard protocol with biopsy at 1, 3, 6, and 12 mo, though clinical symptoms in between these intervals could trigger additional diagnostic bronchoscopies. Baseline characteristics of the study cohort were consistent with previously published data for rates of acute rejection, prevalence of esophageal dysmotility during pre-transplant evaluation, and indication for lung transplantation. Lastly, distinct HRM diagnoses were categorized according to established classification criteria for analysis, and we were able to control for potential

confounding of specific measures of reflux based on MII-pH monitoring results that were collected on all patients.

There are also several limitations to our study. This is a retrospective cohort study with results that are limited to a single academic institution with high volume of lung transplantation. The sample size is relatively limited within the IEM group, though consistent with prior studies published on the association between esophageal motility and lung transplant outcomes. While a small number of recent studies have suggested dynamic changes in esophageal motility post-transplant, post-transplant motility measurements were not obtained routinely as part of our study. Finally, due to the retrospective nature and inclusion period of our study cohort, Chicago classification v3.0 was used to define IEM. However, the most current Chicago classification v4.0 mainly further restricted the diagnosis of IEM with more stringent criteria than v3.0. Therefore, the use of Chicago classification v3.0 to define IEM would likely have biased our results towards the null, as some patients in our IEM group would have been classified as normal under v4.0. The fact that our results remained significant despite this potential bias would strengthen the observed relationship between IEM and acute allograft rejection.

CONCLUSION

In summary, our study demonstrated that IEM on pre-transplant esophageal motility testing was associated with decreased time to development of acute rejection after lung transplantation. Our study provides additional evidence for the association between esophageal dysmotility and poor lung transplant outcomes. It builds upon prior studies on esophageal aperistalsis and survival outcomes in lung transplantation by providing additional evidence for acute rejection in the less severe phenotype of IEM. It also suggests esophageal dysmotility may mediate long-term lung transplant outcomes through a pathway starting with acute rejection. Further studies are needed in delineating transplant outcomes by underlying pulmonary diagnosis, analyzing longer term outcomes such as chronic rejection and 3- and 5- year survival outcomes in

the context of esophageal dysmotility, and comparing pre- and post-transplant esophageal function testing results on lung transplant outcomes.

ARTICLE HIGHLIGHTS

Research background

Gastroesophageal reflux is associated with poor outcomes after lung transplantation. However, the impact of esophageal dysmotility and role of esophageal manometry remains unclear. Ineffective esophageal motility (IEM) is a disorder of esophgeal motility associated with decreased esophageal clearance, that may worsen transplant outcomes.

Research motivation

Esophageal evaluation remains poorly standardized in lung transplantation, and this work suggests that routine esophageal motility testing to identify IEM may help identify patients at risk for acute rejection.

Research objectives

To evaluate the relationship between IEM and acute rejection after lung transplantation, controlling for confounders including coexisting pathologic acid and nonacid reflux.

Research methods

This was a retrospective cohort study of lung transplant recipients that underwent pre-transplant esophageal testing including manometry and pH at a tertiary referral center.

Research results

Ineffective esophageal motility (IEM) on pre-transplant esophageal manometry was associated with higher risk of acute rejection on time-to-event analysis. On multivariable Cox regression analysis, IEM remains independently associated with increased acute rejection, even after controlling for pathologic reflux. In addition,

increased non-acid reflux was also an independent risk factor for acute rejection in the multivariable model.

Research conclusions

Lung transplant candidates with IEM had a greater risk of developing acute rejection, independent of pathologic acid and nonacid reflux. Additionally, nonacid reflux was independently associated with acute rejection. These findings suggest that IEM and other disorders affecting esophageal clearance may contribute to the pathophysiology of allograft injury, independent of a reflux-associated pathway.

Research perspectives

Future research should focus on the implementation of standardized esophageal motility testing in lung transplantation, investigation of the impact of IEM and other disorders of esophageal motility on longer term transplant outcomes including chronic rejection and survival, and assessment of changes in esophageal motility after transplant and its effect on transplant outcomes.

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