Relapse Rate of Symptomatic Non Erosive Reflux Disease (NERD) and Erosive Reflux Disease (ERD) after Standard Proton Pump Inhibitor (PPI) therapy

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by

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RELAPSE RATE OF SYMPTOMATIC NON EROSIVE REFLUX DISEASE (NERD) AND EROSIVE REFLUX DISEASE (ERD) AFTER STANDARD PROTON PUMP INHIBITOR (PPI) THERAPY

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Significance:GERD is a chronic condition because majority experience recurrence of symptoms despite completion of the standard PPI therapy.Thus,this study aims to determine the relapse rate of symptomatic NERD and ERD after standard PPI treatment in our institution as well as factors associated with relapse.The result will guide clinicians to further improve GERD management such as consideration of intermittent PPI treatment for NERD while continuous PPI treatment for ERD.

Methodology:The research design is a prospective,cohort study.Total of 270 patients with pretreatment GERDQ scores of >8 were classified into NERD and ERD by endoscopic findings.Patients were given the standard PPI therapy(4 weeks for NERD and 8 weeks for ERD)after which the clinical response was assessed using post-treatment GerdQ questionnaire.Only patients who responded to treatment were followed up monthly for relapse.Factors associated with GERD relapse were also identified.

Results:Among 270 patients,83(61.5%) NERD and 98(72.6%) ERD patients responded to standard PPI therapy(*P-value=0.052*).The relapse rate of GERD within 6 months after completion of standard treatment was 66.2% for NERD and 66.3% for ERD,which was not statistically significant between the 2 groups(*P-value=0.993*).Among all factors considered,only NSAID use (*OR=3.18,95% CI=1.26–8.03,P-value=0.014*) was associated with ERD relapse while NSAID use (*OR=6.98,95% CI=2.17–22.47,P-value=0.001*)and smoking (*OR=0.21,95% CI=0.07-0.64,P-value=0.006*)were associated with NERD relapse.

Conclusion:NERD responded less well to PPI treatment than those with ERD.The relapse rate of GERD in our institution was high,hence,patients should have longer treatment duration and should be carefully followed up.NSAID use increased ERD relapse while NSAID use and smoking increased the possibility of NERD relapse in our institution.

Keywords: Relapse rate, Non erosive reflux disease, Erosive reflux disease, GerdQ score

INTRODUCTION:

According to the 2006 Montreal consensus, GERD is defined as "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications. This definition is also adopted by the Asia-Pacific GERD consensus and the American Gastroenterological Association [1]. Symptom-wise, heartburn is an excellent marker of GERD and association with acid regurgitation makes it possible in about 90% of cases to establish the diagnosis of GERD [2].

Only about one-third to one-half of patients with GERD have endoscopically positive findings such as erosions and ulcers while other patients with GERD symptoms have no obvious mucosal breaks on endoscopic examination. Erosive reflux disease (ERD) is defined endoscopically by visible breaks of the distal esophageal mucosa while non erosive reflux disease (NERD) is characterized by the presence of classic GERD symptoms in the absence of esophageal mucosal injury on upper endoscopy [3].

As mentioned, NERD refers to the absence of esophageal mucosal lesions on upper endoscopy in patients with typical GERD symptoms and no recent acid suppressive treatment within the last two weeks. According to local guideline on GERD, the diagnosis of NERD, as implied in its definition by all current guidelines, can be made only after an upper endoscopy has been performed in patients who have consulted for disturbing symptoms [4].

In the past two decades, gastroesophageal reflux disease (GERD), initially thought to be a disease only common in the West, is described increasingly in Asia, including the Philippines. In Asia, time trend studies during the last two decades reveal that the prevalence of ERD or erosive esophagitis has increased from 1.8% in 1995 to 12.6% in 2002. A recent local report indicated that the prevalence of erosive esophagitis a common complication of GERD, has more than doubled, from 2.9% to 6.3%, between the two time periods of 1994 to1997 and 2000 to 2003, respectively. On the other hand, it is estimated that 11–12% of the general population have non-erosive reflux disease (NERD) and a considerably higher proportion of symptomatic patients presenting for endoscopy may suffer from NERD, i.e., 37-87% [4].

The recurrent bothersome symptoms of GERD and its associated morbidities result in loss of productivity and a diminished quality of life despite compliance and completion of the standard

treatment regimen. Furthermore, concerns that long-term symptomatic GERD may be a risk factor for adenocarcinoma of the distal esophagus has put the disease high in the consciousness of and a source of anxiety for both physicians and patients[4]. These are common reasons for clinic visits and consultations thus, it is my objective to determine the relapse rate of symptomatic NERD after 4 weeks and ERD after 8 weeks of the recommended proton pump inhibitor (PPI) therapy among patients in Veterans Memorial Medical Center (VMMC).

OBJECTIVES

General Objective:

- to determine the relapse rate of symptomatic NERD after 4 weeks and ERD after 8 weeks of standard PPI therapy among VMMC patients

Specific Objectives:

- to identify the presenting clinical symptom and baseline clinical profile of NERD and ERD patients
- to determine the clinical response of NERD after 4 weeks of standard PPI therapy
- to determine the clinical response of ERD after 8 weeks of standard PPI therapy
- to compare the relapse rate of symptomatic NERD and ERD after standard PPI therapy
- to identify the risk factors associated with GERD relapse in our institution

REVIEW OF RELATED LITERATURE:

GERD can be diagnosed clinically. Heartburn and acid regurgitation are often considered the typical symptoms of GERD and an office diagnosis of GERD may be made when these two are present. Heartburn is defined as a burning sensation in the retrosternal area (behind the breastbone) while regurgitation is the perception of flow of refluxed gastric content into the mouth or hypopharynx. Up to 49% of patients with GERD may have heartburn while 42% have acid

regurgitation [4].It should be emphasized that GERD may be related to other dyspeptic symptoms, which may have atypical presentations, such as labyrinthitis, chronic cough, asthma, non-cardiac chest pain, or even be asymptomatic [2]. Other symptoms of reflux esophagitis include epigastric pain, retrosternal pain, nausea and vomiting [5].

According to American College of Gastroenterology, a presumptive diagnosis of GERD can be established in the setting of typical symptoms of heartburn and regurgitation. Empiric medical therapy with a PPI is recommended in this setting. A response to therapy would ideally confirm the diagnosis [6]. Similarly, the local clinical practice guideline on GERD (2015) also states that clinical diagnosis of GERD can be made if the typical symptoms of acid regurgitation and/or heartburn are present. In this setting, upper endoscopy is not necessary and empiric acid suppressive therapy can be started in patients without alarm features [4].

Locally-validated standardized questionnaires is utilized to reinforce the clinical diagnosis of GERD, as well as, to assess response to PPI treatment. Several symptom-based questionnaires have been formulated as diagnostic tool so as to ultimately reduce the need for endoscopy and other diagnostic procedures. In the Philippines, the more commonly used questionnaires are Frequency Scale for the Severity of Gerd (FSSG) and Gastoesophageal Reflux Disease Questionnaire (GerdQ). Sensitivity and specificity rates ranged from 55% to 80% and 54% to 80%, respectively. A local validation of the GerdQ has been performed by Castillo-Carandang et al., while Sollano et al. validated the FSSG and utilized the questionnaire in determining treatment response among 1,578 Filipino patients with GERD. These questionnaires cannot be recommended as the sole screening tool for diagnosis of GERD but they remain as an important complementary tool for case identification and in disease management [4].

The six items in the GerdQ were derived from the Reflux Disease Questionnaire (RDQ), Gastrointestinal Symptom Rating Scale (GSRS), and GERD Impact Scale (GIS). The items include positive predictors of GERD (heartburn, regurgitation, sleep disturbance, over-the-counter (OTC) medication use) and negative predictors of GERD (epigastric pain, nausea). The highest possible score is 18, with three points as the highest score for each item. A GerdQ score of >8 was reported to have a sensitivity of 65%, a specificity of 71%, and an accuracy of 70% for diagnosing GERD, which was superior to the primary care physician clinical diagnosis (sensitivity 63%, specificity 63%) and almost equal to the gastroenterologist clinical diagnosis (sensitivity 67%, specificity 71%). It has been made available free-of-charge, by AstraZeneca in various countries

in Europe, the Americas, and Asia-Pacific including the Philippines due to its potential uses in clinical practice namely: (1) diagnosis of GERD with an accuracy similar to that of the gastroenterologists; (2) assessment of the relative impact of the disease on patients' lives and assistance in choice of treatment; and (3) measurement of response to treatment over time [1].

Aside from the Philippines, Japan also had a validation study of the GerdQ questionnaire. GerdQ cutoff score was set at 8 and GerdQ score of more than eight significantly predicted the presence of reflux esophagitis [6]. Furthermore, a Norwegian journal also compared symptom control achieved with empirical therapy for GERD, in an algorithm based on the GerdQ with that of current care after endoscopy. It concluded that a symptom-based approach using GerdQ reduced health care costs without loss in efficacy. An algorithm based on GerdQ may provide physicians with a tool for a more structured care of patients [7].

As for the treatment, PPI therapy is still the most effective therapy for NERD. Initial treatment should comprise a standard once daily dose 30 min before breakfast. In the assessment of therapeutic efficacy, a standard dose course of empiric PPI therapy should be evaluated at 2–4 weeks, but some patients may take up to 12 weeks to respond. For patients with NERD who fail to respond after 4 weeks, increasing the dose of PPI to twice daily is a common practice, but there is little objective evidence that this approach provides additional symptom relief [10]. On the other hand, as per American College of Gastroenterology (ACG) and local GERD guideline, standard dose PPI once daily for eight weeks, taken 30 minutes before morning meal, is the cornerstone of therapy for erosive esophagitis. If eight weeks of standard once daily PPI treatment achieved only a partial relief of symptoms, administration of the same PPI twice daily or switch to a different PPI is recommended [4]. According to ACG, it would be expected that approximately 70-80% of patients with ERD would demonstrate complete relief on PPI therapy and 60% of patient with NERD. According to the local guideline, the commonalities that exist among many attempts to define refractory GERD are (1) the dose of PPI (once a day escalated to twice daily due to inadequate response to initial therapy) and (2) the period of treatment (ranges from 4 to 8 weeks) before the symptoms are labeled refractory to treatment [4].

Evaluation of the response to GERD treatment can be done by clinical and endoscopic assessment. Jeonget.al., studied symptom improvement in both NERD and ERD patients. Presence of symptoms was assessed in each patient at baseline and post-treatment using a questionnaire.

Subsequent symptomatic recurrence on the cessation of therapy in each improved patients was checked by telephone survey or outpatient interview [8]. Other studies made by Jonasson et al. and Suzuri et al. have emphasized the use of GerdQ questionnaire in diagnosis and treatment efficacy. Another study by Tielemans et al., studied online follow-up of individuals with GERD using a patient-reported outcomes instrument. Follow-up GerdQ questionnaires were sent after 4, 12 and 24 weeks, and those who had a total GerdQ score $\geq$ 8 and responded to at least the baseline and 4-week questionnaires were included in the analyses. Outcomes were defined as "symptom improvement", which was defined as a GerdQ score < 8 if the respondent scored ≥ 8 on the previous questionnaire. They labeled "stable symptoms " as GerdQ score ≥ 8 at two subsequent completed questionnaires during follow-up while they defined "relapse" as GerdQ ≥ 8, in case the previous GerdQ score had been < 8 [9]. Most of the journals reviewed have symptom-based approach in assessing response after initial PPI treatment.

Gastro-esophageal reflux disease (GERD) is a chronic condition, with 50-80% of patients experiencing relapse within one year following completion of initial treatment. A study by Jeong et al., entitled "Clinical Analysis of Recurrence Rate and Symptom Improvement in Gastro-esophageal Reflux Disease Patients" concluded that 40% of GERD patients recurred within 6 months following the completion of 8 week therapy with Lansoprazole. Recurrence rate, recurrence time, and rate of symptom improvement were not significantly different between NERD group treated with half dose and ERD group treated with full dose Lansoprazole. According to a study by Scholten et al., relapse rates of up to 81% to 90% have been reported in patients with healed erosive esophagitis 6 to 12 months after drug therapy was withdrawn and it is generally accepted that symptoms will persist in most patients [11].

Risk factors associated with GERD relapse in primary care patients who responded adequately to short-term treatment with a proton pump inhibitor were analyzed by Lopez-Colombo et.al. They concluded that consumption of citrus fruits and NSAIDs increased the possibility of GERD relapse among the other factors like lower basic educational level, overweight, obesity, smoking, and the consumption of 4-12 cups of coffee per month, citrus fruits, NSAIDs, chocolate, Aspirin, carbonated beverages, spicy food 7-16 times/month, and spicy food $\geq$ 20 times/month [10].

Once healing is achieved, the majority of patients with erosive esophagitis will require continued long-term (maintenance) acid suppressive treatment, usually with a lower dosage of their initial acid-suppressive therapy. This is because GERD is a chronic, usually lifelong disease that often relapses once treatment is stopped. According to the local GERD guideline, when symptoms relapse after standard GERD treatment, on demand or intermittent PPI treatment is suggested for NERD while continuous PPI treatment is recommended for moderate to severe erosive esophagitis.

SIGNIFICANCE OF THE STUDY

GERD is a chronic condition because of the fact that majority of patients experience recurrence of symptoms despite compliant and completion of the standard treatment regimen. Thus, the researcher hopes to determine the relapse rate of symptomatic NERD and ERD after completion of the standard PPI therapy as well as to determine factors associated with GERD relapse among our patients. The result will guide clinician to further improve case management of GERD such as consideration longer drug treatment duration for GERD patients in our institution.

METHODOLOGY

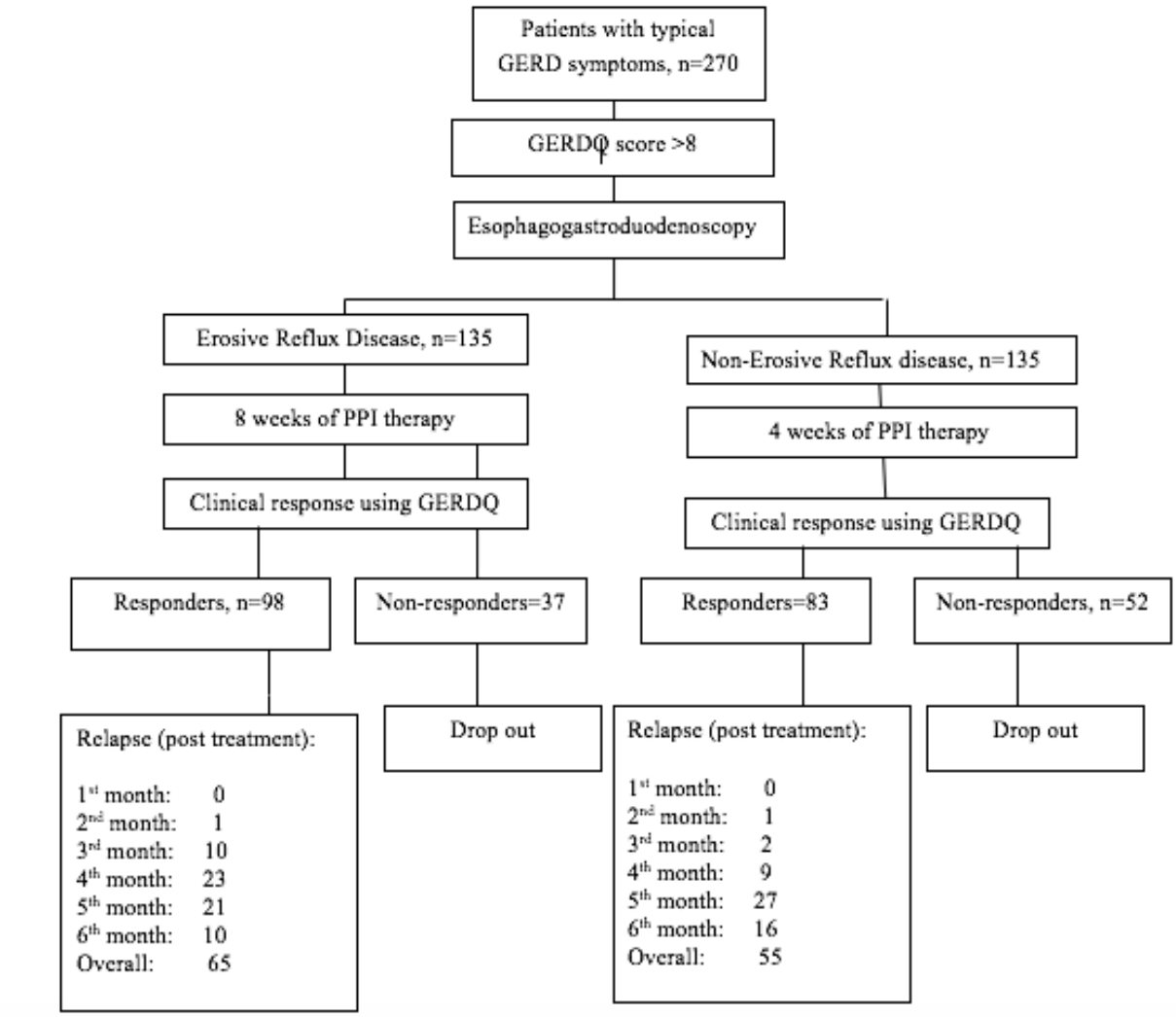
Study area

The study was conducted at the outpatient department and endoscopy unit of Veterans Memorial Medical Center.

Study design

The research design is a prospective, cohort study.

Study Process



*heartburn, acid regurgitation, dysphagia, odynophagia, burping, hiccups, nausea/ vomiting

Intervention

Patients considered eligible for the study who had signed an informed consent was included in the 8 month term study. If indicated, medical risk evaluations were accomplished prior to enrollment. The purpose of the study as well as the risks and possible complications of the esophagogastroscopy were properly explained to the patient and their relatives.

A thorough face to face interview was conducted and the presence of symptom were assessed in each patient at the baseline using GERDQ questionnaire. Subjects with pretreatment GERDQ scores of >8 were considered in the study. In addition, clinical profiles of each subjects were obtained.

All study subjects underwent upper gastrointestinal endoscopic examinations, which were performed by the fellow-in-training with the assistance of a consultant who accompanied the trainee through all endoscopic examinations in the study.

The subjects were divided into NERD group and ERD group by endoscopic findings. The endoscopic findings of erosive esophagitis in the lower esophagus were classified using Los Angeles classification of esophagitis (LA-A to D).

Patients were given once daily 8 week PPI treatment for the ERD. After 8 weeks, the clinical response was reassessed using post treatment GerdQ questionnaire. The “responders and “non responders” were identified at the end of 8 week of PPI treatment. The “responders” were defined as a GerdQ score < 8 if the respondent scored ≥ 8 on the previous questionnaire while the “non responders” were defined as GerdQ score ≥ 8 at two subsequent completed questionnaires during follow-up. Only those “responders” were followed up monthly to determine relapse using GerdQ questionaire. “Relapse ” was defined asGerdQ ≥ 8, in case the previous GerdQ score had been < 8. Monthly follow ups were accomplished via interview, phone calls or online mails.

On the other hand, patients under the NERD group were given once daily 4 week PPI treatment. After 4 weeks, the clinical response was reassessed using GerdQ questionnaire. Similarly, the “responders and “non responders” were identified at the end of 4 week of PPI treatment. Only those “responders” were followed up monthly to determine relapse using GerdQ questionaire.“Relapse ” was defined as GerdQ ≥ 8, in case the previous GerdQ score had been < 8. Monthly follow ups were accomplished via interview, phone calls or online mails.

A multiple logistic regression model was carried out using NSAID use, weight gain, smoking and alcohol consumption as variables for both ERD and NERD group to discover possible associations with GERD relapse.

Study Population

Inclusion criteria:

- Age 18 or over with typical symptoms of GERD diagnosed at VMMC and willing to sign informed consent

Exclusion criteria:

- gastric and/or duodenal ulcer
- pyloric stenosis
- previous surgery of the esophagus and/or gastrointestinal tract (except for appendectomy and cholecystectomy)
- malignancy and/or any other severe disease
- received antacids, sucralfate, prokinetics, H2 blockers and/or proton pump inhibitors for more than 7 days in the 4 weeks prior to the start of the study.
- regular intake of glucocorticosteroids or non-steroidal anti-inflammatory drugs

Sample Size

For this research, 270 patients with gastroesophageal reflux disease (GERD) who satisfies the inclusion criteria will be included in the analysis based on a 5% level of significance, 80% power of the test, and observed 59% and 42% prevalence[9] of erosive and non-erosive reflux disease, respectively.

Statistical Analysis

All patients were screened according to the inclusion/exclusion criteria and only valid data from these patients were included in the analysis. Missing data were not replaced or estimated. Descriptive analysis of categorical data were tabulated using frequency and percentages [*n(%)*] while mean and standard deviation [*mean±SD*] for continuous profile. Fisher's Exact test and Pearson Chi-square test were used to compare categorical data between patients in ERD and NERD, whichever was applicable. Student's *t*-test was used to compare continuous data between groups. *P*-values less than 0.05 were deemed statistically significant. All computations were aided with statistical software Stata version 15 (StataCorp, Texas, USA).

Multiple logistic regression was also computed to determine the risk factors associated with relapse rate among responder patients. Goodness of fit was explored based on the Hosmer-Lemeshow test. *P*-values less than 0.05 were deemed significant. All computations were aided with statistical software Stata version 15 (StataCorp, Texas, USA).

RESULTS

The analysis of this study included 270 patients diagnosed with GERD at VMMC. Out of this total, half (135 patients) of them comprised the NERD group while the other half comprised the ERD group. Among the ERD group, 135 patients were confirmed to have erosive esophagitis [LA grades A 108 (80%), LA-B 14 (10.4%), LA-C 10 (7.4%), LA-D 3 (2.2%)] diagnosed by upper endoscopy.

Table 1 below presented the baseline clinical profile of GERD patients in VMMC. Most of them were male (57.0% in NERD, 61.5% in ERD) and were not significantly different between groups (*P-value=0.413*). The average age was statistically equal between groups (*P-value=0.374*) at 60.8 years old (*SD=15.3*) among NERD and 59.2 (*SD=13.7*) among ERD. Majority of BMI ranges at 18.5-24.9 kg/m^2 (68.2% in NERD, 72.6% in ERD, *P-value=0.367*). Incidence of hiatal hernia was significantly higher among ERD patients (32.6%, *P-value=0.003*) whereas diabetes mellitus (DM) was significantly prevalent among NERD patients (20.7%, *P-value=0.003*).

Table 1 also showed the distributions of patients who take alcohol (56.3% in NERD, 54.1% in ERD, *P-value=0.714*) and smoked (34.8% in NERD, 25.9% in ERD, *P-value=0.112*) between groups. As well as the prevalence of H pylori-positive (69.6% in NERD, 71.1% in ERD, *P-value=0.790*) and hypertension (76.3% in NERD, 68.9% in ERD, *P-value=0.172*). Both 50 patients (37.0%) in NERD and ERD had treatment history of GERD (*P-value>0.999*).

Table 1. Baseline characteristics GERD patients.

Characteristics	NERD (*n=135*)	ERD (*n=135*)	*P*-value
Age (in years), *mean±sd*	60.8±15.3	59.2±13.7	0.374
Sex, *n(%)*			0.413
Female	58 (43.0)	51 (37.8)	
Male	77 (57.0)	83 (61.5)	
BMI, *n(%)*			0.367
<18	36 (26.7)	27 (20.0)	
18.5-24.9	92 (68.2)	98 (72.6)	
>25	7 (5.2)	10 (7.4)	
Hiatal hernia, *n(%)*	23 (17.0)	44 (32.6)	0.003*
Alcohol, *n(%)*	76 (56.3)	73 (54.1)	0.714
Smoking, *n(%)*	47 (34.8)	35 (25.9)	0.112
H pylori-positive, *n(%)*	94 (69.6)	96 (71.1)	0.790
Hypertension, *n(%)*	103 (76.3)	93 (68.9)	0.172
DM, *n(%)*	28 (20.7)	11 (8.2)	0.003*
Previous treatment history of GERD, *n(%)*	50 (37.0)	50 (37.0)	>0.999

Note: *Significant at 0.05 level

As to the data in Table 2, the most of the clinical symptoms observed among patients include heart burn (56.3% in NERD, 60.0% in ERD, *P-value=0.537*) and acid regurgitation (41.5% in NERD, 36.3% in ERD, *P-value=0.382*) but were not significantly different between groups. There were also few cases of burping (0.7% in ERD, *P-value>0.999*), hiccups (0.7% in NERD, *P-value>0.999*), nausea (0.7% in NERD, *P-value>0.999*), and chronic cough (0.7% in NERD, 3.0% in ERD, *P-value>0.370*).

Table 2. Clinical symptoms of patients.

Symptoms	NERD (*n=135*)	ERD (*n=135*)	*P*-value
Heart burn, *n(%)*	76 (56.3)	81 (60.0)	0.537
Acid Regurgitation, *n(%)*	56 (41.5)	49 (36.3)	0.382
Burping, *n(%)*	0 (0.0)	1 (0.7)	>0.999
Hiccups, *n(%)*	1 (0.7)	0 (0.0)	>0.999
Nausea/vomiting, *n(%)*	1 (0.7)	0 (0.0)	>0.999
Chronic cough, *n(%)*	1 (0.7)	4 (3.0)	0.370

Among 270 patients enrolled in this study, there were 83 (61.5%) and 98 (72.6%) cases of responder in NERD and ERD, respectively (Table 3). The responders after GERD treatment were higher in the ERD group. However, the statistical data showed no significant difference between the two groups (*P-value=0.052*).

Table 3. Post-treatment clinical response.

Response	NERD (*n=135*)	ERD (*n=135*)	*P*-value
Responder (GerdQ score < 8 if the respondent scored ≥ 8 on the previous questionnaire), *n(%)*	83 (61.5)	98(72.6)	0.052
Non-responder (GerdQ score ≥ 8 at two subsequent completed questionnaires), *n(%)*	52 (38.5)	37(27.4)	

Note: *Significant at 0.05 level

The results in Table 4 revealed the relapse rate of GERD according to the study period (monthly) and also on the overall. Relapse rate was highest at 5th post treatment month for NERD (32.5%) and 4th post treatment month for ERD (23.5%). Based on the data, the relapse rate on the third (*P-value=0.040*) and the fourth (*P-value=0.027*) post-treatment month was significantly higher among ERD patients. The overall relapse rate of GERD within 6 months after completion standard PPI treatment was 66.2% for NERD and 66.3% for ERD, respectively. However, the relapse rate was not significantly different between the two groups (*P-value=0.993*).

Table 4. Relapse rate by study period and overall.

Period	NERD (*n=83*)	ERD (*n=98*)	*P*-Value
Relapse after 1 month post treatment	0 (0.0)	0 (0.0)	-
Relapse after 2 months post treatment	1 (1.2)	1 (1.0)	0.906
Relapse after 3 months post treatment	2 (2.4)	10 (10.2)	0.040*
Relapse after 4 months post treatment	9 (10.8)	23 (23.5)	0.027*
Relapse after 5 months post treatment	27 (32.5)	21 (21.4)	0.092
Relapse after 6 months post treatment	16 (19.3)	10 (10.2)	0.083
Overall relapse rate	55 (66.2)	65 (66.3)	0.993

Note: *Significant at 0.05 level.

A multiple logistic regression model was performed to determine the risk factors that were associated with relapse among ERD and NERD responder patients. Variables included in the analysis were concomitant NSAID use, weight gain, smoking and alcohol consumption. Table 5 and 6 below presented the result. Among all factors considered, only NSAID use (*OR=3.18, 95% CI=1.26–8.03, P-value=0.014*) was significantly associated with ERD relapse (*Hosmer-Lemeshow test=8.1, P-value=0.0879*) as presented by table 5. On the other hand, NSAID use (*OR=6.98, 95% CI=2.17–22.47, P-value=0.001*) and smoking (*OR=0.21, 95% CI=0.07-0.64, P-*

value=0.006) were significantly associated with NERD relapse (*Hosmer-Lemeshow test=1.97, P-value=0.8533*) as presented by table 6.

Table 5. Association between risk factors and ERD relapse

Factors	Odds Ratio	95% CI	*P*-value
NSAID use	3.18	1.26 - 8.03	0.014*
Weight Gain	0.66	0.14 - 3.05	0.595
Smoking	0.43	0.17 - 1.09	0.075
Alcohol	0.70	0.24 - 2.05	0.510

Note: *Significant at 0.05 level

Table 6. Association between risk factors and NERD relapse

Factors	Odds Ratio	95% CI	*P*-value
NSAID use	6.98	2.17 - 22.47	0.001*
Weight Gain	0.43	0.08 - 2.34	0.328
Smoking	0.21	0.07 - 0.64	0.006*
Alcohol	1.15	0.28 - 4.74	0.843

Note: *Significant at 0.05 level

DISCUSSION

The most common clinical presenting symptom of both ERD and NERD among patients in VMMC is heartburn (56.3% in NERD, 60.0% in ERD, *P-value=0.537*) followed by acid regurgitation (41.5% in NERD, 36.3% in ERD, *P-value=0.382*). This is consistent with the study made by Hoon Oh and Sollano et al., stating that heartburn and acid regurgitation are often considered the typical symptoms of GERD and an office diagnosis of GERD can be made when these two symptoms are present. In addition, a local study by Sollano et al. stated that up to 49% of patients with GERD may have heartburn and 42% have acid regurgitation.

Table 1 above presented the baseline clinical profile of the patients with GERD in our institution. Most of them were male for both groups with an average age of 60.8 years old among NERD and 59.2 years old among ERD patients. Majority GERD patients in our institution had normal BMI and ranged from 18.5 to 24.9 kg/m^2. This is in contrast with several studies

implicating an association between abdominal diameter and reflux-type symptoms mostly in the white population. However, there was no consistent association in the black and Asian population. According to a population-based, cross-sectional study conducted at Iran, there is no relationship between BMI and symptoms of GERD in a community of Asia. They concluded that high BMI plays a more important role to cause symptoms of GERD among Western population in comparison with Asian populations. Another cross-sectional study conducted at Kathmandu, Nepal found no statistically significant finding between the proportion of obesity measured by BMI with GERD. In addition, a population-based, cross sectional interview study made in Sweden also concluded that gastroesophageal reflux symptoms occur independently of BMI.

Table 1 also showed the baseline clinical profile of GERD patients in our institution. According to our study, baseline clinical profile of ERD and NERD patients had no significant statistical difference, hence, it did not vary considerably between the two groups.

Only the incidence of hiatal hernia and prevalence of diabetes between the two groups had statistical difference. The incidence of hiatal hernia was significantly higher among ERD patients (32.6% ERD; 17% NERD) whereas diabetes mellitus was significantly prevalent among NERD patients (20.7% NERD; 8.2% ERD).

A total of 61.5% of NERD patients responded to 4 week treatment of PPI and a total of 72.6% of ERD patients responded to 8 week treatment of PPI. According to ACG, it would be expected that approximately 60% of patient with NERD and 70-80% of patients with ERD would demonstrate complete relief on PPI therapy. This result is also consistent with the study of Heading et al., which concluded that patients with NERD have been found to respond to treatment less well than those with ERD. It is usually attributed to inclusion of some patients in the NERD group who do not have reflux disease, notably patients with ‘functional heartburn’, who are expected to respond poorly to acid suppression. Furthermore, a study of Lee Goh et al., investigated that Asian patients with GERD, especially those with NERD, may have lower response rates to PPI than Western populations. They reported that the interpretation and reporting of reflux symptoms is subject to ethnic variation such that Asian populations experience more atypical symptoms like chest pain while Western populations report more of heartburn. Also, they concluded that one of

the problems in defining GERD in Asia is that there is no direct translation of 'heartburn' in Asian languages making the diagnosis of GERD challenging. Hence, ethnic variation in symptom reporting cannot be ruled out as a possible cause for the differences between response rates of Asian populations and the rest of the world. In addition, the lower symptom response rate to PPI treatment for patients with NERD is likely due to heterogeneity and that patients with NERD have been reported to have a longer lag time for sustained symptom response than patients with ERD.

According to Jeong et al., GERD is a chronic condition, with 50-80% of patients experiencing recurrence within one year following completion of initial treatment. In our study, the relapse rate of GERD within 6 months following completion of treatment is 66.2% and 66.3% for NERD and ERD, respectively with no statistical difference in the relapse rate between the two groups (P-value 0.993). The relapse was highest on the 5^{th} month of NERD (19.3%) and 4^{th} month of ERD (23%) after treatment suspension. The result was consistent with the study of Lee et al., wherein 44.3% in the ERD group and 43.2% in the NERD group had symptomatic relapses after completion of 8 weeks of PPI treatment, however, these differences were not statistically significant (P-value 0.875). Similarly, the study of Yang et al. concluded that there is no statistical difference in the recurrence rate between the ERD (27.1%) and NERD (25.6%) patients (P = 0.849) after the initial response to 4-8 week of treatment with PPI.

The multiple logistic regression analysis further investigated the risk factors that could have lead to GERD relapse in our population. Among all factors considered, only NSAID use either prescribed, taken by self medication or part of patient's maintenance medications were significantly associated with relapse in both ERD and NERD group. Our institution delivers health care primarily to Veteran patients and their dependents. More than half of our patients belong to the elderly population in which polypharmacy is common. Moreover, 65-75% of our study population were hypertensive while up to 20% were diabetic. Hence, majority of them had encountered and at risk for cardiovascular events necessitating constant anticoagulation for primary or secondary prophylaxis. Part of their maintenance medication includes Aspirin (NSAID), Clopidogrel (anti-platelet) and novel oral anticoagulants. In addition, NSAIDS, either prescribed or self medicated, were still observed among our elderly patients as pain relievers for muscular or arthritic pain.

These findings coincide with those described in other studies like Lopez-Colombo et al. wherein he concluded in his multivariate analysis that the consumption of an NSAID ≥ 1 tablet per month and consumption of citrus fruits increased the possibility of GERD relapse. In addition, a large French population study mentioned by Ruszniewski et al., confirmed that NSAID use is a significant predictor of GERD symptoms that increases the risk of such symptoms by approximately 60%. Indeed, in their study, NSAID was the strongest risk factor identified. Daily use of aspirin was also associated with a significantly increased risk of GERD symptoms.

As we know, the associations between NSAID use and peptic ulcer disease are well-established. But in contrast, data concerning the relationship between NSAID use and GERD are limited. According to Ruszniewski et al., NSAID may act to increase the duration of acid reflux. In a prospective double-blind, randomized, placebo-controlled cross over study in 17 patients with symptomatic GERD, which used 24-hr esophageal pH monitoring at baseline and during treatment with Ibuprofen or placebo. The results showed that Ibuprofen significantly increased the percentage of time during the 24-h period that the esophageal pH was below 4 compared with both baseline and placebo treatment ($P < 0.05$ in both cases).

In our study, smoking was also significantly associated with GERD relapse but only in the NERD group. In relation to the study of Hershcovici et al., smoking may promote acid reflux by several mechanisms including attenuation of the tone at the lower esophageal sphincter, a delay in gastric emptying, an increase in gastric acid and pepsin production and a decrease in salivary bicarbonate secretion. Their study demonstrated that smoking was an independent predictor of reflux symptoms in NERD patients. In another study by Kahrilas et al., they stated that smoking had significant impact on gastro-esophageal reflux due to the fact that Nicotine reduces the lower esophageal sphincter pressure.

According to the local GERD guideline, when symptoms relapse after standard GERD treatment, on demand or intermittent PPI treatment is suggested for NERD while continuous PPI

treatment is recommended for moderate to severe erosive esophagitis. Similarly, according to Lee et al., on-demand therapy has been effective for long-term treatment of NERD while continuous maintenance therapy has been reported to be more effective than on-demand therapy in patients with ERD. These findings suggest that patients with ERD require more consistent acid suppression to stay in remission. In addition, the study of Lee et al. concluded that the relapse rates (44.3% in ERD and 43.2% in NERD) is very high such that GERD patients should be carefully followed up so that adequate treatment could be provided.

According to López-Colombo et al., given that it is a pathology that tends to become chronic, a longer treatment period of approximately 8-12 weeks could reduce the relapse rate of GERD and improve the quality of life of the affected individuals. However, in patients with persistent or recurrent symptoms, response is related to their predominant symptom. In patients with persistent GERD symptoms, longer treatment with PPIs would offer better results and additional studies would be indicated. The findings of the systematic review reported by Donnellan sustained the idea that prolonged period of treatment of esophagitis prevents relapse, in relation to both symptoms of GERD and endoscopic alterations.

CONCLUSION:

In conclusion, the most common clinical presenting symptoms of GERD patients in our institution are heartburn and acid regurgitation. The baseline clinical profile of ERD and NERD does not vary considerably between the two groups. The clinical response of NERD and ERD patients who receive the standard treatment are different. NERD have been found to respond to treatment less well than those with ERD. The relapse rate of GERD in our institution is high, hence, GERD patients should have a longer drug treatment duration and should be carefully followed up. The consumption of NSAID increased the possibility of ERD relapse while consumption of NSAID and smoking increased the possibility of NERD relapse in our institution.

RECOMMENDATION:

This study aims to specifically determine the clinical response of NERD and ERD after standard PPI therapy and to determine the relapse rate within 6 months for those who responded adequately. We recommend future studies regarding extended drug treatment duration for GERD and other risk factors associated with GERD relapse in our population. We also recommend lifestyle modifications as part of management in these patients for reducing the relapse rates after successful treatment with PPI.

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