The Yield of Combined Multichannel Intraluminal Impedance and pH Monitoring (MII-pH Monitoring) among Suspected Refractory Gastroesophageal Reflux Disease: A St. Luke's Medical Center Experience

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Abstract

Background: Multichannel intraluminal impedance and pH monitoring (MII-pH monitoring) allows accurate recording of gastroesophageal reflux at all pH levels. In the Philippines, there is no local data on the yield of these tests in the investigation of patients with refractory gastroesophageal reflux disease (GERD). *Objective:* The objective of this study is to determine the phenotypic presentation and diagnostic yield of MII-pH monitoring among Filipino patients with suspected refractory GERD. *Methodology:* This is a retrospective, cross-sectional study involving suspected refractory GERD patients who underwent MII-pH monitoring. *Results:* A total of 50 subjects were included. Most presented with typical symptoms of reflux, such as heartburn (44%) and regurgitation (40%). Most common study indication was refractoriness to proton pump inhibitors (PPI) (86%). Patients under phenotypic group of persistent acid reflux (abnormal acid exposure with positive symptom association) revealed prevalence of 20%. Majority were males, with esophagitis, and normal esophageal motor function. Patients under the phenotypic group of hypersensitive esophagus (normal acid exposure with positive symptom association), revealed a prevalence of 18%. Patients were mostly female who presented without esophagitis, 56% with normal manometric findings. Patients under the group of functional heartburn (normal acid exposure with negative symptom association) revealed prevalence of 62%. Majority were female, with normal manometric findings and without esophagitis. *Conclusion:* Among refractory GERD patients, functional heartburn was the most common diagnosis using MII-pH monitoring, showing higher prevalence compared to previous studies. MII-pH monitoring is helpful in the work-up of refractory GERD patients as it can redirect the course of management.

Keywords: retrospective, cross-sectional, MII-pH monitoring, refractory GERD

Introduction

Gastroesophageal reflux disease (GERD) is a common disorder with a high incidence rate of 10% to 20% of adults in the Western population, occurring at least once a week,[1,2] and is lower but increasing dramatically in Asian countries,[3,4] including Japan and the Philippines[5]. The Montreal worldwide consensus in 2005 defined GERD as ''a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications,''[6] a definition that serves to differentiate normal individuals with occasional symptomatic reflux from patients with either life-altering symptoms (including extra-esophageal complaints) or asymptomatic reflux that produces mucosal injury and risk for neoplasia. Heartburn, estimated to occur daily in 7% of the U.S. population, is the most common symptom of GERD.[7] In addition to heartburn, regurgitation and difficulty swallowing are typical symptoms; while chronic cough, asthma, and laryngitis are atypical or extra-esophageal manifestations. While the clinical symptoms of heartburn and regurgitation are the most reliable for making a presumptive diagnosis based on history alone,

these are not as sensitive as most believe.

Symptom-based diagnosis of GERD is a problem, as demonstrated by Dent and colleagues, who found typical symptoms in only 49% of the patients with proven GERD.[8] Since the time that Alison described reflux esophagitis in 1946, the armamentarium of clinically available tools to diagnose GERD has become more sophisticated, as new technologies and advances have been introduced into the research and clinical arena.[6] This has been propelled by the necessity to probe into the nature of esophageal symptoms in the absence of endoscopic evidence of esophageal mucosal lesions and more recently to understand the causes of persistent esophageal symptoms among GERD patients already on potent acid suppression treatment.

In the evaluation of refractory reflux symptoms, the first step is assessing drug compliance and lifestyle modification. The second step is to increase the dose of the PPI. The third step involves investigation as to whether the GERD is due to a structural or functional cause. Structural evaluation includes endoscopy with biopsy and barium esophagogram, while functional assessment involves manometry, ambulatory pH-impedance monitoring and gastric scintigraphy.[9]

Esophageal manometry is a test wherein intraluminal sensors are positioned in the esophagus to quantify the contractile characteristics of the esophagus and segregate it into functional regions.[10] No manometric findings have adequate sensitivity and specificity to diagnose GERD. However, the test is useful in correctly positioning pH electrodes.

The current gold standard for gastroesophageal reflux testing is ambulatory pH monitoring, a method based on detection of changes in acid content in the esophageal lumen.[11] Johnson and DeMeester introduced ambulatory pH monitoring for the detection of reflux episodes in 1975. The DeMeester scoring system for 24-hour pH monitoring has 90.3% sensitivity and 90.0% specificity to diagnose GERD.[12] Since its introduction, pH-metry has become a commonly used technique for the evaluation of patients with symptoms suggestive of GERD and has been established as the gold standard for documenting gastroesophageal reflux. A fall below pH 4 in esophageal pH has been conventionally taken to indicate acid reflux. Although pH 4 tends to underestimate acid reflux, it is still considered the most appropriate threshold for clinical use.[13]

Intraluminal impedance monitoring is a method to assess intraluminal bolus transit without use of fluoroscopy.[14] It detects retrograde bolus movement and can determine the nature and proximal extent of reflux.[13]

MII-pH has been shown to allow accurate recording of gastroesophageal reflux at all pH levels and is emerging as a useful tool to study both acid and non-acid reflux.[15] The combined test increased the sensitivity of reflux monitoring to close to 90%.[3] The principles of pH impedance were first described in 1990 by Silny et al.[16] and depend on changes in resistance to alternating current (i.e., impedance) between two metal electrodes (impedance measuring segment) produced by the presence of bolus inside the esophageal lumen. MII-pH is able to detect bolus movement in the esophagus, both in the oral and aboral direction, and thus enables measurement of and distinction between swallows and reflux. Since MII registers retrograde flow of gastric contents into the esophagus in a pH-independent fashion, combining the technique with pH-metry allows the recognition of non-acid as well as acid reflux. Moreover, MII-pH monitoring provides detailed characterization of the reflux episode, including determination of the composition (gas, liquid, or mixed) and the height reached by the refluxate.[17]

In the Philippines, only our institution offers combined pH-impedance study and high-resolution esophageal manometry. To date, there is no local data on the yield of these tests in the investigation of the patients with suspected refractory GERD and its exact prevalence in the country, as well as on the phenotypic profiles of Filipino patients being referred for esophageal reflux monitoring.

The main objective of this study is to determine the phenotypic presentation and diagnostic yield of combined MII-pH monitoring among Filipino patients with suspected refractory GERD at St. Luke's Medical Center. Specifically, the study aims to (1) describe the demographic and clinical profiles (such as symptoms, EGD findings, response to PPI and manometric findings) of patients referred for MII-pH monitoring; (2) describe the result of combined MII-pH monitoring among patients with suspected refractory GERD; (3) describe patients' characteristics according to phenotypic group: persistent acid reflux, hypersensitive esophagus, and functional heartburn; and (4) determine the proportion of GERD, non-erosive reflux disease (NERD),

hypersensitive esophagus, and functional heartburn among patients with suspected refractory GERD.

Methodology

Study Design

This is a retrospective, cross-sectional chart review of adult patients with suspected refractory GERD who underwent combined MII-pH monitoring at St. Luke's Medical Center. Summary of study methodology is shown in **Figure 1**.

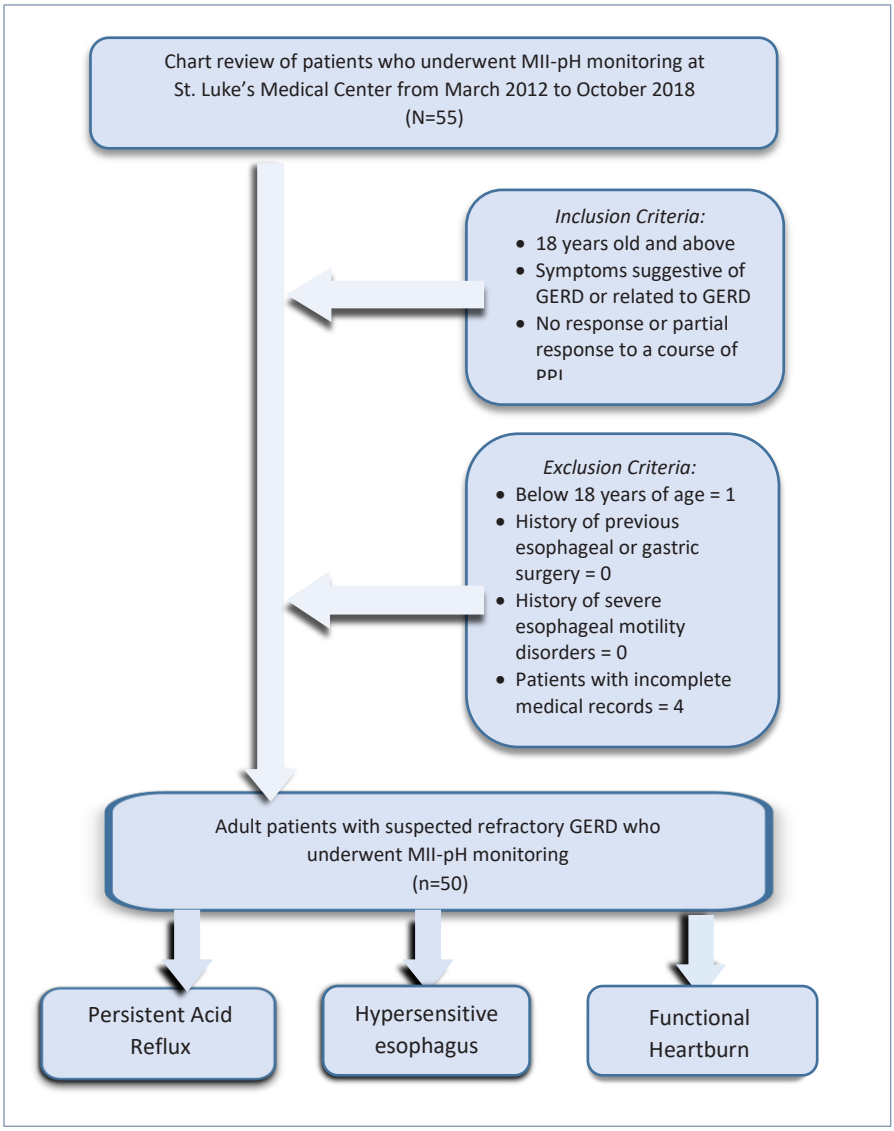

Figure 1. Flow diagram of study method

Patients aged ≥18 years old with symptoms suggestive or related to GERD with partial or no response to a course of PPI and referred for MII-pH monitoring from March 2012 to October 2018 were included in this study. The exclusion criteria were the following: history of previous esophageal or gastric surgery and severe esophageal motility disorders. Those with incomplete medical records were not included.

Study Setting and Time Coverage

This study was conducted at St. Luke's Medical Center (SLMC), a private hospital in Quezon City,

involving patients' records from March 2012 to October 2019.

Sampling and Sample Size

The researchers reviewed the chart of all patients with suspected refractory GERD referred for MII-pH monitoring at St. Luke's Medical Center for a period of six years between March 2012 and October 2018.

Outcomes Measured

The outcomes measured in this study were the proportions of patients with persistent acid reflux (i.e., patients with abnormal acid exposure with positive symptom association), those with hypersensitive esophagus (i.e., normal acid exposure with positive symptom association), and functional heartburn (i.e., normal acid exposure with negative symptom association).

Data Collection

Subject demographics (age, gender, height) and symptoms were gathered from data records accomplished prior to manometry and MII-pH. All subjects underwent esophagogastroduodenoscopy prior to the procedure. MII-pH study was performed either on or off acid suppression therapy depending on the indication of the study.

Ethical Considerations

The clinical protocol and all relevant documents were reviewed and approved by the SLMC Institutional Ethics Review Committee.

All study data were recorded and investigators were responsible for data protection and confidentiality. Anonymity of patient records was ensured. Each patient's document was coded and did not contain any identifying information. Investigators were also responsible for data integrity such as accuracy, completeness, legibility, and originality. All collected data were stored at the institution database and will be shredded one year after publication.

Data Management and Analysis

Impedance-pH Monitor

Esophageal impedance pH monitoring was performed using Digitrapper pH-Z system (Given Imaging, Sierra Scientific Instruments, Los Angeles, California), an ambulatory system, which includes a portable data-logger with impedance-pH catheters containing single-channel pH at 0 cm and 8 impedance electrodes (-3, -1, 1, 3, 5, 9, 11, 13). The impedance amplifier delivers AC voltage in a range of 1-2 kHz with resulting current flow variations in response to intraluminal impedance changes. All subjects underwent high-resolution esophageal manometry for LES localization and assessment of esophageal motor function. The impedance-pH catheter was inserted transnasally after topical anesthesia with 2% lidocaine and positioned in the esophageal body to record pH at 5 cm above the upper border of the manometrically determined LES. Subjects were advised to do the following prior to the procedure: fast for six hours, stop PPIs for a week, H2RAs for 48 hours, and antacids for 24 hours. Subjects were encouraged to maintain normal daily activities, eat usual meals and remain upright during the day. A diary was provided to record meal times, posture changes and symptoms. The study duration was 24 hours. Tracings were uploaded into a computer and displayed on a single screen for computer-assisted manual analysis (Accuview software).

Data Analysis

Demographic data were extracted from patient records. Analysis included identification, enumeration, and characterization of individual reflux events and esophageal exposure to volume and acid. The analysis of pH monitoring included the following parameters:

1. Total number of reflux episodes;
2. Total number of pathological episodes of reflux (pH <4 for more than five minutes);
3. Percentage of reflux time compared with total monitoring time (total reflux time);
4. Percentage of reflux time compared with the time while the patient was in the upright position (reflux time in erect position);
5. Percentage of reflux time compared with the time the patient was lying down (reflux time in supine position);
6. Johnson and DeMeester composite scoring system score[24] (based on the above-mentioned parameters).

Normal values of the above-mentioned parameters are the following:

1. Total reflux time up to 5%;

2. Reflux time in erect position up to 8%;
3. Reflux time in supine position up to 4%;
4. Johnson and deMeester score up to 14.72 (>6 or 7 up to 10).

The symptom index (SI) and the symptom-association probability (SAP) values were determined by the analysis software. SAP estimates the likelihood that symptoms are due to reflux by examining two-minute segments of the event and pH recorders. The numbers of two-minute segments with and without symptoms, and with and without reflux were tabulated. Fisher's exact test was performed by the software and SAP was calculated. A SAP greater than or equal to 95% is positive.

Statistical Analysis

Descriptive statistics for categorical variables were reported as frequency and percentage, whereas continuous variables were reported as mean and standard deviation, or median and range, as appropriate.

Results

This retrospective descriptive study was conducted to determine the phenotypic presentation and diagnostic yield of combined multichannel intraluminal impedance-pH monitoring among Filipino patients with suspected refractory GERD at St. Luke's Medical Center. The demographic and clinical profile is shown in **Table 1.**

Table 1. Demographic and clinical profile of patients (N=50)

Mean age in years	**mean (range)**
Male	44.66 (23-68)
Female	44.94 (24-65)
Height in cm, mean (range)	**156.54 (142.24-175.26)**
Typical symptoms	**n (%)**
Heartburn	22 (44)
Regurgitation	20 (40)
Atypical symptoms	**n (%)**
Non-cardiac chest pain	9 (18)
Chronic cough	2 (4)
Dysphagia	3 (6)
EGD Findings	**n (%)**
Negative esophagitis	38 (76)
Esophagitis	
A	4 (8)
B	0 (0)
C	0 (0)
D	0 (0)
Barrett's esophagus	0 (0)
Not known	8 (16)
Response to PPI	**n (%)**
Non-responsive	43 (86)
Partial response	7 (14)
Responsive	0 (0)
Therapy while on MII-pH monitoring	**n (%)**
On	8 (16)
Off	42 (84)
Manometric findings	**n (%)**
Normal	26 (52)
Hypotensive LES and peristalsis	9 (18)
Weak peristalsis with large break	4 (8)
Weak peristalsis with small break	6 (12)
Frequent failed peristalsis	4 (8)

Fifty patients were included in this study. Majority of the patients were in their 4th to 5th decade of life, with a mean age of 44.66 years. The mean height was 156.54 cm (ranging from 142.24 to 175.26 cm). Most of the patients presented with typical symptoms of reflux, specifically heartburn (44.00%) and regurgitation (40.00%), followed by atypical symptoms such as non-cardiac chest pain (18.00%), dysphagia (6.00%) and chronic cough (4.00%). In terms of EGD findings, 76% of patients had no signs of esophagitis upon examination and 8% presented with mild esophagitis (LA Grade A). The most common indication for referral was non-response to proton-pump inhibitors (86.00%). Most patients were off therapy (84.00%) during MII-pH monitoring. Manometric findings most commonly revealed normal esophageal motor function (52%) followed by hypotensive LES and peristalsis (18%), weak peristalsis with small break (12%), weak peristalsis with large break (8%), and frequent failed peristalsis (8%) (**Table 2**).

Table 2. Combined MII-pH summary of findings of included patients (N=50)

DeMeester score (n, %)	n (%)
<14.72	40 (80)
>14.72	10 (20)
Total number of reflux cases	mean (range)
Acid	10.58 (0-88)
Non-acid	11.52 (0-82)
% Total reflux time, minutes	n (%)
<5	47 (94)
>5	3 (6)
% reflux in supine	n (%)
<4	42 (84)
>4	8 (16)
% reflux in erect	n (%)
<8	49 (98)
>8	1 (2)

Of the 50 patients included in the study, 80% exhibited normal DeMeester score of <14.72. Mean total number of acid reflux episodes was 10.58 (ranging from zero to 88), and mean number of non-acid reflux episodes was 11.52 (ranging from zero to 82). For the percentage of reflux time, total acid exposure time was 94%, 98% during upright position and 84% during supine position. These were within physiologic limits in majority of patients. Excessive esophageal acid exposure was noted highest at supine position (eight of 50 patients, 16%) followed by total reflux time (6%) and during upright position (2%).

Table 3 shows the patients' characteristics according to phenotype. It is of note that patients with persistent acid reflux phenotype (i.e., abnormal acid exposure with positive symptom association) revealed overall prevalence of 20% (10 out of 50 patients). The mean age of patients in this group was 45, majority of whom were males (60%), around 40% presented with esophagitis on EGD, alongside with normal manometric findings (60%), and positive SI (60%) / positive SAP (100%).

Patients of the hypersensitive esophagus phenotype of (i.e., normal acid exposure with positive symptom association) revealed overall prevalence of 18% (nine out of 50 patients). Patients involved were noted to be on their 4th to 5th decade of life, majority were females (77.78%), all of whom presented without esophagitis on EGD (100%), 55.56% with normal esophageal motor function on manometry, and all patients had positive SAP (100%)/negative SI (100%).

On the other hand, patients under the group of functional heartburn (i.e., normal acid exposure with negative symptom association) revealed overall prevalence of 62% (31 out of 50 patients). Most patients were in their 4th to 5th decade of life, majority were

females (52.94%), and presented with normal manometric findings (48.39%). All patients presented without esophagitis on EGD (100.00%) with negative SAP (100%)/negative SI (100%). In this study, overall prevalence of functional heartburn was higher compared to the reported 21% overall prevalence rate of Yamasaki, et.al.

Table 2. Patients' characteristics according to phenotype: persistent acid reflux, hypertensive esophagus, and functional heartburn

Characteristics	Persistent Acid Reflux (n=10)	Hypertensive Esophagus (n=9)	Functional heartburn (n=31)
Overall prevalence, n (%)	10 (20)	9 (18)	31 (62)
Age in years, mean age (range)	45 (30-68)	46 (31-64)	45 (23-65)
Male gender, n (%)	6 (60)	2 (22.22)	13 (41.94)
Esophagitis, n (%)	4 (40)	0 (0)	0 (0)
Total number of reflux, mean (range)	35 (3-88)	26 (3-50)	16 (0-82)
Symptom Index (SI), mean (range)	61 (0-100)	28 (0-100)	4 (0-49)
Positive SI, n (%)	6 (60)	O (0)	0 (0)
Symptom Association Probability (SAP), mean (range)	97 (91-100)	97 (91-99.7)	9 (0-88.1)
Positive SAP, n (%)	10 (100)	9 (100)	0 (0)
Manometric Findings, n (%)			
Normal	6 (60)	5 (55.56)	15 (48.39)
Hypotensive LES and peristalsis	4 (40)	0 (0)	5 (16.13)
Weak peristalsis with large break	0 (0)	0 (0)	4 (12.90)
Weak peristalsis with small break	0 (0)	2 (22.22)	4 (12.90)
Frequent failed peristalsis	0 (0)	2 (22.22)	3 (9.68)

Discussion

Acid suppression with PPI is the mainstay of treatment for GERD. However, despite treatment, there is still an estimated 10-40% of patients who fail to respond symptomatically. Although the definition for refractory GERD remains controversial, most authors have defined it as having poor response to PPI with <50% improvement in the chief complaint after at least 12 weeks of PPI therapy.[1]

In clinical practice, PPI failure has become the most common presentation of GERD-related symptoms. The underlying mechanisms for PPI failure include timing adherence and compliance, persistent esophageal acid exposure, and reflux hypersensitivity.

Intraluminal pH monitoring is now a widely accepted clinical tool for investigating refractory GERD. It is indicated in patients with typical GERD symptoms who fail four weeks of PPI therapy, those with atypical symptoms who fail six to eight weeks of PPI therapy, those being considered for endoscopic or surgical reflux therapy, and those who have undergone endoscopic or surgical reflux therapy and who continue to have GERD symptoms. In addition, the use of combined impedance-pH monitoring enables the detection of not only acid but also all types of reflux, and has been shown to substantially increase the diagnostic yield compared to pH alone.[2] In one of the largest studies which correlated impedance patterns and symptom occurrence in PPI non-responders, the impedance reflux profile in this subset of patients was heterogeneous and the majority of reflux events were not associated with symptoms. Thus, the treatment of patients with PPI failure should focus beyond reflux, such as visceral hypersensitivity and hypervigilance.[3]

Figure 2 shows the proportion of patients according to phenotypic group. Among suspected refractory GERD patients referred to our institution, diagnosis through MII-pH study revealed a majority of patients having functional heartburn (62%), which was higher compared

to the reported overall prevalence from other studies, followed by persistent acid reflux (20%) and hypersensitive esophagus (18%).

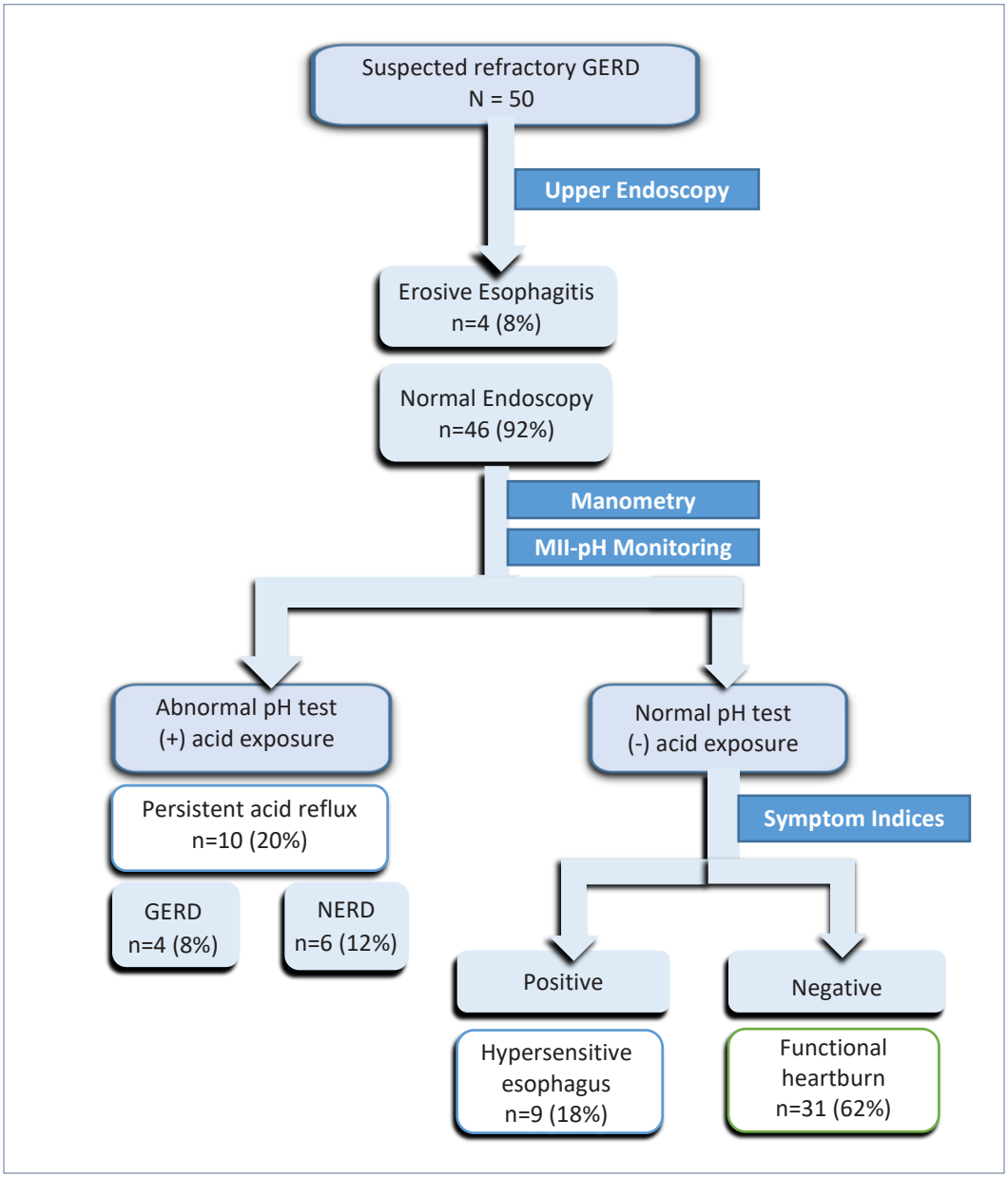

Figure 2. Proportion of patients according to phenotypic group

It can be noted that only 4 out of 50 patients (8.00%) revealed true refractory gastroesophageal reflux disease and 31 out of 50 patients (62.00%) with suspected refractory GERD belongs to the phenotypic group of functional heartburn.

In conclusion, MII-pH monitoring is helpful in the work-up of patients with suspected refractory GERD as it will redirect the course of management.

Conflict of Interest

The authors declare no conflict of interest.

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