**Original Article**

# Diagnostic utility of 24h esophageal impedance pH monitoring (Off PPI) in patients with refractory GERD referred to the hospital during 9 years

Running head: esophageal impedance pH monitoring

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**Abstract**

Gastric reflux is one of the most important causes of the referral of patients to the internal clinic, which in some cases causes problems for patients due to resistance to common treatments. Therefore, timely diagnosis and treatment of this group of patients is very important. The purpose of the present study was to determine the Off-PPI 24h PH Impedance (Off PPI) analysis in patients with Refractory GERD attending to Taleghani Hospital since 2009 to 2016. In this observational descriptive-comparative Off-PPI study, 572 patients with refractory GERD who were referred to Taleghani Hospital in Tehran from 2002 to 2010 were selected and the results of 24h PH Impedance (Off PPI) analysis were then assessed. The results of 24h PH Impedance (Off PPI) indicated that 7% of cases were belonged to Pure Acid Reflux followed by weakly Acid (1%), non-acid (0.3%), mixed & gas (5.2%), functional (58.4%) and esophageal hypersensitivity (28%). Furthermore, weakly acid plus acid was also found to be 8% and Weakly Acid + Acid + Non-Acid were determined as 8.3%. Regarding the obtained results, it may be concluded that nearly more than half of the patients with Refractory GERD would have functional disorder in 24h PH Impedance (Off PPI) analysis.

**Keywords:** Gastric reflux, PH Impedance, Acid plus acid, Diagnosis

**Introduction**

Reflux or GERD is one of the common gastrointestinal disorders, with many risk factors such as diabetes and hypertension 1. This disorder is present in 16% of the general population and can be associated with common clinical symptoms, such as heartburn and chest pain 2. However, clinical symptoms in GERD patients are not limited to gastrointestinal symptoms and can also be manifested as non-gastro-intestinal symptoms, including respiratory disorders, sleep disturbances, and atorvastinuratory symptoms 3. The disease causes a 2.5-hour absence from the workplace, a 23 percent reduction in efficiency, and a 30 percent reduction in the normal performance of the individual. In general, there is a significant reduction in the quality of life in patients suffering from GERD (4). It also imposes huge costs on individuals and health systems 5. Therefore, treatment for GERD patients is important for improving their quality of life. Treatment in this area is divided into two categories of therapeutic and surgical treatments, both of which not only reduce the severity of the symptoms of the patients, but also significantly improve their quality of life 6, 7. It is worth noting that, in both short and long term, the effectiveness of surgical treatments is far more than pharmaceutical treatments, and drug therapies are particularly effective on clinical symptoms such as dysphagia 6, 8. However, 40% of patients do not show any proper therapeutic response, and they refer to refractory GERD, which requires the adoption of other therapies 9. The causes of GERD Refractory include Acid Reflux, Non Acid Reflux, Esophageal Hypersensitivity, and Functional Heart Burn 10. Moreover, only a few studies have been done in Iranian patients 11-13.Regarding the importance of reducing disease burden, the current study was aimed to evaluate the causes of refractory GERD in patients who referred to Taleghani Hospital from 1988 to 1995 as Off-PPI.

**Methods**

This study was conducted on the basis of a descriptive cross*-*sectional study of Off-PPI. A total of 572 patients with refractory GERD who referred to Tehran Taleghani Hospital from 2009 to 2017 were evaluated. Endoscopy results and response to medical treatment were controled as interventional factors. In the manometer, the absence of motion disorders, such as achalasia and diffuse esophageal spasm (DES), was confirmed.

The required data were extracted from patients' files, including the age, sex, duration of GERD symptoms, pH and Impedance parameters, and SAP, as well as proximal extension and BCT. Then, the prevalence of different parameters of 24h PH Impedance (Off PPI) was extracted from them using file contents. Finally, data analysis was performed using SPSS software version 24. The mean, and standard deviations were used to evaluate quantitative variables, where qualitative variables were presented as absolute and relative frequency. The tests used in this field included Chi-Square and analysis of variance. The significance level for the relationships between variables was considered 0.5.

Inclusion criteria

Failure of medical treatment with protein pumps inhibitors (PPIs) for at least one month, once or twice daily 12.

Exclusion criteria

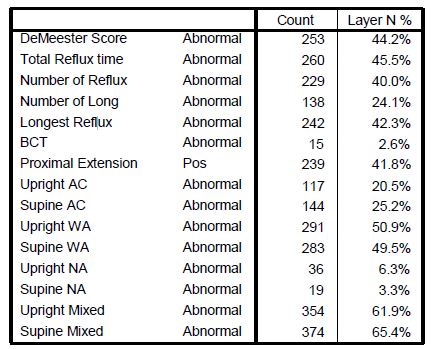
Patients who have had anti-reflux surgery, either PPI or H2-blocker, 2. Patients with atypical GERD symptoms, 3. Motion disorders, such as achalasia and diffuse esophageal spasm, 4. Non-Iranian patients, 5. Patients with abnormal manometry, 6. Age younger than 18 or over 80 years old. 7. Systemic disease

Ethical considerations

In this study, the information remained confidential.

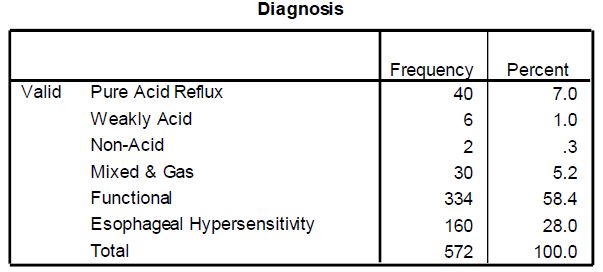
**Results**  
In this study, 572 subjects were studied. Their mean age was 38.2 years (range 18-80 years), and mean duration of clinical symptoms was 5.1 years (from 1 to 16 years). Also, 48.3% were males and 51.7% were females. Demeester Score was abnormal in 44.2% of patients and Total Reflux Time in 45.5% of patients. The frequency of reflux and the frequency of long-term reflux was 40% and 24.1%, respectively. In 2.6% of patients, BCT was abnormal and Proximal Extension was observed in 41.8% of subjects. AC findings in the upright and supine positions were attributed to frequencies of 20.5% and 25.2%, respectively. WA findings in the Upright and supine positions were abnormal in 50.9% and 49.5% respectively. Abnormal NA findings in the upright and supine positions were observed at 6.3 and 3.3 percent. Mixed findings were abnormal in 61.9% and 65.4%, based on the upright and supine positions (Table 1).

**Table 1:** Frequency distribution of data based on various findings in patients



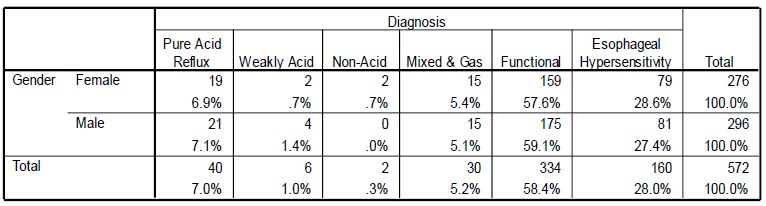
SAP findings were related to the symptoms of the patient in 55.8% of the patients, while 30.2% of the patients had SAP findings without any association with the symptoms of the patient. They were also Results in 7% of cases were Pure Acid Reflux followed by Weakly Acid (1% ), Non-Acid (0.3%), Mixed & Gas (5.2%) , Functional (58.4% ) and Esophageal Hypersensitivity (28%). Furthermore, Weakly Acid plus Acid was also found to be 8% and Weakly Acid + Acid + Non-Acid were determined as 8.3% (Table 2).

**Table 2:** Frequency of diagnosis in patients

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Analysis of variance (ANOVA) did not show a significant difference in the frequency distribution of diagnosis based on the age of the patients (P = 0.216). The frequency distribution of diagnosis did not show a significant statistical relationship in terms of gender based on Chi-square test (P = 0.721). The prevalence of functional conditions in men and women was revealed to be 59.1 and 57.6%, respectively while the cases of hypersensitivity were reported in 27.4% of men and 28.6% of women (Table 3).

**Table 3:** Distribution of diagnosis based on gender



The frequency of diagnosis showed that the duration of symptoms was not statistically significant (P = 0.429) based on ANOVA test.

**Discussion**

Gastroesophageal reflux disease (GERD) is a long-term condition in which stomach contents enter the esophagus and cause symptoms or complications. Complications include esophagitis, esophageal strictures, and Barrett's esophagus. There are a number of risk factors involved in the disease, including obesity, pregnancy, smoking, hiatus hernia, and taking some special medications. Drugs that affect gastric reflux are described to be as follow: antihistamines, calcium channel blockers, antidepressants and sleep medications. Diagnosis among people who do not respond in simple ways may be done in other ways, such as [gastroscopy](https://en.wikipedia.org/wiki/Gastroscopy), [esophageal pH monitoring](https://en.wikipedia.org/wiki/Esophageal_pH_monitoring), and or Impedance-PH Monitoring 13-16. Impedance-PH Monitoring is not available at some centers and its cost is one of its disadvantages. In this study, we investigated the various causes of GERD refractory in patients who were referred to Taleghani patient in Tehran from 2009 to 2017 (13-13). All subjects in this study were Off PPI, meaning that patients did not take PPI and anti-acid for 2 weeks before testing. The test results showed that 7% of the cases belonged to Pure Acid Reflux based on 24 h PH Impedance (Off PPI), followed by Weakly Acid (1% ), Non-Acid (0.3%), Mixed & Gas (5.2%) , Functional (58.4% ) and Esophageal Hypersensitivity (28%). In addition, Weakly Acid + Acid + Non-Acid cases were found to be 8.3%, where is the most common cause of refractory cases followed by hypersensitivity, which is consistent with other studies in this area 17. These results are consistent with other studies in this area 17. Penagini et al. (2015) in Italy evaluated 50 patients with refractory GERD. They determined that 15 of the patients (30%) had Functional Heart Burn 18, while this rate was about 2 times higher in our research. In a cross-sectional study, Frazzoni et al., examined 80 patients with refractory GERD, 35% of them had Functional Heart Burn 19, which was lower than the result of our study. In another study, Savarino et al performed an analytical cross-sectional study in Italy with 219 patients suffering from refractory GERD that 39% had Functional Heart Burn 20. In the present study, this was higher which could be due to the 3-fold sample size.

Jung et al, (2007) in the United States, assessed 2298 patients with refractory GERD, and found that 3% of men and 4% of women had suffered from functional disorders such as Functional Heart Burn 21. The results of the study are in agreement with the results of the current study. Because ,it does not show a significant statistical difference based on gender. In another study by Savarino et al. In 2009 found that 27% of patients with refractory GERD suffered from Functional Heart Burn 22, which was half the amount, obtained in our study. The higher number of the present study can be because of the examination center as a referral hospital. A cross-sectional study by mohammed khan et al in 2014 found that almost 60% of patients with refractory PPIs NERD and SAP (+) had no acid reflux, and about half of NERD patients on PPI had normal MII-pH monitoring, which was equally divided into two groups: Functional Heart Burn and hyper-sensitive esophagus 23. We did not find this equal ratio in our study and the frequency of functional cases was higher. Herregods et al. Reported in an analytical cross-sectional report that roughly one third of patients referring to GERD symptoms have problems other than reflux, the most common of which is Functional Heart Burn. This justifies why these patients do not benefit from anti-acid therapy 24, and in our study this is clearly proven. Moreover, different studies on various subjects have published the regarding to above results 25-29

**Conclusions**

Overall, the results of this study suggest that more than half of patients with refractory GERD in the 24h PH Impedance analysis (Off PPI) have functional disorders. With regard to the high incidence of functional and hypersensitivity cases, we can treat the remaining cases according to the prevalence before making expensive and inaccessible tests. It is advisable to use a course of treatment for Functional and Hypersensitivity, such as SSRI (fluoxetine, etc.). The above findings can be used in the development of Refractory GERD Guideline for Iranian patients in order to localize information. Moreover, similar studies are needed in different races of Iranian patients with different dietary habits.

**Conflict of interest**

None

**References**

1. Chen T, Lu M, Wang X, et al. Prevalence and risk factors of gastroesophageal reflux symptoms in a Chinese retiree cohort. BMC Gastroenterol. 2012;12:161
2. Sharma PK, Ahuja V, Madan K, Gupta S, Raizada A, Sharma MP. Prevalence, severity, and risk factors of symptomatic gastroesophageal reflux disease among employees of a large hospital in northern India. Indian J Gastroenterol. 2011;30:128-34
3. Malfertheiner P, Hallerbäck B. Clinical manifestations and complications of gastroesophageal reflux disease (GERD). Int J Clin Pract. 2005;59:346-55
4. Wahlqvist P. Symptoms of gastroesophageal reflux disease, perceived productivity, and health-related quality of life. Am J Gastroenterol. 2001; 96:S57-61.
5. Gisbert JP, Cooper A, Karagiannis D, et al. Impact of gastroesophageal reflux disease on work absenteeism, presenteeism and productivity in daily life: a European observational study. Health Qual Life Outcomes. 2009; 7:90.
6. Ciovica R, Gadenstätter M, Klingler A, Lechner W, Riedl O, Schwab GP. Quality of life in GERD patients: medical treatment versus antireflux surgery. J Gastrointest Surg. 2006; 10:934-9.
7. Scholten T. Long-term management of gastroesophageal reflux disease with pantoprazole. Ther Clin Risk Manag. 2007; 3:231-43.
8. Wetscher GJ, Glaser K, Gadenstaetter M, Profanter C, Hinder RA. The effect of medical therapy and antireflux surgery on dysPHagia in patients with gastroesophageal reflux disease without esophageal stricture. Am J Surg. 1999; 177:189-92.
9. Fass R, Gasiorowska A. Refractory GERD: what is it? Curr Gastroenterol Rep. 2008; 10:252-7.
10. Fass R. Functional heart burn. Gastroenterol Hepatol. 2014; 10:381-3.
11. Talaie R, Forootan M, Donboli K, et al. 24-hour ambulatory PH-metry in patients with refractory heartburn: a prospective study. J Gastrointestin Liver Dis. 2009; 18(1):11-5.
12. Forootan M, Ardeshiri M, Etemadi N, Maghsoodi N, Poorsaadati S. Findings of impedance PH-monitoring in patients with atypical gastroesophageal reflux symptoms. Gastroenterol Hepatol Bed Bench 2013; 6:S117-S121.
13. Mirbagheri SA, Sadeghi A, Amouie M, et al. Pyloric injection of botulinum toxin for the treatment of Refractory GERD accompanied with gastroparesis: a preliminary report. Dig Dis Sci. 2008; 53:2621-6.

# [Ates F](https://www.ncbi.nlm.nih.gov/pubmed/?term=Ates%20F%5BAuthor%5D&cauthor=true&cauthor_uid=24745809), [Francis DO](https://www.ncbi.nlm.nih.gov/pubmed/?term=Francis%20DO%5BAuthor%5D&cauthor=true&cauthor_uid=24745809), [Vaezi MF](https://www.ncbi.nlm.nih.gov/pubmed/?term=Vaezi%20MF%5BAuthor%5D&cauthor=true&cauthor_uid=24745809). Refractory gastroesophageal reflux disease: advances and treatment. [Expert Rev Gastroenterol Hepatol.](https://www.ncbi.nlm.nih.gov/pubmed/24745809" \o "Expert review of gastroenterology & hepatology.) 2014;8:657-67.

# [Serra Pueyo J](https://www.ncbi.nlm.nih.gov/pubmed/?term=Serra%20Pueyo%20J%5BAuthor%5D&cauthor=true&cauthor_uid=24355558). Update on gastroesophageal reflux disease. [Gastroenterol Hepatol.](https://www.ncbi.nlm.nih.gov/pubmed/24355558" \o "Gastroenterologia y hepatologia.) 2014;37:73-82.

# Haider SH, Kwon S, Lam R, et al. [Predictive Biomarkers of Gastroesophageal Reflux Disease and Barrett's Esophagus in World Trade Center Exposed Firefighters: a 15 Year Longitudinal Study.](https://www.ncbi.nlm.nih.gov/pubmed/29449669) Sci Rep. 2018;8:3106.

1. Pritchett, Jason M. Efficacy of esophageal impedance/PH monitoring in patients with refractory gastroesoPHageal reflux disease, on and off therapy. Clinical Gastroenterology and Hepatology. 2009; 7: 743-8.
2. Penagini R, Sweis R, Mauro A, Domingues G, Vales A, Sifrim D. Inconsistency in the Diagnosis of Functional Heartburn: Usefulness of Prolonged Wireless PH Monitoring in Patients with Proton Pump Inhibitor Refractory GastroesoPHageal Reflux Disease. J Neurogastroenterol Motil. 2015; 21:265-72.
3. Frazzoni M, Conigliaro R, Mirante VG, Melotti G. The added value of quantitative analysis of on-therapy impedance-PH parameters in distinguishing refractory non-erosive reflux disease from functional heartburn. Neurogastroenterol Motil. 2012;24(2):141-6, e87.
4. Savarino E, Marabotto E, Zentilin P, et al. The added value of impedance-PH monitoring to Rome III criteria in distinguishing functional heartburn from non-erosive reflux disease. Dig Liver Dis. 2011; 43:542-7.
5. Jung HK, Halder S, McNally M, et al. Overlap of gastro-oesoPHageal reflux disease and irritable bowel syndrome: prevalence and risk factors in the general population. Aliment PHarmacol Ther. 2007; 26:453-61.
6. Savarino E, Pohl D, Zentilin P, et al. Functional heartburn has more in common with functional dyspepsia than with non-erosive reflux disease.Gut. 2009; 58:1185-91.
7. [Khan MQ](https://www.ncbi.nlm.nih.gov/pubmed/?term=Khan%20MQ%5BAuthor%5D&cauthor=true&cauthor_uid=25273120), [Alaraj A](https://www.ncbi.nlm.nih.gov/pubmed/?term=Alaraj%20A%5BAuthor%5D&cauthor=true&cauthor_uid=25273120), [Alsohaibani F](https://www.ncbi.nlm.nih.gov/pubmed/?term=Alsohaibani%20F%5BAuthor%5D&cauthor=true&cauthor_uid=25273120)., et al. Diagnostic utility of impedance-PH monitoring in refractory non-erosive reflux disease. Journal of neurogastroenterology and motility 2014; 20: 497-505.
8. [Herregods TV](https://www.ncbi.nlm.nih.gov/pubmed/?term=Herregods%20TV%5BAuthor%5D&cauthor=true&cauthor_uid=26088946), [Troelstra M](https://www.ncbi.nlm.nih.gov/pubmed/?term=Troelstra%20M%5BAuthor%5D&cauthor=true&cauthor_uid=26088946), [Weijenborg PW](https://www.ncbi.nlm.nih.gov/pubmed/?term=Weijenborg%20PW%5BAuthor%5D&cauthor=true&cauthor_uid=26088946)., et al. Patients with refractory reflux symptoms often do not have GERD. Neurogastroenterology Motility 2015; 27: 1267-73.
9. Foroutan M, Loloei B, Irvani S, Azargashb E. Accuracy of rapid urease test in diagnosing Helicobacter pylori infection in patients using NSAIDs. Saudi J Gastroenterol 2010;16(2):110-112.
10. Keshavarz MA, Moradi S, Emami Z, Rohani F.Association between serum 25(OH) vitamin D and metabolic disturbances in polycystic ovary syndrome.Neth J Med. 2017 ;75(5):190-195.
11. Forootan M, Tabatabaeefar M, Mosaffa N, Ashkalak HR, Darvishi M.Investigating Esophageal Stent-Placement Outcomes in Patients with Inoperable Non-Cervical Esophageal Cancer.J Cancer. 2018 ;9(1):213-218.
12. Moradi S, Sahebi Z, Ebrahim Valojerdi A, Rohani F, Ebrahimi H.The association between the number of office visits and the control of cardiovascular risk factors in Iranian patients with type2 diabetes.PLoS One. 2017;12(6):e0179190.
13. Zare Mehrjardi M, Bagheri SM, Darabi M.Successful ultrasound-guided percutaneous embolization of renal pseudoaneurysm by autologous blood clot: Preliminary report of a new method.J Clin Ultrasound. 2017;45(9):592-596.