



Delayed gastric emptying time among patients with refractory GERD using gastric scintigraphy: A pilot study

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Abstract

Introduction: For patients with gastroesophageal reflux disease (GERD) refractory to acid-suppressive treatment, evaluation for the presence of gastroparesis should be considered since delayed gastric emptying may possibly aggravate symptoms of heartburn, regurgitation, and other symptoms that may overlap with GERD. Studies concerning gastric emptying in GERD have long since provided conflicting results. **Objectives:** To determine the gastric emptying time using gastric scintigraphy in typical and refractory GERD and to determine whether delayed gastric emptying can predict severity and frequency of symptoms in GERD.

Methods: A pilot study was done between October 2019 and November 2022 wherein 30 patients were recruited with 15 patients classified as typical GERD and 15 patients as refractory GERD. Patients were asked to complete a closed ended questionnaire which included Gastroparesis Cardinal Symptom Index (GCSI), GERD impact score (GIS), and the Quality of Life and Reflux and Dyspepsia (QOLRAD). All patients underwent gastric emptying scintigraphy at St. Luke's Medical Center Quezon City, Department of Nuclear Medicine. Delayed gastric emptying was defined as more than 60% of solid meal remaining at 2 hours, or more than 10% remaining at 4 hours.

Results: The mean age of the patients was 41.1 ± 11.86 years. 53.3% (n=16) of the patients were female. Overall, out of 30 patients, 2 patients (6.7%) had delayed gastric emptying, 3 (10%) had rapid gastric emptying and normal results for the rest of the patients (83%). In the refractory GERD group, there was 1 patient (6.7%) with delayed gastric emptying and 1 patient (6.7%) with rapid gastric emptying. While in the typical GERD group, 1 patient (6.7%) had delayed gastric emptying and 2 patients (13.3%) had rapid gastric emptying. There was no statistically significant difference in the gastric emptying time between typical and refractory GERD ($p=0.830$). Symptom scores between refractory and typical GERD were statistically significant based on the QOLRAD score ($p=0.004$). There was no significant difference in the GCSI ($p=0.075$), QOLRAD ($p=0.722$) and GIS ($p=0.455$) scores among those with delayed, rapid and normal gastric emptying.

Conclusion: This pilot study showed that there was no significant difference in gastric emptying time between typical and refractory GERD. Among patients with delayed gastric emptying time, there was no difference with regards to the severity of gastrointestinal symptoms among patients with typical and refractory GERD. However, the quality of life among patients with refractory GERD was worse in patients with typical GERD. A multidisciplinary approach to therapy can be employed to improve the quality of life among these patients.

Keywords: Refractory GERD, Delayed Gastric Emptying Time, Gastric Emptying Scintigraphy

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Introduction

Unresponsiveness to aggressive proton pump inhibitor therapy remains a common problem among GERD patients as up to 45% of the diseased population report persistent, troublesome, refractory symptoms, as based on some observational primary care and community-based studies.¹ Based from the 2013 American College of Gastroenterology, evaluation for the presence of gastroparesis should be considered in patients with GERD that is refractory to acid suppressive treatment since delayed gastric emptying may possibly aggravate symptoms of heartburn, regurgitation, and other symptoms associated with GERD.² The gold standard method of measuring gastric emptying time is gastric emptying scintigraphy,³ which was employed in this study. A recent systematic review of 9 studies found that those with persistent reflux symptoms despite PPI therapy had a reduced health-related quality of life, with 8-16% lower scores on physical health, and 2-12% lower scores on mental health.⁴ Among the many factors involved, delayed gastric emptying has been reviewed to potentially affect treatment response among GERD patients on proton-pump inhibitor therapy, although recent studies remain scarce.⁵

This pilot study was done to investigate gastric emptying in patients with typical and refractory GERD as it may provide an impetus for future targets for non-PPI therapies towards a more effective management of refractory GERD. Being a pilot study, preliminary data gathered may help determine the feasibility of conducting this study on a larger scale and help identify potential issues and pertinent modifications in the research methodology.

Review of Related Literature

GERD is one of the most common outpatient diseases encountered by primary care physicians and gastroenterologists on a daily basis. Over the past decades, proton-pump inhibitors have been the gold standard and mainstay of management of GERD. Despite its increased use, there remains a challenge in the management amongst those with refractory GERD symptoms with partial or complete lack of response to PPI therapy. In a 2014 systematic review of epidemiologic studies, the range of GERD prevalence estimated to be 18.1% - 27.8% in North America, 8.8% - 25.9% in Europe, 2.5% - 7.8% in East Asia, 8.7% -

33.1% in the Middle East, 11.6% in Australia and 23.0% in South America. Among the different regions, North America and East Asia were found to have a significant increase in GERD prevalence.⁶

The diagnosis of GERD can often be made clinically especially for those presenting with typical symptoms of heartburn and acid regurgitation. In the absence of alarm features, empiric therapy with PPI can be started and upper endoscopy is not required for diagnosis.⁷ However, the definition of refractory GERD has no established consensus. A recent international guideline defines refractory GERD as GERD that is unresponsive to standard dose PPI therapy for at least 8 weeks.⁸ Local guidelines suggest evaluating refractory GERD in patients who failed to achieve symptom control and/or healing of esophagitis with PPI twice daily for at least 8 weeks. It also suggests ascertaining patient compliance and correct timing of PPI therapy prior to considering refractory GERD.⁹ Recent advances in the understanding of this disease involves investigation into medication non-compliance, differences in PPI metabolism, residual acid reflux or acid pocket, non-acid reflux/weakly acidic/alkaline reflux, mechanisms such as transient lower esophageal sphincter relaxation, lower esophageal sphincter pressure, and gastroparesis as seen in variable subset of patients who suffer from refractory GERD.¹⁰ Studies also suggest investigation of refractory symptoms that includes upper endoscopy to exclude non-reflux esophageal disorders and further evaluation through 24-hour ambulatory pH-impedance monitoring and/or esophageal manometry.⁸ A recent multimodality structural and functional evaluation involving 275 GERD patients who had failed empiric PPI therapy showed that 40% had non-esophageal reflux disease, 19.3% had erosive esophagitis, 16% had functional heartburn, 5.8% had gastroparesis, and 5.8% with other esophageal dysmotility.¹¹ Among the various etiologies, the prevalence of gastroparesis in refractory GERD was noted by other studies as well. Delayed gastric emptying occurs in 10 - 33% of GERD patients.¹² In the subset of those with refractory symptoms, anywhere between 8 to 10% additionally suffer from gastroparesis.¹³ In a study comparing clinical characteristics of responders and non-responders of reflux patients on PPI therapy, those who have gastroparesis symptoms have significantly reduced

odds of being a responder to PPI. Using the validated Gastroparesis Cardinal Symptom Index (GCSI) questionnaire, gastroparesis symptoms that were classified as severe were 2-fold more frequently in the subgroup of patients who failed twice daily PPI regimen versus patients who fully responded to PPI once daily ($P = 0.010$) or patients who failed PPI once daily ($P = 0.042$).⁵

Study Objective:

To determine the gastric emptying time in typical versus refractory GERD using gastric scintigraphy and to determine whether delayed gastric emptying can predict severity and frequency of symptoms in GERD.

Methodology:

Study Design

A pilot study was conducted via convenience sampling from October 2019 to November 2022 wherein patients were recruited from St. Luke's Medical Center Quezon City (SLMC-QC) social service and private outpatient clinics.

Criteria for participant selection

Inclusion Criteria were as follows:

1. Typical GERD group: patients who were at least 18 years of age, clinically diagnosed with GERD who presented with symptoms of acid regurgitation and heartburn without alarm features, responded fully with once daily dosing of PPI therapy for a maximum of 8 weeks
2. Refractory GERD group: patients who were at least 18 years of age, with GERD who presented with symptoms of acid regurgitation and heartburn but did not respond or partially responded with once or twice daily dosing of PPI therapy for at least 8 weeks
3. Duly signed informed consent form

Exclusion Criteria were as follows:

1. Previous acute viral infection for at least a month, presence of a neurological condition or disease, prior esophageal, gastric, or

bariatric surgery, intake of narcotic opiate analgesics, anticholinergic agents and GLP-1 medications, and those who were noncompliant to PPI therapy

2. Patients with alarm features:
 - a. new onset dyspepsia in patient ≥ 60 years
 - b. evidence of gastrointestinal bleeding (hematemesis, melena, hematochezia)
 - c. iron deficiency anemia
 - d. unexplained weight loss
 - e. dysphagia
 - f. odynophagia
 - g. persistent vomiting
 - h. gastrointestinal cancer in a first-degree relative

Operational Definitions

Gastroesophageal Reflux Disease (GERD) - patients who presented with symptoms of acid regurgitation and heartburn

Typical GERD - patients whose heartburn or acid regurgitation responded to once daily dosing of PPI therapy within 8 weeks

Refractory GERD - patients with symptoms of heartburn and acid regurgitation who did not respond or partially responded to once or twice daily dosing of PPI therapy for at least 8 weeks

Delayed gastric emptying – more than 60% of the solid meal remaining at 2 hours, or more than 10% of the meal remaining at 4 hours by gastric scintigraphy¹⁴

Normal gastric emptying – greater than or equal to 70% meal retention at 30 minutes, 30% to 90% meal retention at one hour, less than or equal to 60% meal retention at two hours and less than or equal to 10% meal retention at four hours¹⁴

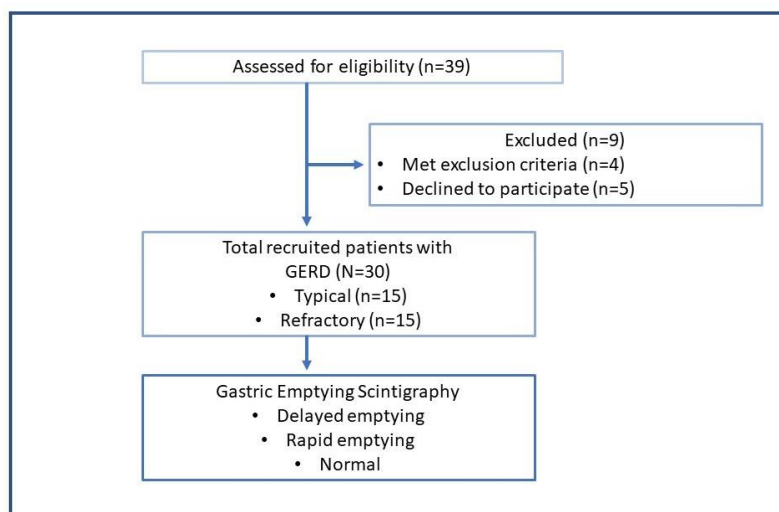
Rapid gastric emptying - when there is less than 70% solid meal retention at 30 minutes, or less than 30% solid meal retention at 1 hour¹⁴

Description of Study Procedure

The study recruited patients through convenience sampling until at least 30 patients were reached with 15 participants for each group. A total of 39 patients were screened for eligibility. Nine participants were excluded in the study, with 5 declining to participate in the study and 4 patients having met the exclusion criteria (Figure 1). Patients were recruited from SLMC QC social service department and private outpatient clinics. Upon identification of a possible study recruit, the co-investigators called the identified patient and explained the study procedure with the necessary

preparation for gastric scintigraphy and obtained informed consent. Patients were interviewed using a closed-ended questionnaire which included information regarding: age, sex, comorbidities, such as hypertension, diabetes, coronary artery disease, obesity, asthma, and hypercholesterolemia, family history of GERD, personal and social history of tobacco and alcohol use, type of PPI, and severity of GERD symptoms using the Gastroparesis Cardinal Symptom Index (GCSI), Quality of Life and Reflux and Dyspepsia (QOLRAD) and GERD impact scale (GIS).

Figure 1 . Study flow diagram



Gastroparesis Cardinal Symptom Index (GCSI)

The GCSI is a valid and reliable instrument for measuring symptom severity in patients with gastroparesis. It is composed of 3 subscales: post-prandial fullness/early satiety (4 items); nausea/vomiting (3 items), and bloating (2 items). (None = 0, very mild=1, mild=2, moderate=3, severe=4, and very severe=5). The GCSI score is composed of the average of all 3 subscales.¹⁵

Quality of Life in Reflux and Dyspepsia (QOLRAD)

The heartburn version of the QOLRAD questionnaire is an instrument that specifically measures the quality of life of patients with the said disease. It includes 25 items integrated into five domains: Emotional distress, Sleep disturbance, Food/drink problems, Physical/ social functioning and Vitality. Questions are rated on a 7-point Likert scale (All of the time =0, Most of the time =1, Quite a lot of the time =2, Some of the time =3, A little of the time = 4, Hardly any of the time =5, None of the time = 6). The lower the total score, the more severe the impact on daily functioning.¹⁶

GERD Impact Scale (GIS)

The GIS is a 9 - item validated self-questionnaire designed to communicate the frequency of reflux symptoms and their effect on their lives. Questions specifically pertain to acid-related symptoms, chest pain, extra-esophageal symptoms, the impact of symptoms on sleep, work, meals and social occasions, and the use of additional non-prescription medication. Four response options are provided to describe frequency. Daily =4, Often =3, Sometimes =2, Never =1.¹⁷

Gastric Emptying Scintigraphy

All patients underwent gastric emptying scintigraphy at St. Luke's Medical Center Quezon City Department of Nuclear Medicine. Patients were required to fast for 8 to 12 hours and all medications that may affect gastric emptying time had been stopped 2 days prior to the procedure. Patients were given a standardized meal composed of 4 ounces of egg white mixed with 37 MBq of unfiltered Technetium-99m sulfur colloid before cooking, 2 slices of toasted white bread, 30 g strawberry jelly and one (120 mL) cup of water. Immediately after consuming the meal, patients laid supine on the imaging bed. The gamma camera heads were positioned anteriorly and posteriorly with the stomach at the center of the field of view. Dynamic imaging was done at 30 seconds/frame for 3600 seconds using a 128 x 128 matrix. 1-minute static imaging of the same region was done at 2, 3 and 4 hours after meal ingestion. A region of interest (ROI) was drawn around the stomach at the 1st minute of imaging (T0) of the anterior and posterior images. The ROI was used for the other images at the 1st (T1), 2nd (T2), 3rd (T3) and 4th (T4) hour of imaging. Geometric mean with decay-corrected counts were obtained from each of the targeted time points and the % retained activity would be calculated. Delayed gastric emptying was defined as when there was more than 60% of the solid meal remaining at 2 hours or more than 10% of the meal remaining at 4 hours. Normal gastric emptying was defined as greater than or equal to 70% meal retention at 30 minutes, 30% to 90% meal retention at one hour, less than or equal to 60% meal retention at two hours and less than or equal to 10% meal retention at four hours. Rapid gastric emptying was defined as less than 70% solid meal retention at 30 minutes or less than 30% solid meal retention at 1 hour.

Data Analysis

Descriptive statistics were used to summarize the clinical characteristics of the patients. Frequency and percentages were used for binomial/ordinal data. Mean and standard deviations were calculated for continuous scale data. Microsoft Excel and STATA version 15.0 (StataCorp SE, College Station, TX, USA) was used for data analysis.

Chi Square Test was used to determine the relationship between the type of GERD and gastric emptying time. Student's T-test was used to determine the relationship of the frequency and severity of gastrointestinal symptoms scores (GCSI, QOLRAD and GIS) with the type of GERD while one-way analysis of variance (ANOVA) was used for comparing symptoms scores with gastric scintigraphy results. Level of significance was set at Alpha = 0.05.

Ethical Considerations

The clinical protocol and relevant document were reviewed and approved by the St. Luke's Medical Center Institutional Ethics Review Committee. Investigators were responsible for ensuring that all activities met ethical standards. Patient confidentiality was strictly implemented by ensuring anonymity of patient records. Each patient document was coded and did not contain any identifying information available to the public. Investigators were held responsible for all recorded data by ensuring its integrity in terms of accuracy, completeness, legibility, originality, timeliness and consistency. All study related documents, such as all versions of the protocol and signed informed consent forms, were kept and stored by the Principal Investigator in strict confidentiality for 5 years, after which they would be shredded. The anticipated risks and discomforts to subjects, such as small amount of radiation exposure, discomfort during preparation prior to test, including fasting, and expected benefits, were disclosed and explained to the subjects. These would also be part of the informed consent process. All patients included in the study participated voluntarily and signed informed consent was obtained at the start of recruitment.

Results

A total of 30 patients were included in the study, half of which had refractory GERD and the other half with typical GERD. The mean age of the patients was 41.1 ± 11.86 years. 53.3% (n=16) of the patients were female. There was an equal number of females

(n=8) and males (n=7) for both groups. The most commonly used proton pump inhibitor was Omeprazole (66.7%, n=20) followed by Esomeprazole (16.7%, n=5), Rabeprazole (10%, n=3). Demographic characteristics of both groups were similar at baseline as shown in Table 1.

Table 1. Baseline Characteristics of Study Patients (N=30)

Characteristics	Refractory GERD		Typical GERD
	N (%)	n (%)	n (%)
Age (Mean \pm SD)	41.1 \pm 11.86		
Gender			
Male	14 (46.7)	7 (46.7)	7 (46.7)
Female	16 (53.3)	8 (53.3)	8 (53.3)
Proton Pump Inhibitor (PPI)			
Lansoprazole	1 (3.3)	1 (6.7)	0 (0)
Omeprazole	20 (66.7)	9 (60)	11 (73.3)
Rabeprazole	3 (10)	2 (13.3)	1 (6.7)
Pantoprazole	1 (3.3)	1 (6.7)	0 (0)
Esomeprazole	5 (16.7)	2 (13.3)	3 (20)
Comorbidities			
Hypertension	11 (36.7)	6 (40)	5 (33.3)
Diabetes Mellitus	8 (26.7)	5 (33.3)	3 (20)
Coronary Artery Disease	1 (3.3)	0 (0)	1 (6.7)
Obesity	8 (26.7)	4 (26.7)	4 (26.7)
Asthma	8 (26.7)	6 (40)	2 (13.3)
Dyslipidemia	10 (33.3)	5 (33.3)	5 (33.3)
Cigarette Smoking	3 (10)	2 (13.3)	1 (6.7)
Alcohol Use	10 (33.3)	3 (20)	7 (46.7)
Family History	12 (40)	6 (40)	6 (40)

Overall, out of 30 patients, 2 patients (6.7%) had delayed gastric emptying, 3 (10%) had rapid gastric emptying and the rest of the patients had normal results (83%). As shown in Table 2, the refractory GERD group had 1 (6.7%) with delayed gastric emptying and 1 patient (6.7%) with rapid gastric emptying. In the typical GERD group, 1 (6.7%)

had delayed gastric emptying and 2 patients (13.3%) had rapid gastric emptying. There was no statistically significant difference in the gastric emptying time between typical and refractory GERD ($p=0.830$).

Table 2. Comparison of Gastric Emptying Time between Typical and Refractory GERD

Gastric Scintigraphy Result	Refractory GERD		Typical GERD		Pearson Chi-Square Tests	
	n	%	n	%		
Delayed	1	6.7	1	6.7	Chi-square	.373
Rapid	1	6.7	2	13.3	df	2
Normal	13	86.7	12	80.0	Sig.	.830
Total	15	100.0	15	100.0		

In Table 3, symptom scores between refractory and typical GERD were statistically significant based on the QOLRAD score ($p=0.004$). The mean QOLRAD score (mean \pm SD) for the refractory and typical group was 75.3 ± 35.9 and 112.0 ± 27.8 respectively, which showed that the refractory group had significantly lower quality of life. Symptom

severity based on GCSI showed higher values (mean \pm SD) for refractory GERD (15.5 ± 8.7) vs. typical GERD (10.73 ± 5.86) but were not statistically significant ($p=0.089$). GIS scores also showed higher values (mean \pm SD) for refractory GERD (2.3 ± 0.55) vs. typical GERD (1.92 ± 0.58) but also had no statistical significance ($p=0.089$).

Table 3. Comparison of Symptom Scores Between Refractory and Typical GERD

	Refractory GERD		Typical GERD		p-value
	Mean	Std. Deviation	Mean	Std. Deviation	
GCSI	15.5	8.7	10.7	5.8	0.089
QOLRAD	75.5	35.9	112.0	27.8	0.004
GIS	2.3	.55	1.9	.58	0.072

Symptom severity scores were also evaluated based on gastric scintigraphy results as shown on Table 4. There was no significant difference in the GCSI

($p=0.075$), QOLRAD ($p=0.722$) and GIS ($p=0.455$) scores among those with delayed, rapid and normal gastric emptying.

Table 4. Comparison of Symptom Scores with Gastric Scintigraphy Results

	N	GCSI			QOLRAD			GIS		
		Mean	SD	p	Mean	SD	p	Mean	SD	p
Delayed	2	2.5	3.5	0.075	97.0	35.3	0.722	2.1	.63	0.455
Rapid	3	9.6	9.5		110.0	41.5		1.7	.79	
Normal	25	14.4	7.1		91.6	37.2		2.1	.57	
Total	30	13.1	7.7		93.8	36.6		2.1	.59	

Discussion

This pilot study aimed to determine the gastric emptying time in typical and refractory GERD using gastric scintigraphy. Although the pathophysiology of GERD was not fully understood, it was recognized to be a multifactorial disease.¹⁸ Delayed gastric emptying time may be among the factors that could be implicated among patients who continue to have GERD symptoms despite adequate PPI therapy. The delay in gastric emptying associated with gastroparesis can lead to prolonged gastric retention of food that may have a propensity to reflux.¹⁹ Studies concerning gastric emptying in GERD had long since provided conflicting results. Reasons for discrepant findings included studies having different methodologies (i.e. different techniques of measuring gastric emptying and different kinds of test meals) and statistical approach.²⁰ Majority of the previous studies only had descriptive statistics with no statistical analysis.^{11,21} Eligibility criteria for refractory GERD and the control population (if present) had also been varied. Severity of symptoms as well as presence of other gastrointestinal (GI) disorders were at times not accounted for.^{20,22}

Results of our study showed that there was no significant difference in gastric emptying time between typical and refractory GERD. In our study, only 2 patients (6.7%) one from each of the typical and refractory GERD group had delayed gastric emptying time. This was in contrast to a descriptive study done by Buckles et al.²¹, where 13 (26%) of 49 patients diagnosed with GERD were found to have delayed gastric emptying time after 4 hours. The decreased prevalence of delayed gastric emptying may be due to the small sample size used in our study.

In evaluating for refractory reflux symptoms, it was also important to assess drug compliance and lifestyle modification followed by increasing the dose of PPI. If the patient remained to have symptoms despite these measures, a structural cause for the GERD symptoms must be evaluated like endoscopy with biopsy and barium esophagogram, while functional assessment involved manometry, ambulatory pH-impedance monitoring, and gastric scintigraphy.²³ A study was conducted by Galindo et al.¹¹ wherein multimodality structural and functional evaluation of 275 GERD patients who had failed empiric PPI therapy was done. This study revealed that 5.8% (16 out of 275) of patients unresponsive to

PPI therapy had gastroparesis. This was similar to our study wherein only 1 of 15 patients with refractory GERD (6.7%) had delayed gastric emptying time. However, in the study of Galindo, part of the inclusion criteria was that all of the multimodal evaluation tests were done (endoscopy and esophageal biopsies, esophageal manometry, ambulatory esophageal pH monitoring, and gastric emptying scanning) in contrast to our study which only relied on symptomatic criteria. Local guidelines for GERD suggested to ascertain patient's compliance, correct timing of PPI therapy as well as to increase PPI therapy to twice daily for at least 8 weeks prior to considering refractory GERD.⁹

In the same study by Schwizer et al.²², it was shown that 9% (7 out of 76) of the patients had rapid gastric emptying time which was similar to our results of 10% (3 out of 30). Rapid gastric emptying could promote esophagitis by increasing intragastric pressure and thereby causing transient LES relaxation. It was likely indicative of poor accommodation of the stomach and impaired postprandial receptive relaxation. Hence, there would be accelerated exposure of the duodenum to nutrients, particularly lipids. Usually, once there was inflow of fatty chyme into the duodenum, there was a negative feedback mechanism resulting in the inhibition of antral contraction and an increase in pyloric resistance. Consequently, the duodenum was overwhelmed and therefore could not appropriately initiate the feedback loop, causing similar symptoms, as seen in dumping syndrome.^{22,24} Similar symptoms that may occur included nausea, vomiting, diarrhea or belching in patients.

Although our study did not reach the approximate prevalence of patients with GERD with delayed gastric emptying, it confirmed that the majority of patients with GERD did not have delayed gastric emptying. A logical conclusion was that, while delayed gastric emptying may play a role in the pathogenesis of GERD, it was not necessary for GERD to develop. Instead of being the primary cause of GERD, delayed gastric emptying was more likely to be a potential cofactor aggravating this condition.²¹

We also attempted to correlate the symptoms of GERD, its impact, and the patient's quality of life in patients with refractory GERD using three different questionnaires namely: Gastroparesis cardinal symptom index (GCSI), Quality of life in reflux

and dyspepsia, and the GERD impact scale. Although the severity of symptoms was the same in the typical and refractory GERD group, we found out that there was a significant difference with regards to the quality of life among patients with refractory GERD (p value = 0.004). Multiple studies have shown that GERD had an impact on the affected individuals, interfering with different aspects of their daily living such as physical activity, impairing social functioning, disturbing sleep and reducing productivity at work.^{25,26} This finding was significant especially to healthcare providers since it reflected the severity of symptoms among patients with refractory GERD and the gap between the current modalities being offered among these patients.

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Conclusion and Recommendation

This pilot study showed that there was no significant difference in gastric emptying time between typical and refractory GERD. Among patients with delayed gastric emptying time, there was no difference with regards to the severity of gastrointestinal symptoms among patients with typical and refractory GERD. However, the quality of life among patients with refractory GERD was worse than patients with typical GERD. A multidisciplinary approach to therapy could be employed to improve the quality of life among these patients.

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