

Proximal and Distal Gastric Retention Patterns in Gastroparesis and the Impact of Gastric Per Oral Endoscopic Myotomy: a retrospective Analysis Using Gastric Emptying Scintigraphy

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Key words: GPOEM, POP, gastroparesis, gastric emptying scintigraphy

Word count: 2597

ABSTRACT:

Introduction: Gastroparesis is a debilitating disease of insufficient gastric emptying and visceral hypersensitivity characterized by nausea, vomiting, early satiety and bloating. Gastric emptying scintigraphy (GES), in combination with typical symptoms and normal esophagogastroduodenoscopy, is used to diagnose the disease. Gastric per-oral endoscopic pyloromyotomy (G-POEM or POP) has emerged as a novel technique for treating gastroparesis with up to 80% success rate. This procedure involves a myotomy of the distal stomach. We hypothesize that responders to this therapy are characterized by more distal dysmotility when compared with non-responders, as defined by GES retention patterns. *Methods:* We use regional gastric emptying measurements from diagnostic GES to determine proximal or distal predominance of disease for each patient. We then compare treatment response and symptoms in each patient to total gastric half-emptying time, proximal gastric half-emptying time and a ratio comparing the two values. *Results:* 47 patients underwent G-POEM during the study period. A significant difference ($P < 0.01$) was found in proximal:total half-emptying time ratio between responders and non-responders. A significant difference between pre- and post-procedural proximal:total half-emptying time ratios were identified for each patient. No correlations were identified between motility patterns and symptoms or in motility patterns among the different etiologies of the disease. *Conclusion:* Proximal:total half-emptying time ratio may represent an important patient selection factor for G-POEM versus other

treatment modalities going forwards. Local retention patterns in GES may not inform symptom profile in gastroparesis.

Abbreviations: Gastric Emptying Scintigraphy (GES); Gastric Per-Oral Endoscopic Myotomy (G-POEM); Gastroparesis Cardinal Symptom Index (GCSI); Retention Index (RI)

INTRODUCTION:

Gastroparesis is a chronic disorder of gastric motility with debilitating symptoms, including nausea, vomiting, early satiety, bloating and distension. There are multiple etiologies, including diabetic, post-infectious, post-surgical and idiopathic. Current therapies include lifestyle and dietary modifications, medications (such as metoclopramide, domperidone and erythromycin), and procedural therapies (such as pyloric botulinum toxin, gastric electrical stimulation, pyloroplasty or subtotal gastrectomy), but none is particularly effective. (1-3)

The condition is diagnosed using a combination of typical symptoms, a gastric emptying study (GES) demonstrating abnormal food retention, and a normal esophagogastroduodenoscopy to rule out obstruction. (3) GES involves consuming a radioactive tracer in the form of a meal, with imaging to examine food retention at different time-points. While this study is typically used to assess global gastric function, it may also give insight into regional gastric motility and the underlying pathophysiologic mechanisms of gastroparesis, in particular by comparing proximal and distal food retention. (4-9) Specifically, half-emptying time ($T_{1/2}$) has been used to act as a proxy for global and regional stomach function. (7,9,10)

Multiple therapies aimed at the distal stomach have been developed, such as pyloric botulinum toxin and pyloric stenting. (2,11,12) Among these distally acting

therapies, gastric per-oral endoscopic pyloromyotomy (G-POEM or POP) has been recently introduced as a promising, novel therapeutic modality. (13-16) This procedure involves a small endoscopic incision into the antral muscle to reduce tone and promote gastric emptying, utilizing technical concepts similar to the per oral endoscopic myotomy (POEM) procedure for achalasia. (17) Despite exciting initial results of G-POEM, a subset of patients has disease refractory to the procedure. It is currently unclear what factors predispose a patient to successful G-POEM. (13-15)

The purpose of this study is to use GES to compare proximal and distal food retention patterns in patients who have undergone G-POEM and to explore correlations among local dysmotility patterns, symptomatology, and treatment effectiveness. We hypothesize that, as a distal therapy, it would stand to reason that those patients with primarily distal retention are most likely to receive benefit from G-POEM. (12,18) On the other hand, it is expected that those patients with a more proximal burden of disease would receive less benefit from this procedure. Additionally, we aim to identify a correlation between certain retention profiles and specific symptoms.

MATERIALS AND METHODS:

This is a retrospective study examining local motility patterns in patients with severe, refractory gastroparesis and the correlation to G-POEM success.

Refractory disease was defined as those patients who had failed lifestyle changes and at least two medical therapies. The study was approved by the Institutional Review Board (IRB) at Emory University. Beginning in June 2015, patients were evaluated as candidates for G-POEM, based on a protocol approved by the IRB. All patients who received G-POEM during the study period were included; liquid, oatmeal and anterior-imaging only studies were excluded. Only standard and comprehensive GES studies were included as described in the following.

Patients were diagnosed using a 4-hour gastric scintigraphy test in most cases, and all patients were requested to have a follow-up gastric emptying study about 2 months after G-POEM, as well. The GES used a protocol consistent with the Consensus Recommendations for Gastric Emptying Scintigraphy by the American Neurogastroenterology and Motility Society and the Society of Nuclear Medicine. (4) A Technetium (Tc)-99m sulfur colloid radiolabeled meal consisting of the egg-white equivalent of two large eggs, two slices of bread, and jam with water was administered. Imaging was performed in the anterior and posterior projections at 0, 1, 2, 3 and 4 hours. A geometric mean activity of decay-corrected counts in the two projections was calculated at each time point and represented the primary data used.

The G-POEM procedure was performed as has been previously described. (15) It was performed by an advanced endoscopist, frequently assisted by a trainee, with the patient under general anesthesia in the endoscopy suite. Following a routine esophagogastroduodenoscopy, the endoscopist performed a 2-cm incision into the gastric mucosa at the 5 o'clock position, approximately 5 cm from the pyloric ring. This was followed by dissection of submucosal fibers from the mucosal entry site to the pyloric ring and to form a submucosal tunnel. Following myotomy inside the tunnel, the tunnel was rinsed with saline and the mucosal entry site was closed with hemostatic clips.

Outcome measures were recorded using the Gastroparesis Cardinal Symptoms Index (GCSI), with follow-up at 1, 6, 12, 18, and 24 months when available. The GCSI is a validated tool for quantifying the severity of gastroparesis symptoms, using 3 categories and 9 subsets. (19) The categories include postprandial fullness/early satiety (4 subsets), nausea/vomiting (3 subsets), and bloating (2 subsets). Each subset is scored 0-5 with 5 for highest severity, and each symptom category is averaged for a total GCSI score ranging from 0-5. This score was obtained for each patient before the procedure and was used as a primary follow-up metric. Successful treatment response was defined as a reduction in total GCSI score of 1 points with a 25% reduction in at least 2 of the 3 subsets. (15)

Data collected for each patient include patient demographics, etiology of disease, and the GCSI metrics described above at 1-month, 6-month, 12-month and 24-month intervals as available.

GES from our institution were processed for 4-hour total gastric retention as well as proximal and distal retention. Only those studies performed at our institution were used for this advanced processing; those who did not have GES performed at our institution were diagnosed elsewhere and only global GES measurements were included. Regions of Interest were drawn manually on the Xeleris 3 Functional Imaging Workstation. The proximal and distal stomach was defined using the *incisura* as an anatomical landmark for each patient, such that the proximal stomach represents the fundus and the body. Examples are shown in Figure 1. Data recorded include tracer retention at 0, 1, 2, 3, and 4 hours as well as $T_{1/2}$ for the total stomach, proximal stomach and distal stomach.

Primary gastric-emptying data collected include total gastric, proximal gastric, and antral tracer kilicounts at each time point, as well as total gastric $T_{1/2}$, proximal gastric $T_{1/2}$, and the proximal:total $T_{1/2}$ ratio. The proximal:total gastric $T_{1/2}$ ratio was defined as the Retention Index (RI) for this study; therefore, a RI of 1 denotes completely proximal retention and a RI of 0 denotes completely pyloric retention. These data were compared between responders and non-responders and between idiopathic and diabetic disease etiologies using the student's T test. $P < 0.05$ was considered significant. These values were also compared to patient

symptoms before and after the procedure as well as symptom reduction from the procedure using Pearson correlations. All statistics were performed on Microsoft Excel.

RESULTS:

From June 2015 through October 2017, 47 patients had G-POEM performed at our institution. Demographics are shown in Table 1. Initial average GCSI was 3.52 with a SD of 0.69. Most of the patients responded to G-POEM therapy.

Of the 47 patients, 12 pre-procedure GES studies were included, 19 post-procedure GES studies were included, and 5 patients had GES studies from both before and after the procedure. Grubbs' Test for a single outlier was run for the pre-procedural total and proximal $T_{1/2}$ data, and one additional patient was excluded with $P < 0.001$. For the post-procedural total and proximal gastric $T_{1/2}$ data, Iglewicz and Hoaglin's robust test for multiple outliers was run for a modified Z score ≥ 3.5 , and two additional patients were identified as outliers and excluded. The outlier patients' data were incompatible with the remainder of the cohort's data or what would be expected, suggesting an improperly performed test or measurement error. An exclusion flowchart is demonstrated in Figure 2.

For all included patients, RI (the proximal:distal gastric $T_{1/2}$ ratio) was calculated both before and after the procedure. Pre-procedure RI by etiology is demonstrated in Table 2. No significant difference in RI was found between diabetic and idiopathic disease.

RI values did not inform symptoms' profile as presented in Figure 3.

5 patients (all of whom were responders to GPOEM) had GES studies performed at our institution and available for localized measurement both before and after the procedure. A 0.06 decrease in RI was found, which was shown to be statistically significant using a 2-tailed, paired student's T test. This data is represented in Table 3.

11 patients (10 responders, 1 non-responder) had total $T_{1/2}$ available before and after the procedure. Within this group, pre-procedure total gastric $T_{1/2}$ averaged 206.6 with a standard deviation of 75.2; post-procedure total gastric $T_{1/2}$ averaged 122.9 with a standard deviation of 36.7. This represents a reduction in $T_{1/2}$ of 83.7 minutes following the procedure. This reduction in gastric $T_{1/2}$ was statistically significant with a p-value of 0.0028.

Responders and non-responders were categorized as explained above with 23 responders and 16 non-responders at the latest available follow-up date. All other patients were not available for follow-up. Response rates were not significantly different by etiology.

Pre-procedure RI for responders ranged from 0.847 to 1.056 with an average of 0.924 and standard deviation of 0.0686. Pre-procedure RI for non-responders ranged from 0.705 to 0.829 with an average of 0.794 and standard deviation of 0.0593. This represents a 0.13 difference in RI between the two groups. The two averages were compared using a 2-tailed T test yielding a p-value < 0.01.

RI compared to GCSI reduction for each patient is displayed in Figure 4.

Post-procedure RI and reduction in RI for each patient was compared to total GCSI and each symptom category using Pearson correlations. These Pearson correlations were all non-significant, with values <0.01 .

When total gastric $T_{1/2}$ and proximal $T_{1/2}$ were compared to GCSI reductions, all Pearson correlations were < 0.01 . No significant difference was found in total gastric $T_{1/2}$, proximal $T_{1/2}$, or post-procedure RI between responders and non-responders. Results are shown in Table 4.

DISCUSSION:

The results of this study indicate that there is no major difference in RI among the many etiologies of gastroparesis. Diabetic and idiopathic gastroparesis are the two most common etiologies, both in this study and in the general population, and these two etiology groups had a nearly identical pre-procedural RI, without a significant difference between the two. The response rates between these two groups are very similar as well. This suggests that these etiologies of gastroparesis may follow similar pathophysiologic mechanisms as they have similar retention patterns and response rates to G-POEM. The fact that local motility patterns and response rates to the procedure are nearly identical between these two etiologies indicates that etiology should not be a major factor when considering who may benefit most from this procedure. Of note, all of the post-surgical patients responded to the procedure. There were not enough post-surgical patients with available pre-procedure GES to calculate a meaningful average RI.

The next finding is that there is no obvious correlation between local motility and symptomatology as expressed by the near-zero Pearson correlations between symptom score and RI, both before and after the procedure. This indicates that RI is not a useful metric for predicting a patient's symptoms. Indeed, some studies have suggested that proximal and distal dysfunction independently correlate to different symptom profiles of gastroparesis or functional dyspepsia.

(5, 21-23) However, neither proximal nor distal motility measurements in GES correspond to symptoms in this study.

Our analysis shows a significant change in RI for each patient following the procedure. In fact, every patient with available data had an increase in RI. This demonstrates that the procedure is achieving a clear and significant effect on gastric emptying; an increase in RI indicates either an increase in proximal $T_{1/2}$ or a decrease in total gastric $T_{1/2}$. Considering that the procedure acts distally, the latter mechanism is much more likely. This is confirmed, as we also demonstrate a clear reduction in total gastric $T_{1/2}$ following the procedure. This suggests that the procedure functions in a manner similar to our hypothesis: a reduction of tone lessens retention, decreasing total gastric $T_{1/2}$, increasing RI, and promoting emptying.

We show a clear and significant difference in pre-procedural RI between responders and non-responders. It needs to be noted that while statistically significant, this is a very small data set of five patients; however, as a novel procedure with limited research thus far, this still represents a valuable cohort size. In our study, the responder groups demonstrated a significantly higher RI or a more proximal retention pattern. This difference is the opposite of what we expected: an antral therapy should provide greatest benefit to those patients with primarily distal disease.

It is unclear why those patients with more proximal disease would receive the greatest benefit from therapy. One possibility is that rather than a longer $T_{1/2}$ in the proximal stomach, these patients are actually demonstrating a faster emptying in the entire stomach, perhaps indicating a less severe disease at presentation. It would stand to reason that patients with less severe motility defects are less likely to be refractory to the procedure. However, no significant difference in absolute proximal or total $T_{1/2}$ between the two groups was identified.

Another possibility is that while the procedure decreases pyloric tone, it may simultaneously disrupt antral motility. One primary mechanism of gastroparesis that has been suggested is pylorospasm, which is often coupled with antral hypomotility. (12, 24) Assuming this mechanism, patients with a more distal burden of disease may have greater antral hypomotility at baseline. They would thus be more sensitive to further antral disruption. Patients with a more proximal burden of disease may be less likely to have significant antral dysmotility before the procedure and would thus be less sensitive to this negative sequela. Further research into this concept is necessary for us to understand the pathophysiology of gastroparesis as well as how the G-POEM procedure works on a functional basis.

Regardless of the underlying pathophysiology, RI demonstrates significant promise as a patient-selection factor going forwards. In fact, all of the patients in

the responder group had a RI greater than 0.838, while all patients in the non-responder group had a value less than this number, or a more distal pattern of retention. This is displayed in Figure 4 with the dashed line representing this cutoff value. A prospective study comparing outcomes of patients with RI greater than and less than the above-listed value would be an important study to identify appropriate candidates for this procedure and help further to develop the current gastroparesis treatment algorithm.

CONCLUSION

In conclusion, our study finds that patients with a more proximal burden of gastroparesis are more likely to benefit from G-POEM. The calculated RI based on local gastric motility measurements shows significant promise as a possible tool in determining who should receive this procedure, but warrants further investigation before implementation into clinical practice. Some limitations of this study include sample size and a lack of healthy control patients. As this is a novel procedure, there is a limited number of patients available for study. This must be addressed as the procedure gains popularity and more gastroenterologists are trained to perform it. Additionally, many patients only had GES from outside institutions available to us, which we could not process for local motility measurements. While the sample size is small, our results are significant and suggest that further research into this topic across multiple centers may yield promising results for future patient selection. This investigation only involved patients with gastroparesis, who by definition will have GES

abnormalities. A more thorough analysis is needed to compare these patients' motility values to those of healthy controls without disease. Finally, the retrospective and single-center nature of this trial brings limitations, and a more robust analysis should be performed in a prospective nature.

AUTHOR CONTRIBUTIONS:

RS: Collected patient demographics and data pertaining to the procedure from PowerChart. Collected quality-of-life and symptom data by calling patients and conducting surveys. Performed literature review. Performed image post-processing and data calculation. Performed statistical analysis. Wrote and edited final manuscript.

YZ: Performed image post-processing, edited the manuscript.

PM and SD: Collected patient demographics and data pertaining to the procedure from PowerChart. Collected quality-of-life and symptom data by calling patients and conducting surveys, edited the manuscript.

JG and RH: Trained RS and YZ on post-processing imaging. Created proximal and distal gastric emptying study, edited the manuscript.

QC: created study concept, initiated the study, Wrote IRB. Designed study, performed all G-POEM procedures. Edited the manuscript.

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Etiology	Male	Female	Total	Average Age
Idiopathic	1	18	19	43 ± 12
Diabetic	1	14	15	48 ± 16
Post-surgical	2	3	5	66 ± 11
Post-infectious	0	2	2	29 ± 7
Post-XRT	1	0	1	52
Ehlers-Danlos	0	1	1	33
Unrecorded	1	3	4	54 ± 6
Total	6	41	47	47 ± 15

Table 1. Patient demographics by etiology. XRT = radiation therapy. Ages expressed as average ± standard deviation.

Etiology	Average Pre-Procedural RI
Idiopathic	0.877 ± 0.12
Diabetic	0.872 ± 0.052
Total	0.880 ± 0.090

Table 2. Average pre-procedural RI by etiology. RI expressed as average ± standard deviation.

Pt #	RI Pre-G-POEM	RI Post-G-POEM
1	0.973	0.847
2	1.052	0.952
3	1.090	1.057
4	0.882	0.858
5	0.936	0.898
Average \pm SD	0.987 \pm 0.0847	0.922 \pm 0.0856

Table 3. RI before and after G-POEM in patients with both studies available.

	Responders	Non-Responders	P-value
Pre-GPOEM TGT _{1/2}	169 ± 42	218 ± 80	0.11
Pre-GPOEM PGT _{1/2}	149 ± 37	141 ± 27	0.68
Post-GPOEM TGT _{1/2}	131 ± 42	108 ± 37	0.31
Pre-GPOEM RI	0.924 ± 0.069	0.794 ± 0.059	0.006
Post-GPOEM RI	0.924 ± 0.070	0.886 ± 0.070	0.19

Table 4. Absolute T_{1/2} compared between responders and non-responders expressed as average ± standard deviation. TGT_{1/2} = Total Gastric Half Emptying Time. PGT_{1/2} = Proximal Gastric Half-Emptying Time. There was insufficient complete data to compare Post-GPOEM PGT_{1/2} between responders and non-responders.

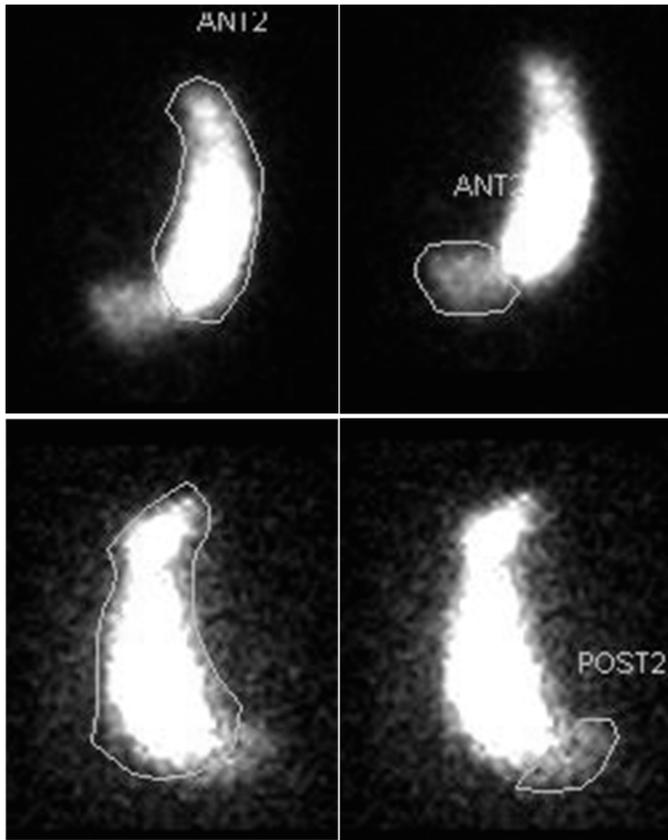


Figure 1. Example of ROI selection, using the *incisura* as an anatomical landmark. Top-left: Proximal stomach in the anterior view. Top-right: distal stomach in the anterior view. Bottom-left: proximal stomach in the posterior view. Bottom-right: distal stomach in the posterior view.

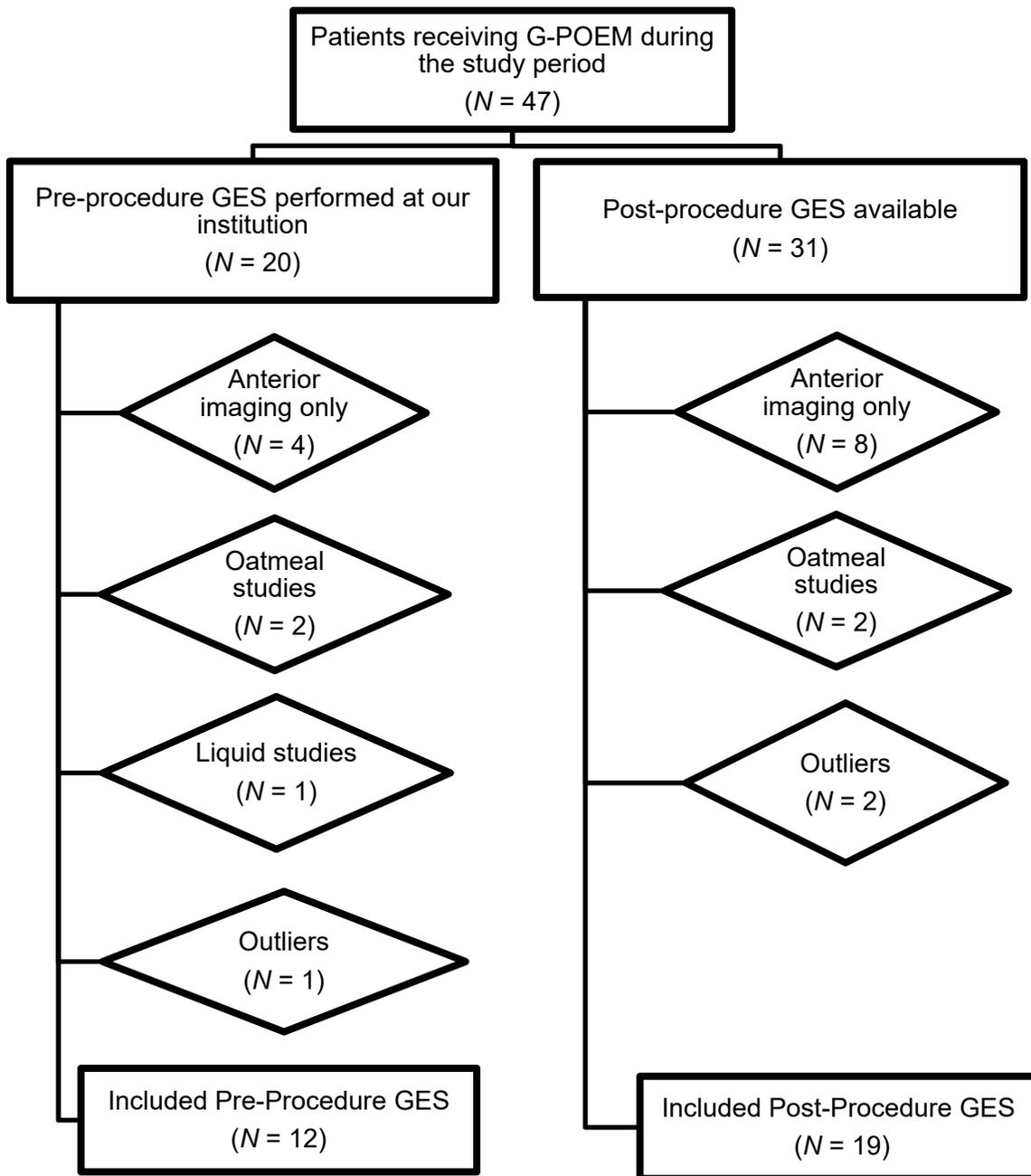


Figure 2. Flowchart reflecting patient exclusion from this study.

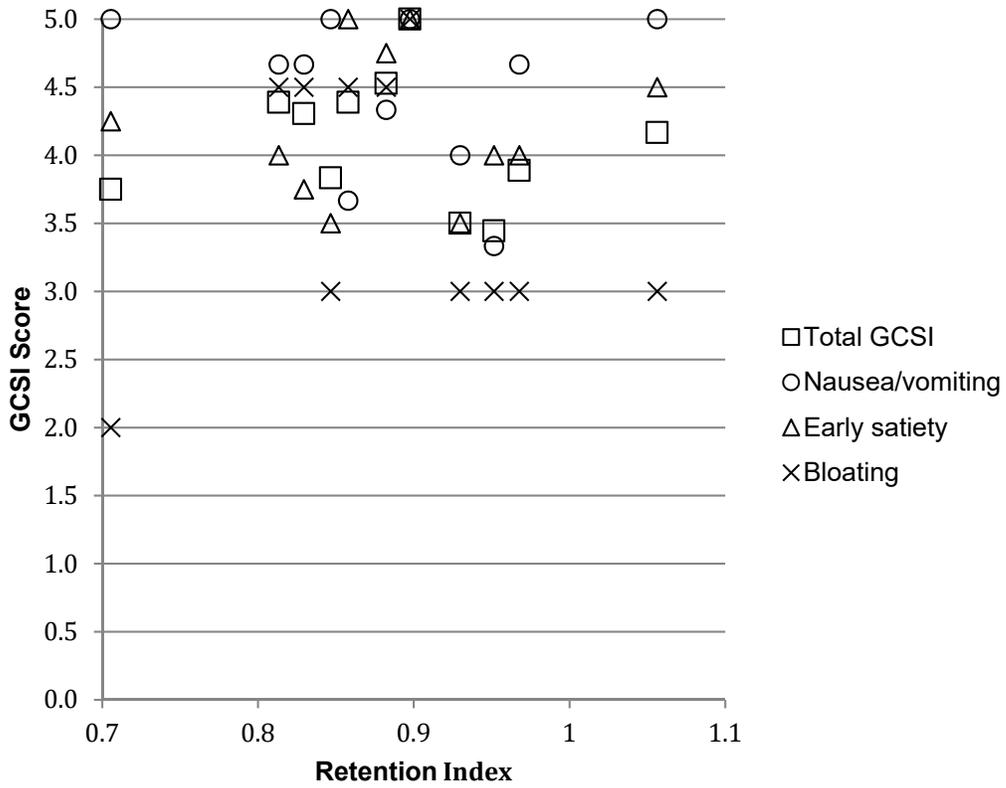


Figure 3. Total GCSI and Symptom Categories vs. RI for each patient.

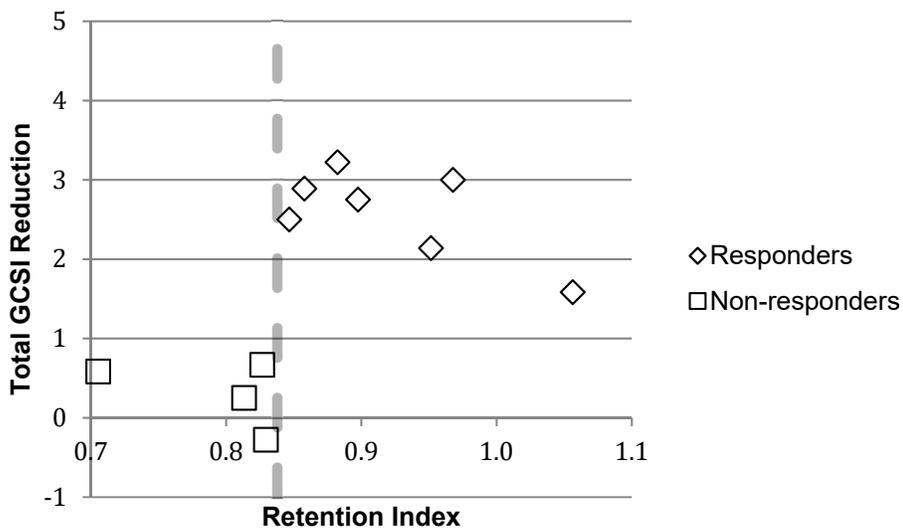


Figure 4. GCSI Reduction vs. Pre-Procedural RI. Dashed line represents RI value of 0.838.