Published in final edited form as:

Am J Gastroenterol. 2018 January ; 113(1): 31–38. doi:10.1038/ajg.2017.263.

Psychosocial Distress and Quality of Life Impairment are Associated with Symptom Severity in PPI Non-Responders with Normal Impedance-pH Profiles

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Abstract

Introduction—Up to 50% of patients with reflux symptoms do not manifest a satisfactory symptom response to proton pump inhibitor (PPI) therapy. The primary aim of this study was to identify factors associated with symptom perception among PPI non-responder phenotypes.

Methods—This prospective observational cohort study was performed from 9/2014–1/2017 at a single academic medical center, and included PPI non-responders who underwent 24-hour impedance-pH monitoring and completed a questionnaire set measuring patient-reported symptom severity, quality of life (QOL), and psychosocial distress.

Participants were separated into cohorts based on impedance-pH results; On PPI: -acid exposure time (AET)/-symptom reflux association (SRA), +AET, and -AET/+SRA; off PPI: Functional (-AET/-SRA), GERD (+AET), RHS (-AET/+SRA). The primary outcome was abnormal GERD symptom severity defined by GerdQ 8.

Results—One hundred ninety-two participants were included. Impedance-pH on PPI was performed on 125: 72 (58%) -AET/-SRA, 42 (34%) +AET, and 11 (9%) -AET/+SRA. Among the -AET/-SRA group, younger age, higher dysphagia scores, QOL impairment, and brief symptom index were associated with GerdQ 8. Among the +AET group, higher number of reflux associated symptoms and lower distal contractile integral was associated with GerdQ 8. Impedance-pH off PPI was performed on 67 participants: 39 (58%) functional, 16 (24%) GERD,

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Potential Conflict of Interest (Financial, Professional or Personal): None

Specific Author Contributions

RY: Study oversight; study concept and design; acquisition of data; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; finalization of manuscript.

MT: Study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content; finalization of manuscript.

LK: Acquisition of data; Interpretation of data; critical revision of the manuscript for important intellectual content; finalization of manuscript.

PJK: Interpretation of data; critical revision of the manuscript for important intellectual content; finalization of manuscript.

JEP: Study concept and design; analysis and interpretation of data; drafting of manuscript; critical revision of the manuscript for important intellectual content; finalization of manuscript.

and 12 (18%) RHS. Among the functional group, a higher QOL impairment and dysphagia scores were seen with GerdQ 8.

Conclusion—Perceptions of reflux symptoms are associated with psychosocial distress, reduced QOL and sensation of dysphagia among PPI non-responders with normal impedance-pH. Among PPI refractory GERD patients, patient-reported symptom severity is associated with physiologic differences, as opposed to psychosocial factors.

Keywords

Functional heartburn; Patient reported outcomes; Esophageal hypersensitivity; Esophageal hypervigilance

Introduction

The prevalence of gastroesophageal reflux disease (GERD) in the US is estimated to be greater than 20%^{1,2}. Although acid suppression with proton pump inhibitor (PPI) therapy is extremely effective at healing erosive GERD, less than 50% of patients are satisfied with symptom control with PPI therapy^{3,4}. Given the high prevalence of GERD and rates of PPI non-response, the health care burden of PPI non-responders is substantial⁵.

Currently, a well-defined therapeutic algorithm for PPI non-responders is lacking. This deficit relates largely to heterogeneous physiologic profiles and a poor understanding of the factors driving symptom perception in PPI non-responders⁵. Up to 50% of PPI non-responders have normal physiologic and anatomic profiles (i.e., normal esophageal acid exposure, an intact antireflux barrier, and absence of a major motility disorder)⁶. Despite a lack of objective evidence of reflux, patients often perceive troublesome symptoms of reflux. Understanding symptom genesis in PPI non-responders with normal reflux testing is of great interest and has the potential to guide individualized and effective treatment strategies⁷.

In this study, our aim was to identify predictors of patient reported symptom severity among PPI non-responder phenotypes based on impedance-pH profiles. We hypothesized that psychosocial distress is associated with symptom severity among PPI non-responders with normal impedance-pH profiles.

Methods

Study Design & Setting

We performed a prospective observational cohort study from September 2014 to January 2017 at a single academic medical center. The Northwestern University IRB approved this study and participants provided written informed consent.

Participants

Eligible participants included adult patients (age 18 years or older) who underwent high-resolution esophageal manometry and 24-hour combined multichannel intraluminal impedance and pH monitoring (MII-pH) while on or off PPI therapy for evaluation of troublesome esophageal symptoms despite at least eight weeks of double dose PPI therapy.

Patients undergoing evaluation prior to or following lung transplant, with a diagnosis of scleroderma, or with a major esophageal motility disorder of achalasia (types 1, 2, or 3), esophagogastric junction (EGJ) outflow obstruction, absent contractility, hypercontractile esophagus, or distal esophageal spasm were excluded.

Data Source and Measurement

Prior to MII-pH testing, participants completed a self-administered questionnaire set to obtain a baseline assessment of symptom burden, quality-of-life (QOL), and symptom-specific anxiety, discomfort, affect and stress. Patient-reported symptom questionnaires included the GerdQ, a validated instrument for evaluating GERD symptoms⁸, the Reflux Symptom Index (RSI), a validated laryngeal symptom questionnaire^{9,10}, and the Impaction-Dysphagia Questionnaire (IDQ) and Brief Esophageal Dysphagia Questionnaire (BEDQ), symptom questionnaires to evaluate dysphagia symptoms^{11,12}. QOL was measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) Global 10 Survey¹³. Symptom-specific psychosocial distress was measured using the Discomfort Intolerance Scale (DIS)¹⁴, a measure of the ability to tolerate uncomfortable sensations, the Heartburn Vigilance Scale (HVS), adapted from the validated Pain Vigilance and Awareness Questionnaire^{15,16}, and the Brief Symptom Inventory (BSI), a validated psychosocial symptom scale¹⁷. For all questionnaires, a higher score indicated increased severity, impairment, and/or distress.

We additionally collected baseline clinical data for each participant including age, gender, symptoms, PPI dosage, size of hiatal hernia, and endoscopy results as well as physiologic data including MII-pH results of the percent time esophageal acid exposure was below a pH of 4.0 (acid exposure time, AET), number of reflux episodes, symptom-reflux association (SRA) using the symptom index and symptom association probability, and number of reflux associated symptoms (Sandhill Scientific Inc.; Highlands Ranch, CO), and high-resolution esophageal manometry results of motility diagnosis according to Chicago Classification version 3.0¹⁷, median integrated relaxation pressure (IRP), mean distal contractile integral (DCI), and the EGJ contractile integral (EGJ-CI) (Manoscan 360; Medtronic, Minneapolis, MN).

AET greater than 5.0% was considered abnormal. Positive symptom-reflux association required a symptom index greater than 50% in the setting of a symptom association probability greater than 95%.

Outcomes

The primary outcome was patient-reported GERD symptom severity measured by the GerdQ score, a validated six-item patient-reported outcome tool for GERD which calculates symptom severity over the preceding week based on response to four positive predictors (heartburn, regurgitation, sleep disturbance, and antacid use) and two negative predictors (epigastric pain and nausea) of GERD. Scores range from 0 to 18; a higher GerdQ indicates greater symptom severity and a score of 8 is the proposed cut-off⁸. In this study, the primary outcome was dichotomized as abnormal GerdQ score (≥ 8) or normal GerdQ score (<8).

Data Analysis

A complete case analysis was performed and missing data was not imputed. All eligible cases from September 15, 2014 to date of final data collection, January 23, 2017, were included without a predetermined sample size. Baseline data, physiologic data, and questionnaire scores were compared among the three cohorts using analysis of variance for continuous variables and Chi Square analysis for categorical variables.

The primary analysis included the cohort of participants who underwent MII-pH ON PPI. For the primary analysis participants were categorized into three cohorts based on their MII-pH on PPI profile: -AET/-SRA, +AET, -AET/+SRA.

Since data from MII-pH ON PPI can include GERD overlap, we performed a post-hoc analysis of the cohort of participants who underwent MII-pH OFF PPI. For the secondary analysis participants were categorized into three cohorts based on their MII-pH on PPI profile: Functional - normal AET, negative symptom-reflux correlation; GERD - abnormal AET regardless of symptom-reflux correlation; and Reflux hypersensitivity (RHS) - normal AET, positive symptom-reflux correlation. Both analyses aimed to identify predictors of abnormal GerdQ scores among the PPINR profiles. For each analysis, bivariate differences in baseline clinical variables, physiologic data and questionnaire scores between participants with an abnormal GerdQ (≥ 8) versus normal GerdQ (<8) score were analyzed via two-tailed t-test or Mann Whitney U test for continuous variables as appropriate, and Chi Square analysis for categorical variables. P-values less than 0.05 were considered significant. All analyses were conducted using STATA 14.2 (College Station, TX).

Results

Participants

Over the study period 298 PPI non-responders underwent MII-pH and completed the questionnaire set (99 off PPI and 199 on PPI). One hundred six met exclusion criteria (12 with a history of scleroderma, 34 for pre/post lung transplant, 10 without complete GerdQ scores, and 50 with a major motility disorder). Thus, this data analysis includes 192 participants (67 off PPI and 125 on PPI).

Primary Analysis – MII-PH on PPI Therapy

Baseline Characteristics—Based on MII-pH on PPI results, the 125 participants were grouped as follows: 72 (58%) -AET/-SRA, 42 (34%) +AET, and 11 (9%) -AET/+SRA. Table 1 displays the baseline characteristics of these cohorts. The groups were balanced with regards to distribution of age and sex. Notably, the +AET cohort had a higher proportion of hiatal hernias greater than 3cm in size (33% vs 8%, $p < 0.01$) and symptoms of heartburn (69% vs 42%, $p = 0.02$) compared to the -AET/-SRA group. Compared to the -AET/-SRA group both the +AET and -AET/+SRA groups had significantly lower EGJ contractile integrals (71.4 ± 49.7 vs 49.7 ± 47.4 and 43.6 ± 24.9 mmHg, $p < 0.05$ for both comparisons). With regards to questionnaire data, the BEDQ score was significantly higher in the +AET group (8.2 ± 7.8) compared with the -AET/-SRA group (4.5 ± 6.7 ; $p = 0.02$).

Predictors of Abnormal GerdQ Score Among PPI Non-responder Profile

Among the –AET/–SRA group 63% had an abnormal GerdQ (8). Compared to those with a normal GerdQ, the –AET/–SRA group with an abnormal GerdQ was younger (53.3 ± 15.1 vs 46.6 ± 12.3 years, $p = 0.05$). There were no significant differences between physiologic data between. With regards to questionnaire results, the –AET/–SRA group with an abnormal GerdQ compared to those with a normal GerdQ reported a significantly higher mean RSI score (24.9 ± 10.8 vs 15.5 ± 9.2 , $p < 0.01$), median IDQ score (8 (1–14) vs 1 (0–4), $p < 0.01$), mean BEDQ score (5.7 ± 7.6 vs 2.2 ± 3.4 , $p = 0.04$), higher mean PROMIS QOL score (24.3 ± 10.8 vs 18.1 ± 9.3 , $p = 0.02$), and higher median BSI score (10 (8.5–23.5) vs 5 (1–11), $p = 0.02$). (Table 2).

Among the +AET group 64% had an abnormal GerdQ. Compared to those with a normal GerdQ, the +AET group with an abnormal GerdQ more often presented with heartburn (47% vs 81%, $p = 0.02$) and regurgitation (7% vs 41%, $p = 0.02$). Those with an abnormal GerdQ had significantly higher number of reflux associated symptoms (0.5 ± 0.9 vs 3.9 ± 6.0 , $p = 0.04$) and greater proportion with a positive symptom-reflux association (17% vs 58%, $p = 0.02$) on MII-pH testing, as well as a significantly lower DCI (1786 ± 1141 vs 910 ± 1010 mmHg-s-cm, $p = 0.05$). There were no significant differences between questionnaire scores.

Among the 11 RHS participants, 8 (73%) had an abnormal GerdQ score. Descriptive data is available in Supplemental Table 1. Given the small sample size, further analysis of this cohort was not conducted.

Post-hoc Analysis – MII-pH off PPI Therapy

Based on MII-pH results off PPI therapy, the 67 participants were grouped as follows: 39 (58%) functional, 16 (24%) GERD, and 12 (18%) RHS. Compared with the GERD and RHS groups, the functional group had a higher proportion of females (44%, 58%, vs 74%, respectively, $p = 0.07$). Among the functional group, 29% had a normal GerdQ score, whereas among the GERD group only 1 patient had a normal GerdQ score and among the RHS group no participants had a normal GerdQ score. Thus, predictors of abnormal GerdQ score were only examined among the functional group.

Predictors of Abnormal GerdQ Score Among PPI Non-responder Functional Profiles

Compared to those with a normal GerdQ, functional participants with an abnormal GerdQ less often presented with laryngeal complaints (47% vs 6%, $p < 0.01$). There were no significant difference between physiologic testing. With regards to questionnaire scores, the functional participants reporting an abnormal GerdQ had higher IDQ scores and PROMIS Global QOL scores, though not statistically significant.

Discussion

A primary treatment goal in the management of PPI non-response is reduction of patient-reported symptom severity. However, PPI non-responders are not one in the same, and symptom genesis in functional heartburn undoubtedly differs than symptom genesis in PPI

refractory GERD. As such, individualized treatment approaches for PPI non-responder phenotypes are essential to improving patient-reported outcomes. In this prospective observational study of 192 PPI non-responders, we examined factors associated with symptom perception within PPI non-responder phenotypes based on MII-pH monitoring results. Heightened symptom severity in the functional (–AET/–SRA off PPI) and functional +/- GERD overlap (–AET/–SRA on PPI) groups was associated with greater perceptions of dysphagia and impaired quality of life whereas physiologic data did not differ by symptom severity. Conversely, symptom severity in the PPI refractory GERD (+AET on PPI) or GERD (+AET off PPI) group was associated with physiologic differences such as symptom-reflux association and reduced esophageal contractility (Figures 1 & 2). These results suggest that mechanisms of symptom perception are heterogeneous across PPI non-responder phenotypes, and individualizing therapies for PPI non-responder phenotypes is of therapeutic value.

Keefer et al. previously demonstrated that esophageal hypervigilance, the heightened awareness of esophageal discomfort coupled with behavior out of proportion to the symptom experience, is elevated among PPI non-responders, regardless of physiologic profile¹⁸. This important work recognizes hypervigilance as a therapeutic target of PPI non-response across all levels of acid burden. In addition, prior studies report an association between symptom severity, and higher levels of anxiety and reduced QOL among GERD patients^{19,20}. Yet, there is a paucity of work exploring factors associated with the patient's symptom experience within PPI non-responder phenotypes.

More than one-third of all PPI non-responders in this study reported abnormal reflux symptom burden despite normal MII-pH profiles; 11 off PPI therapy and 27 on PPI therapy. According to Rome IV, these groups represent functional ($\pm$ GERD overlap) patients²¹. This is not only a prevalent group, but also a mechanistically complex and therapeutically challenging population. While psychological factors are commonly associated with functional heartburn, published studies supporting this notion are scarce²¹. In our study, patients with negative pH results perceived symptoms in association with reduced QOL and greater psychosocial distress, rather than in association with objective findings on MII-pH. These results underscore the importance of reassurance, psychosocial support and coping mechanisms for this particular population. Interestingly, abnormal symptom severity was also related to perceptions of dysphagia, as measured by the IDQ and BEDQ despite the majority demonstrating normal motility on manometry. These results support the idea that functional heartburn and functional dysphagia exist on the same reflux spectrum²¹. As such, use of nonpharmacologic measures recommended for the management of functional dysphagia – such as eating upright, avoiding trigger items, careful chewing of food, and chasing food with liquids – may be a reasonable treatment approach in functional heartburn patients who experience elevated levels of reflux symptoms²¹.

A demonstrable portion of PPI non-responders had abnormal acid exposure on PPI therapy, and met criteria for PPI refractory GERD²¹. Among patients with PPI refractory GERD, increased symptom perception was associated with higher symptom-reflux association and a greater number of reflux associated symptoms on MII-pH monitoring. In fact, 0 patients reporting normal symptom severity had a positive symptom-reflux association whereas 30%

of patients reporting elevated symptom severity had a positive symptom-reflux association. In addition, symptom severity among PPI refractory GERD patients was associated with lower esophageal contractility, suggesting a reduced clearance of refluxate. Conversely, psychosocial factors were not related to symptom perception among patients with PPI refractory GERD. These results suggest that actual reflux events contribute to symptom perception, rather than psychosocial and environmental factors, in patients with PPI refractory GERD. Thus, anti-reflux management strategies such as increased acid suppression, reflux inhibition, and restoration of the anti-reflux barrier are appropriate treatment considerations for PPI refractory GERD patients experiencing troublesome symptoms.

Separate from functional heartburn, reflux hypersensitivity requires a positive symptom-reflux correlation on pH testing; however, current perspectives such as Rome IV posit that reflux hypersensitivity is more akin to functional heartburn than GERD²¹. As expected, a small proportion of patients in this study with reflux hypersensitivity reported normal symptom severity. As a result, the groups were underpowered to detect associations between symptom severity and physiologic or psychosocial factors.

Strengths of this study include the prospective study design, classification of patients based on objective and patient-reported outcome data, and sample size. Since the group of patients with normal MII-pH results on PPI therapy represent a mix of pure functional and functional + PPI controlled GERD overlap, we performed a post-hoc analysis including patients with normal MII-pH results off PPI therapy in order to include a pure functional group. Since certain questionnaires, such as the BSI, were introduced later in the study period, multivariable regression modeling to identify independent predictors of elevated symptom severity was not possible. Finally, this observational study is inherently unable to measure causality between factors and the outcome of interest. Regardless of these limitations, our results support the interplay between psychosocial factors and symptom generation for PPI non-responders with normal physiology.

In conclusion, this prospective cohort analysis highlights variables associated with symptom perception according to PPI non-responder phenotype. Increased symptom perception among PPI non-responders with normal MII-pH results was associated with perceptions of dysphagia, psychosocial distress and reduced QOL. On the other hand, increased symptom perception in PPI refractory GERD was associated with objective symptom-reflux association rather than psychosocial stressors and QOL impairment. These results are important to understanding PPI non-responder phenotypes and formulating personalized management strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: RY: Supported by NIH T32DK101363.

Abbreviations

PPI	Proton pump inhibitor
QOL	Quality of life
AET	Acid exposure time
RHS	Reflux hypersensitivity
GERD	Gastroesophageal reflux disease
RSI	Reflux symptom index
IDQ	Impaction-dysphagia questionnaire
BEDQ	Brief esophageal dysphagia questionnaire
PROMIS	Patient-reported outcomes measurement information system
DIS	discomfort intolerance scale
HVS	heartburn vigilance scale
BSI	brief symptom inventory
IQR	Interquartile range
MII-pH	multichannel intraluminal impedance and pH monitoring

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Study Highlights

1. WHAT IS CURRENT KNOWLEDGE

- Up to 50% of patients with reflux symptoms do not respond adequately to proton pump inhibitor (PPI) therapy.
- Despite normal physiologic profiles, PPI non-responders often perceive elevated levels of reflux symptoms.
- Understanding drivers of symptom perception among PPI non-responder phenotypes is needed.

2. WHAT IS NEW HERE

- In PPI non-responders with normal physiology, symptom perception is associated with psychosocial distress and quality of life impairment.
- Alternatively, in PPI refractory GERD symptom perception is associated with symptom-reflux correlation.

Figure 1.

Questionnaire scores by symptom severity according to PPI non-responder profile. Among functional (+/- GERD overlap), symptom severity is associated with a higher IDQ score and QOL score. * $p < 0.05$, † $p < 0.10$

Figure 2.

Physiologic data by symptom severity according to PPI non-responder profile. Among PPI refractory GERD patients, symptom severity is associated with number of reflux associated symptoms and a lower distal contractile integral. * $p < 0.05$, † $p < 0.10$

Table 1

Baseline data, 24 pH-impedance results on PPI therapy, and questionnaire scores by PPI non-responder cohort.

	Normal (n = 72)	Abnl AET (n = 42)	RHS (n = 11)	P-value
Baseline Characteristics				
<i>Age, years</i>	49.1 ± 13.7	49.9 ± 14.1	43.2 ± 19.6	0.38
<i>Female sex</i>	49 (68%)	23 (55%)	9 (82%)	0.17
<i>Hiatal hernia > 3cm</i>	5 (8%)	12 (33%) [†]	2 (20%)	< 0.01
<i>Size of hiatal hernia</i>	0.5 ± 1.0	1.7 ± 1.8 [†]	1.3 ± 1.3	< 0.01
Symptoms				
<i>Heartburn</i>	30 (42%)	29 (69%) [†]	6 (55%)	0.02
<i>Regurgitation</i>	19 (26%)	12 (29%)	5 (45%)	0.43
<i>Chest pain</i>	11 (15%)	7 (17%)	0 (0%)	0.36
<i>Cough</i>	11 (15%)	5 (12%)	2 (18%)	0.83
<i>Dysphagia</i>	3 (4%)	2 (5%)	0 (0%)	0.77
<i>Laryngeal complaints</i>	11 (15%)	2 (5%)	1 (9%)	0.22
24 pH-impedance results				
<i>Total acid exposure time</i>	1.5 ± 1.4	15.1 ± 9.0 [†]	1.7 ± 1.5 [‡]	<0.01
<i>Number of reflux episodes</i>	28.5 ± 21.0	39.9 ± 45.3	66.4 ± 45.6 [†]	<0.01
<i>Number of reflux associated symptoms</i>	0.9 ± 1.7	2.7 ± 5.1	11.9 ± 22.8 ^{†‡}	<0.01
<i>Positive symptom-reflux association</i>	0 (0%)	8 (19%) [†]	11 (100%) ^{†‡}	<0.01
Upper endoscopy results				
<i>Normal esophagus and no hernia</i>	42 (59%)	19 (45%)	3 (26%)	0.10
<i>Hiatal hernia</i>	14 (20%)	13 (31%)	2 (23%)	0.34
<i>Los Angeles Grade A or B esophagitis</i>	5 (7%)	6 (14%)	1 (12%)	0.39
<i>Los Angeles Grade C or D esophagitis, or Barrett's Esophagus</i>	6 (9%)	3 (7%)	1 (12%)	0.97
High resolution esophageal manometry				
<i>Mean distal contractile integral (mmHg-s-cm)</i>	1915 ± 1685	1136 ± 1097	1795 ± 1606	0.07
<i>Median integrated relaxation pressure (mmHg)</i>	11.1 ± 7.4	8.8 ± 5.4	9.2 ± 5.7	0.18
<i>EGJ contractile integral (mmHg)</i>	71.4 ± 49.7	49.7 ± 47.4 [†]	43.6 ± 24.9 [†]	<0.01
<i>Normal esophageal motility</i>	46 (64%)	10 (23%) [†]	1 (12%) [†]	<0.01
<i>Minor motility disorder</i>	26 (36%)	16 (39%)	1 (12%)	0.17
Questionnaire results				
<i>GerdQ</i>	9.6 ± 2.7	9.6 ± 2.8	10.6 ± 2.3	0.51
<i>Abnormal GerdQ</i>	45 (63%)	27 (64%)	8 (73%)	0.80
<i>Reflux symptom index, (n=119)</i>	21.4 ± 11.2	20.8 ± 13.4	26.6 ± 8.2	0.33
<i>Impaction dysphagia questionnaire (n=121)</i>	8.0 ± 10.5	11.0 ± 10.5	7.9 ± 6.1	0.33
<i>Brief esophageal dysphagia questionnaire (n=120)</i>	4.5 ± 6.7	8.2 ± 7.8 [†]	8.9 ± 8.2	0.02

	Normal (n = 72)	Abnl AET (n = 42)	RHS (n = 11)	P-value
<i>PROMIS Global quality of life (n=120)</i>	21.8 ± 10.6	23.9 ± 10.7	22.0 ± 8.8	0.60
<i>Dysphagia intolerance scale (n=57)</i>	24.8 ± 6.3	26.8 ± 6.4	21.3 ± 4.9	0.21
<i>Brief symptom index (n=56)</i>	12.2 ± 11.9	10.3 ± 7.2	9.5 ± 4.8	0.75
<i>Hypervigilance scale (n=53)</i>	46.5 ± 32.8	42.4 ± 29.5	36.5 ± 33.0	0.80

P-value analyzed using ANOVA for continuous variables and Chi Square analysis for categorical variables.

[†]p < 0.05 compared to Normal.

[‡]p < 0.05 comparing Abnormal AET. Data presented as Mean ± Standard deviation, or n (%)

Esophagogastric junction (EGJ), Reflux hypersensitivity (RHS), Patient Reported Outcome Measurement Information System (PROMIS)

Table 2

Assessment of Risk Factors of Abnormal GerdQ Scores Among PPI Non-responders with Normal Acid Exposure and Negative Symptom Reflux Association While on PPI.

-AET/-SRA Cohort (N = 72)	GerdQ < 8	GerdQ ≥ 8	P-value
N (%)	27 (37%)	45 (63%)	
Baseline Variables			
<i>Age, years</i>	53.3 ± 15.1	46.6 ± 12.3	0.05
<i>Female sex</i>	17 (63%)	32 (71%)	0.47
<i>Hiatal hernia > 3cm</i>	2 (10%)	3 (8%)	0.78
<i>Size of hiatal hernia (cm)</i>	0.5 ± 1.0	0.5 ± 1.1	0.93
Symptoms			
<i>Heartburn</i>	9 (33%)	21 (47%)	0.27
<i>Regurgitation</i>	7 (26%)	12 (27%)	0.95
<i>Chest pain</i>	2 (7%)	9 (20%)	0.15
24h ph-impedance results			
<i>Total acid exposure time</i>	0.8 (0.2–1.6)	1.3 (0.2–3.0)	0.22
<i>Number of reflux episodes</i>	22 (11–32)	28 (13–38)	0.43
<i>Number of reflux associated symptoms</i>	0 (0–1)	0 (0–2)	0.10
High resolution esophageal manometry			
<i>Mean distal contractile integral (mmHg-s-cm)</i>	1911 ± 1715	1918 ± 1688	0.99
<i>Median integrated relaxation pressure</i>	12.2 ± 8.7	10.4 ± 6.3	0.36
<i>EGJ contractile integral (mmHg)</i>	80.7 ± 57.8	64.9 ± 42.7	0.24
Questionnaire results			
<i>GerdQ</i>	6.7 ± 1.0	11.4 ± 1.8	<0.01
<i>Reflux symptom index</i>	15.5 ± 9.2	24.9 ± 10.8	<0.01
<i>Impaction dysphagia questionnaire</i>	1 (0–4)	8 (1–14)	<0.01
<i>Brief esophageal dysphagia questionnaire</i>	2.2 ± 3.4	5.7 ± 7.6	0.04
<i>PROMIS global quality of life</i>	18.1 ± 9.3	24.3 ± 10.8	0.02
<i>Dysphagia intolerance scale</i>	23.8 ± 7.0	25.5 ± 5.9	0.46
<i>Brief symptom index</i>	5 (1–11)	10 (8.5–23.5)	0.02
<i>Hypervigilance scale</i>	20 (20–44)	43 (20–85)	0.16

P-values calculated via two-tailed t-test for normally distributed continuous variables, Mann-Whitney U test for non-parametric continuous variables, and Chi Square analysis for categorical variables. Data presented as Mean ± standard deviation, Median (Interquartile range), or n (%) as appropriate.

Proton pump inhibitor (PPI), Patient Reported Outcome Measurement Information System (PROMIS).

Table 3

Assessment of Risk Factors of Abnormal GerdQ Scores Among PPI Non-responders with Abnormal Acid Exposure Time While on PPI.

Abnormal Acid Exposure Time Cohort (N=42)	GerdQ < 8	GerdQ ≥ 8	P-value
N (%)	15 (36%)	27 (64%)	
Baseline Variables			
<i>Age, years</i>	50.8 ± 13.7	49.4 ± 14.5	0.77
<i>Female sex</i>	8 (53%)	15 (56%)	0.89
<i>Hiatal hernia > 3cm</i>	4 (40%)	8 (31%)	0.60
<i>Size of hiatal hernia, cm</i>	1.8 ± 2.1	1.6 ± 1.7	0.79
Symptoms			
<i>Heartburn</i>	7 (47%)	22 (81%)	0.02
<i>Regurgitation</i>	1 (7%)	11 (41%)	0.02
<i>Chest pain</i>	2 (13%)	5 (19%)	0.67
24h impedance-pH results			
<i>Total acid exposure time</i>	13.2 ± 7.0	16.2 ± 9.9	0.32
<i>Number of reflux episodes</i>	38.0 ± 27.7	40.9 ± 53.1	0.84
<i>Number of reflux associated symptoms</i>	0.5 ± 0.9	3.9 ± 6.0	0.04
<i>Positive symptom-reflux association</i>	0 (0%)	8 (30%)	0.02
High resolution esophageal manometry results			
<i>Mean distal contractile integral (mmHg-s-cm)</i>	1786 ± 1141	910 ± 1010	0.05
<i>Median integrated relaxation pressure</i>	10.4 ± 4.8	8.2 ± 5.6	0.34
<i>EGJ contractile integral (mmHg)</i>	58.2 ± 28.2	45.4 ± 52.7	0.52
Questionnaire results			
<i>GerdQ</i>	6.5 ± 1.1	11.4 ± 1.7	<0.01
<i>Reflux symptom index</i>	17.5 ± 12.9	22.9 ± 13.5	0.22
<i>Impaction dysphagia questionnaire</i>	7.9 ± 8.8	12.6 ± 11.1	0.17
<i>Brief esophageal dysphagia questionnaire</i>	2.6 ± 3.4	9.0 ± 7.9	0.09
<i>PROMIS global quality of life</i>	21.1 ± 10.1	25.5 ± 10.9	0.20
<i>Dysphagia intolerance scale</i>	27.0 ± 7.2	26.6 ± 6.0	0.90
<i>Brief symptom index</i>	9.8 ± 7.0	10.7 ± 7.6	0.77
<i>Hypervigilance scale</i>	47.0 ± 30.4	39.6 ± 29.9	0.59

P-values calculated via two-tailed t-test for normally distributed continuous variables, Mann-Whitney U test for non-parametric continuous variables, and Chi Square analysis for categorical variables. Data presented as Mean ± standard deviation, Median (Interquartile range), or n (%) as appropriate.

Proton pump inhibitor (PPI), Patient Reported Outcome Measurement Information System (PROMIS)

Table 4

Predictors of PPI Non Responder Functional Profile (off PPI therapy)

	GerdQ <8	GerdQ ≥ 8	P-value
N (%)	11 (29%)	27 (71%)	
Baseline Characteristics			
<i>Age, years</i>	55.2 ± 14.8	50.3 ± 15.6	0.38
<i>Female sex</i>	13 (87%)	22 (71%)	0.24
<i>Hiatal hernia > 3cm</i>	1 (7%)	5 (17%)	0.39
<i>Size of hiatal hernia</i>	0.4 ± 1.0	0.7 ± 1.5	0.57
Symptoms			
<i>Heartburn</i>	4 (27%)	15 (48%)	0.16
<i>Regurgitation</i>	0 (0%)	5 (16%)	0.10
<i>Chest pain</i>	1 (7%)	7 (23%)	0.18
<i>Cough</i>	4 (27%)	1 (3%)	0.02
<i>Dysphagia</i>	0 (0%)	1 (3%)	0.48
<i>Laryngeal complaints</i>	7 (47%)	2 (6%)	<0.01
24 ph-impedance results			
<i>Total acid exposure time</i>	1.4 ± 1.7	1.9 ± 1.6	0.42
<i>Number of reflux episodes</i>	32.6 ± 16.9	32.9 ± 20.0	0.97
<i>Positive symptom-reflux correlation</i>	0 (0%)	0 (0%)	
High resolution esophageal manometry results			
<i>Mean distal contractile integral (mmHg-s-cm)</i>	1496 ± 1595	1412 ± 1366	0.87
<i>Median integrated relaxation pressure (mmHg)</i>	8.5 ± 5.9	9.2 ± 4.9	0.69
<i>EGJ contractile integral (mmHg)</i>	56.5 ± 27.5	44.0 ± 28.7	0.24
<i>Normal esophageal motility</i>	7 (47%)	15 (50%)	0.83
<i>Minor motility disorder</i>	4 (27%)	11 (37%)	0.50
<i>EGJ outflow obstruction</i>	4 (27%)	4 (13%)	0.27
Questionnaire data			
<i>GerdQ</i>	6.1 ± 0.6	10.1 ± 2.1	<0.01
<i>Reflux symptom index (n=35)</i>	19.4 ± 10.3	18.5 ± 13.0	0.84
<i>Impaction dysphagia questionnaire (n=31)</i>	1.4 ± 2.3	6.6 ± 8.8	0.14
<i>PROMIS global quality of life (n=36)</i>	12.1 ± 6.9	18.7 ± 11.1	0.09
<i>Dysphagia intolerance scale (n=18)</i>	19.0	23 ± 7.8	0.63
<i>Brief symptom index (n=18)</i>	12.0	12.8 ± 16.0	0.96
<i>Hypervigilance scale (n=8)</i>	59 ± 30.2	49.8 ± 12.7	0.56

P-value analyzed using ANOVA for continuous variables and Chi Square analysis for categorical variables.

† p < 0.05 compared to Normal.

‡ p < 0.05 comparing Abnormal AET. Data presented as Mean ± Standard deviation, or n (%)

Esophagogastric junction (EGJ), Reflux hypersensitivity (RHS), Patient Reported Outcome Measurement Information System (PROMIS)