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ESOPHAGEAL DYSMOTILITY ACCORDING TO CHICAGO CLASSIFICATION v3.0 VERSES v2.0: IMPLICATIONS FOR ASSOCIATION WITH REFLUX, BOLUS CLEARANCE AND ALLOGRAFT FAILURE POST-LUNG TRANSPLANTATION

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Run Heading: Chicago Classification v3.0 verses v2.0

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Abbreviations: BOS, bronchiolitis obliterans syndrome; CC, Chicago Classification; DCI, distal contractile integral; DEA, distal esophageal amplitude; DL, distal latency; EGJOO, esophagogastric

junction outflow obstruction; EGJOO, esophagogastric junction outflow obstruction without hypercontractility; EGJOOh, esophagogastric junction outflow obstruction with hyper-contractility; GERD, gastroesophageal reflux disease; HRIM, high-resolution esophageal impedance manometry; IBT, incomplete bolus transit; IEM, ineffective esophageal motility; IRP, integrated relaxation pressure; LTx, lung transplantation; o-CLAD, obstructive chronic lung allograft dysfunction; PPI, proton pump inhibitors; UES, upper esophageal sphincter; LES, lower esophageal sphincter; WPLB, weak peristalsis with large breaks; WPSB, weak peristalsis with small breaks.

ABSTRACT

BACKGROUND: Proximal reflux and incomplete transit of boluses swallowed are risk factors for obstructive chronic lung allograft dysfunction (o-CLAD) post-lung transplantation (LTx). Likewise, so is esophagogastric junction outflow obstruction (EGJOO), but not hypo-contractility, when diagnosed using Chicago Classification (CC) v3.0. Given, peristaltic breaks as defined using CCv2.0 can prolong esophageal clearance, both swallowed and refluxed, but which are deemed within normality using CCv3.0, our aim was to determine whether hypo-contractility as diagnosed using CCv2.0, influences the association with reflux, along with its clearance, and that of boluses swallowed, and thus its association to allograft failure.

METHODS: Esophageal motility abnormalities were classified using CC v3.0 and v2.0 in 50 patients post-LTx (26 female, 55yr(20-73yr)).

RESULTS: Reclassification from CCv3.0 to v2.0 resulted in 7 patients with normal motility being reclassified to hypo-contractility (n=6) or hyper-contractility (n=1); 2 patients with hypo-contractility to normal motility; and 3 patients with EGJOO without hyper-contractility to EGJOO with hyper-contractility. The main consequence of reclassification was that the sub-group exhibiting hypo-contractility became more likely to have abnormal numbers of reflux events (p=0.025) and incomplete bolus transit (p=0.002) than those with normal motility using CCv2.0; associations not seen using CCv3.0. Irrespective of CC used only patients with EGJOO appeared more likely to develop o-CLAD than those with normal motility ($p<0.05$).

CONCLUSIONS: Irrespective of CC used, o-CLAD appears linked to EGJOO. CCv2.0 however, accentuates the increased reflux and incomplete bolus transit associated with hypo-contractility post-LTx, suggesting that these motor abnormalities, though considered minor, may be of importance after lung transplant.

Words: 250

KEY POINTS

- Esophagogastric junction outflow obstruction, but not hypo-contractility defined using Chicago Classification (CC)v3.0, along with proximal reflux and incomplete bolus transit (IBT) are risk factors for obstructive chronic lung allograft dysfunction (o-CLAD) post-lung transplantation.
- Using CCv2.0 results in hypo-contractility being more likely to be associated with abnormal numbers of reflux events and IBT, risk factors for o-CLAD, and associations not seen using CCv3.0.
- Motor abnormalities, such as peristaltic breaks, deemed within normality using CCv3.0, maybe of importance after lung transplantation.

INTRODUCTION

Gastroesophageal reflux is considered a potential risk factor for aspiration and consequently the development of chronic allograft failure in patient's post-lung transplantation (LTx). Early studies assessing esophageal motility abnormalities in these patients therefore mainly focused on factors that might aid the passage of refluxate into the esophagus, such as reduced resting lower esophageal sphincter (LES) pressure, shorter total and abdominal length of the LES, reduced distal esophageal amplitude (DEA) and/or presence of ineffective esophageal motility (IEM), defined in these papers as DEA <30mmHg or when >30% simultaneous waves were present in the distal esophagus.[1-5] These studies however, were inconclusive with some reporting a higher prevalence of IEM and poor acid reflux clearance time in LTx patients with compared to without gastroesophageal reflux disease (GERD),[2] and correlation between bronchoalveolar lavage fluid pepsin and, LES pressure and DEA,[1] but others showing no difference in motility between those with and without GERD.[3, 6] The one study comparing esophageal motility in LTx patients with and without allograft dysfunction, reported no difference.[7] These studies however, only used conventional manometric parameters and definitions in their analyses, which were further confounded by the use of only pH to record reflux events, thus missing non-acid reflux events captured by impedance.

Using high-resolution esophageal impedance manometry (HRIM) with the Chicago Classification (CC), version 3.0, and 24-hr pH/impedance we have recently followed up these initial findings to assess the impact of motor dysfunction as defined by these criteria on both swallowed and reflux bolus clearance and consequently the development of obstructive chronic lung allograft dysfunction (o-CLAD).[8] We showed for the first time that esophagogastric junction outflow obstruction (EGJOO), incomplete bolus transit (IBT) during swallowing, and proximal reflux all increased the risk of o-CLAD. Contrary to expectations, patients with hypo-contractility (e.g. absent contractility, IEM and fragmented peristalsis) were no more likely to present with o-CLAD than those with normal motility. However, examination of the LTx patients with normal motility, revealed a higher than anticipated

incidence of gastroesophageal reflux, incomplete transit of boluses swallowed, and peristaltic breaks that fulfilled CC v2.0 criteria for weak peristalsis with breaks that are considered within normal limits using CC v3.0.

Given studies in both patients with GERD[9] and chronic cough[10] using CC version 2.0, have shown that patients with pathological numbers of peristaltic breaks have prolonged reflux clearance times, higher acid exposure times and slower passage of swallowed boluses than those without breaks, we hypothesized that reclassification of our LTx patients using CC v2.0 might alter our findings to show that those with hypo-contractility had increased incidence of o-CLAD than those with normal motility. In other words, we hypothesize that motor abnormalities that are considered to be normal under CC v3.0, may be clinically important in patients who have undergone lung transplant.

Our aim was therefore to compare CC v3.0 with v2.0 to determine how this influenced the prevalence of dysmotility in patients post-LTx, and to assess how this altered the relationship to reflux exposure time, impaired clearance of swallowed boluses as well as refluxate, and association with o-CLAD.

MATERIALS AND METHODS

Patients

Consecutive post-LTx patients (n=50, 26 female; mean age 55 [range 20-73]years) referred for HRIM and pH/impedance approximately 3 months after surgery at Mayo Clinic in Jacksonville, Florida, between October 2012 and December 2014 with follow-up through July 31, 2015 were included. Patient data included age, sex, body mass index, donor and recipient cytomegalovirus immune status, indication for LTx, LTx date, intra-operative data, post-LTx medication, post-LTx complications, including acute rejection, o-CLAD and death.[8] The Mayo Clinic Institutional Review Board approved the study.

Methods

As described in our recent articles verbatim.[8, 10]

HRIM

HRIM was performed using a solid state catheter with 36 circumferential pressure sensors spaced at 1cm intervals and 18 impedance channels (Medtronic Inc. Shoreview, MN). The catheter was positioned transnasally with the distal sensors for both pressure and impedance in the proximal stomach. Following at least a 30s baseline to identify the upper esophageal sphincter (UES) and LES, ten 5 ml saline swallows were given at least 30s apart with the patient supine.[8, 10]

pH/impedance

pH/impedance (Sandhill Scientific Inc., CO) was performed using a single antimony pH probe (5cm above the LES) with 8 impedance electrodes.[8, 10]

Diagnosis of Obstructive Chronic Lung Allograft Dysfunction

The term CLAD includes the entities of bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS), the former being characterized by obstruction and the latter by a restrictive component.[11, 12] To date all studies reporting on the possible link between reflux, aspiration and lung allograft dysfunction have concentrated on BOS. To our knowledge there is no established link between reflux and RAS.[11, 12] Thus we have focused specifically on "obstructive CLAD",[12] defined per the joint ATS/ERS statement on BOS, including BOS 0-p.[13]

Data analysis

HRIM:

ManoVIEW Analysis software v3.01(Medtronic Inc., Shoreview, MN, USA) was used to manually analyze the recordings. Esophageal motility was classified based upon CC v3.0[14] and CC v2.0.[15] Using

CC v3.0 each 5ml swallow was evaluated to determine: (i) integrated relaxation pressure (IRP), (ii) distal contractile integral (DCI), and (iii) distal latency (DL).[14] Contractile pattern was classified as premature, fragmented or intact.[14] Using CCv2.0, variables evaluated included: (i) IRP, (ii) DCI, (iii) contractile front velocity (iv) DL and (v) the presence, location and size of breaks in the 20 mmHg isobaric contour, defined as small when they were between 2-5cm or large when they were >5cm. Swallows were classified based on these parameters as normal, premature, rapid or hyper-contractile.

CC version 3.0 diagnoses included: (i) achalasia or EGJOO, the latter defined as poor deglutitive relaxation of the LES (median IRP > 15mmHg), with some instances of intact or weak peristalsis, not meeting the criteria for achalasia; (ii) major disorders of peristalsis, such as absent contractility, distal esophageal spasm (DES) and hyper-contractile esophagus; or (iii) minor disorders of peristalsis, such as IEM and fragmented peristalsis.[14]

CC version 2.0 diagnoses included: (i) achalasia or EGJOO (mean IRP > 15mmHg), (ii) motility disorders of the body of the esophagus not seen in health, such as absent peristalsis, distal esophageal spasm, hyper-contractile esophagus or Jackhammer; or (iii) peristaltic abnormalities or conditions, defined by exceeding the statistical limit of normal, such as Nutcracker esophagus, weak peristalsis with large breaks (WPLB), weak peristalsis with small breaks (WPSB), rapid contractions with normal DL, or frequent failed peristalsis.[15, 16]

Impedance recordings were evaluated for each swallow and bolus clearance assessed using both colorized contour functions and superimposed impedance tracings, as previously described.[17] Bolus clearance was defined as ‘complete’ or ‘incomplete’ based on manual evaluation of the colour overlay and line tracing modes.[17] Subjects were classified as complete bolus transit when clearance was seen in ≥ 80% of swallows.[18]

24-hr pH/impedance:

BioVIEW Analysis software (Sandhill Scientific Inc.) was used to identify reflux episodes based on retrograde impedance decrease to 50% of baseline in at least two distal adjacent channels. Meal periods were excluded. In patients off proton pump inhibitors (PPI) >73 episodes was considered abnormal[19]; >48 episodes on b.i.d. PPI.[20] Proximal reflux events were defined as those that reached at least 15cm above LES (Normal ≤31 off PPI, ≤19 on PPI).[19, 20] Since data on abnormal reflux frequency on q.d. PPI are not available, we classified those patients with ≤48 reflux events as normal and those with >73 episodes as abnormal. For proximal reflux events, we defined patients on q.d. PPI with ≤19 reflux events as normal and those with >31 episodes as abnormal (only 3 patients could not be classified and were excluded from any categorical analysis). Bolus clearance time was defined as lapsed time that the bolus was present at each impedance level during a specific reflux episode or time interval between bolus entry and clearance. Total reflux bolus exposure time was the percentage of monitored time that the esophagus was exposed to reflux of any nature.

Acid exposure time was defined as the percentage of total time that pH was below 4 (normal values <4.2 off PPI or <1.6 on PPI).[19, 20]

Statistics

Group differences were evaluated using Student's t-tests or Mann-Whitney U tests. Associations were assessed using Fisher's exact tests. Cox proportional hazards were completed controlling for length of time between LTx and esophageal testing. Significance was evaluated at the 2-tailed, $p < 0.05$ levels.

RESULTS

Demographics of the patient cohort have been previously reported.[8] Briefly, key findings were that 23 (46%) of the patients developed o-CLAD a median (IQR) of 725 (495-1117) days after LTx, and 4 (8%) died 1677 (870-2193) days after LTx (all had o-CLAD).

HRIM

CC v3.0 vs v2.0:

Using CC v3.0, 14 (28%) patients were diagnosed with normal motility and 36 (72%) with abnormal motility; 13 (26%) with EGJOO without hyper-contractility (EGJOO) (achalasia (n=4) and EGJOO (n=9), the latter defined as poor deglutitive relaxation of LES (median IRP>15mmHg), not meeting criteria for achalasia), 12 (24%) with hyper-contractility (Jackhammer (n=8), distal esophageal spasm (n=2), and Jackhammer with distal esophageal spasm (n=2)), 4 (8%) with EGJOO with hyper-contractility (EGJOOh), and 7 (14%) with hypo-contractility (absent contractility (n=1), IEM (n=5) and fragmented peristalsis (n=1)).

As shown in Table 1, analysis based upon CC v2.0 resulted in a larger though not significant number of patients being classified into the hypo-contractility categories compared to CC v3.0 (11 (22%) vs. 7 (14%), p=ns). Six patients with normal motility using v3.0 met v2.0 hypo-contractility criteria (WPLB (n=1), WPSB (n=2) and combined WPLB and WPSB (n=3)). In addition, 1 patient with normal motility using v3.0 met v2.0 hyper-contractility criteria (Jackhammer) and 2 patients with hypo-contractility using v3.0 (IEM (n=2)) were classified as normal using v2.0. As expected, re-analyzing patients using v2.0 resulted in the same number of patients with EGJOO compared to v3.0, but EGJOOh as opposed to EGJOO was more common with v2.0, because the threshold for diagnosing hyper-contractility is higher in v3.0. Thus, using CC v2.0, 9 (18%) patients were diagnosed with normal motility and 41 (82%) with abnormal motility: 10 (20%) with EGJOO, 13 (26%) with hyper-contractility (Jackhammer (n=9), distal esophageal spasm (n=2) and Jackhammer with distal esophageal spasm (n=2)), 7 (14%) with EGJOOh, and 11 (22%) with hypo-contractility (absent peristalsis (n=1), frequent failed peristalsis (n=2), WPLB (n=1), WPSB (n=3) and combined WPLB and WPSB (n=4). These changes in diagnosis were not statistically significant (Table 1).

o-CLAD vs without o-CLAD:

Irrespective of CC used to diagnose abnormal esophageal motility, patients with o-CLAD were more likely to exhibit EGJOO than patients without o-CLAD ($p<0.02$). There were no other differences in other diagnoses between the two classifications (Table 2).

Abnormal & normal esophageal motility: Association with reflux, bolus clearance and o-CLAD:

In summary, using CC v3.0, patients with EGJOO (77%) were more likely to develop o-CLAD than those with normal motility (29%, $p=0.016$)(Table 3). Patients with EGJOO however, were less likely to have abnormal numbers of reflux events (10% v 64%, $p=0.011$) and exhibited reduced reflux bolus exposure time (0.6% v 1.5%, $p=0.011$) compared with those with normal motility (Table 3).

Re-classifying patients using CC v2.0, still resulted in patients with EGJOO (80%) been significantly more likely to develop o-CLAD than those with normal motility (22%, $p=0.019$) but the percentage of patients with abnormal numbers of reflux events was no different from those with normal motility (0 v 33%, NS). Unlike using CC v3.0 however, where patients with hypo-contractility exhibited similar reflux and bolus transit measures to those with normal motility, when using CC v2.0, significantly more patients with hypo-contractility exhibited abnormal reflux (89% v 33%, $p=0.025$) and increased numbers of total (76(69-100) v 39(27-58);$p=0.016$) and proximal (31(15-58) v 13(6-18);$p=0.038$) reflux events than those with normal motility (Table 4). Moreover, all patients with hypo-contractility (100%) exhibited incomplete transit of boluses swallowed compared with only 33% of patients with normal motility ($p=0.002$). This was associated with a greater number of swallows being associated with IBT (60(40-100)) compared with those with normal motility (0(0-30), $p<0.001$)(Table 4).

DISCUSSION

Our study has shown that in patients following LTx, CC v3.0 classified more patients into EGJOO but fewer patients into the hypo-contractility categories than CC v2.0.

Identifying EGJOO has potentially important clinical implications for patient's post-LTx, as it appears to be a significant risk factor for the development of o-CLAD and premature death.[8] Despite a few more patients been captured as EGJOO using CC v3.0, similar percentages of EGJOO patients classified using CC v3.0 (77%) and v2.0 (80%) developed o-CLAD post-LTx. This is maybe related to the fact that unlike CC v3.0, EGJOO patients classified using CC v2.0 cannot exhibit concomitant hyper-contractility and as a sub-group exhibited more swallows associated with IBT than those with normal motility, an additional risk factor for o-CLAD. Indeed, patients classified as EGJOO with hyper-contractility using either CC v3.0 (at least 20% of swallows associated with Jackhammer) or CC v2.0 (at least 10% of swallows associated with Jackhammer) were no more likely to develop o-CLAD than those with normal motility, suggesting hyper-contractility might aid swallowed bolus and refluxate pass through the obstructed EGJ.

Analysis based upon CC v2.0 resulted in 6 patients with normal motility using CC v3.0 meeting v2.0 hypo-contractility criteria; one with WPLB, two with WPSB and 3 with combined WPLB and WPSB. In line with previous studies in chronic cough[10] and GERD[9] this resulted in the hypo-contractility patient sub-group being significantly more likely to exhibit IBT (100% *vs* 33%), abnormal reflux (89% *vs* 33%), and both increased total number and proximal reflux events than those with normal motility. Importantly these observations suggest that motility patterns/abnormalities identified using CC v2.0 which can be associated with risk factors for the development of o-CLAD (e.g. IBT, proximal reflux) might be overlooked when using CC v3.0. The fact that the hypo-contractility sub-group were no more likely to develop o-CLAD than those with normal motility, irrespective CC used, is probably

because the severity of hypo-contractility and motility patterns seen varied between patients, resulting in differing effects on both transit of boluses swallowed and the proximal extent of reflux, the primary factors driving allograft dysfunction.

In conclusion, CC v3.0 may be more helpful at identifying the motor abnormality EGJOO which is a risk factor for o-CLAD post-LTx. However, caution should be applied when diagnosing normal motility using CC v3.0, especially if presenting with WPLB and/or WPSB using CC v2.0, as these motor defects can be associated with IBT or abnormal proximal reflux, both recently identified risk factors for the development of o-CLAD. These observations together with those from other studies reporting that nearly three quarters of LTx patients have oropharyngeal dysphagia,[21,22] highlight the importance of abnormal swallowing, particularly in the presence of EGJOO in the development of o-CLAD. As discussed previously,[8] before appropriate clinical management pathways to treat these patients can be recommended further carefully designed and appropriately powered studies are urgently needed. For now, an individualised approach to management keeping in mind our observations to try to reduce the risk of o-CLAD, can only be recommended.

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Author Contributions:

Performed research – AT

Designed the research study – AT, LAH

Contributed essential reagents or tools – None

Analyzed the data – AT, MDC, LAH

Wrote the paper – AT, MRV, MDC, KRD, LAH

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Table 1: Diagnosis of esophageal motility abnormalities based on Chicago Classification v3.0 and v2.0 in patients post-LTx

	CC v3.0 (n=50)	CC v2.0 (n=50)
Normal contractility, n(%)	14(28)	9(18)
Abnormal contractility, n(%):	36 (72)	41(82)
EGJOO ~~alone~~	13(26)	10(20)
Hyper-contractility	12(24)	13(26)
EGJOO with hyper-contractility	4(8)	7(14)
Hypo-contractility	7(14)	11(22)

Abbreviations: CC, Chicago Classification; EGJOO, esophagogastric junction outflow obstruction; LTx, lung transplantation.
No significant differences identified between groups

Table 2: Individual HRIM parameters, diagnostic classifications based on Chicago Classification v3.0 and v2.0 in LTx patients with and without o-CLAD.

	o-CLAD (n=23)	**Without o-CLAD** (n=27)	**P Value**
*UES resting pressure, mmHg	56.8(46.3-88.3)	56.4(47.0-76.2)	0.888
*UES relaxation pressure, mmHg	3.2(1.0-6.6)	1.7(0.9-7.2)	0.410
*LES resting pressure, mmHg	29.9(27.4-42.9)	34.5(28.9-48.0)	0.202
‡LES-CD separation, >2cm, n(%)	2(9)	0	0.207
*Mean IRP, mmHg (C, v2.0)	13.1(7.6-18.8)	11.3(9.1-14.5)	0.436
*Median IRP, mmHg (C, v3.0)	12.9(7.2-18.6)	11.0(9.1-14.0)	0.386
*CFV, cm/s	4.6(3.4-6.4)	3.2(2.4-4.3)	0.002
*DL, s	6.2(5.3-7.0)	7.4(5.9-8.3)	0.032
*DCI, mmHg-s-cm	1822.0(1125.7-5048.8)	4313.4(1847.6-8373.1)	0.062
‡Chicago v3.0, n(%)			
Normal	4(17)	10(37)	0.109
EGJOO ~~alone~~	10(44)	3(11)	0.011
Hyper-contractility	4(17)	8(30)	0.251
EGJOO with hyper-contractility	1(4)	3(11)	0.368
Hypo-contractility	4(17)	3(11)	0.407
‡Chicago v2.0, n(%):			
Normal	2(9)	7(26)	0.112
EGJOO ~~alone~~	8(35)	2(7)	0.019
Hyper-contractility	4(17)	9(33)	0.170
EGJOO with hyper-contractility	3(13)	4(15)	0.593
Hypo-contractility	6(26)	5(19)	0.380

Results expressed as either * median (IQR) or ‡ percentage for categorical variables.

Abbreviations: CFV, contractile front velocity; DCI, distal contractile integral; DL, distal latency; EGJOO, esophagogastric junction outflow obstruction; HRIM, high-resolution esophageal impedance manometry; IRP, integrated relaxation pressure; LES, lower esophageal sphincter; LES-CD, LES to crural diaphragm distance; LTx, lung transplantation; o-CLAD, obstructive chronic lung allograft dysfunction; UES, upper esophageal sphincter.

Table 3: MII and 24-hr MII/pH findings in LTx patients with various esophageal diagnoses based on Chicago Classification v3.0

	Normal (n=14)	EGJOO~~a~~ (n=13)	Hyper-contractility (n=12)	EGJOOh (n=4)	Hypo-contractility (n=7)
MII findings:					
‡Patients with IBT, n(%)	8(57)	9(69)	4(33)	1(25)	6(86)
*Swallows with IBT, %	30(0-50)	50(20-90)	10(0-30)	5(0-25)	60(30-100)
24-hr MI/pH:					
*Total no. events, n	70(39-90)	37(19-45)	42(13-55)	32(10-38)	72(27-76)
‡Patients with abnormal no. of events, n(%)	9/14(64)	1/10(10)[a]	2/10(20) [a]	0/3(0)	3/5(60)
*Proximal events, n	16(9-26)	11(6-13)	8(3-22)	3(2-11)	31(8-34)
‡Patients with abnormal no. of proximal events, n(%)	5/14(36)	1/10(10)	3/11(27)	0/3(0)	3/6(50)
*Total reflux bolus exposure time, %	1.5(0.8-2.3)	0.6(0.4-0.9)[a]	0.7(0.2-1.9)	0.4(0.3-0.9)[a]	1.7(0.7-6.7)
*Bolus clearance time, s	13(10-14)	11(7-12)	13(9-16)	13(6-16)	17(11-26)
*Acid exposure time, %	3.8(1.1-7.9)	0.9(0.4-3.7)	2.0(0.3-7.2)	1.4(0.9-2.0)	0.3(0.1-16.3)
Post-LTx complications:					
‡Acute rejection, n(%)	8(57)	8(62)	9(75)	3(75)	4(57)
‡o-CLAD, n(%)	4(29)	10(77)[a]	4(33)	1(25)	4(57)
*Time to o-CLAD, days	273(183-1451)	748(578-921)	891(609-1651)	731	672(411-1492)
‡Death, n(%)	0(0)	3(23)	0(0)	0(0)	1(14)

Results expressed as either *median (IQR), †mean (95%CI), or ‡categorical variables.

[a]p<0.05 compared with normal esophageal motility.

Abbreviations: BMI, body mass index; EGJOO~~a~~, esophagogastric junction outflow obstruction without hyper-contractility ~~alone~~; EGJOOh, esophagogastric junction outflow obstruction with hyper-contractility; IBT, incomplete bolus transit; LTx, lung transplantation; MII, multichannel intraluminal impedance; o-CLAD, obstructive chronic lung allograft dysfunction.

Table 4: MII and 24-hr MII/pH findings in LTx patients with various esophageal diagnoses based on Chicago Classification v2.0

	Normal (n=9)	EGJOO~~a~~ (n=10)	Hyper-contractility (n=13)	EGJOOh (n=7)	Hypo-contractility (n=11)
MII findings:					
‡Patients with IBT, n(%)	3(33)	8(80)	4(31)	2(29)	11(100)[a]
*Swallows with IBT, %	0(0-30)	55(30-100)[a]	10(0-29)	10(0-30)	60(40-100)[a]
Impedance findings:					
*Total no. events, n	39(27-58)	36(19-41)	46(13-68)	35(11-53)	76(69-100)[a]
‡Patients with increased no. of events, n(%)	3/9(33)	0/7(0)	3/11(27)	1/6(17)	8/9(89)[a]
*Proximal events, n	13(6-18)	10(6-13)	9(3-22)	7(2-12)	31(15-58)[a]
‡Patients with increased no. of proximal events, n(%)	2/9(22)	0/7(0)	3/12(25)	1/6(17)	6/10(60)
*Total reflux bolus exposure time, %	0.8(0.6-1.9)	0.6(0.4-0.9)	0.8(0.2-1.9)	0.5(0.3-0.9)	1.7(0.9-4.1)
*Bolus clearance time, s	13(11-14)	11(7-12)	12(9-16)	11(7-14)	13(11-17)
*Acid exposure time, %	3.9(1.4-7.9)	1.0(0.5-2.4)	2.1(0.3-6.8)	1.3(0.4-2.6)	1.1(0.2-9.6)
Post-LTx complications:					
‡Acute rejection, n(%)	5(56)	6(60)	10(77)	5(71)	6(55)
‡o-CLAD, n(%)	2(22)	8(80)[a]	4(31)	3(43)	6(55)
*Time to o-CLAD, days	1546(542-2550)	782(650-1037)	891(609-1651)	731(495-771)	315(195-801)
‡Death, n(%)	0(0)	3(30)	0(0)	0(0)	1(9)

Results expressed as either *median (IQR), †mean (95%CI), or ‡categorical variables.

[a]p<0.05 compared with normal esophageal motility.

Abbreviations: BMI, body mass index; EGJOO~~a~~, esophagogastric junction outflow obstruction ~~alone~~ without hyper-contractility; EGJOOh, esophagogastric junction outflow obstruction with hyper-contractility; IBT, incomplete bolus transit; LTx, lung transplantation; MII, multichannel intraluminal impedance; o-CLAD, obstructive chronic lung allograft dysfunction.