

Diagnostic Approach to Gastroesophageal Reflux Disease: The Role of GERD Questionnaire and PPI Test

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ABSTRACT

Gastroesophageal reflux disease (GERD), according to American College of Gastroenterology (ACG), is symptoms or mucosal damage produced by abnormal reflux of gastric contents into the esophagus. In most patients with GERD, showed no abnormalities in the endoscopic picture. This is what underlies the importance of a diagnostic tool in the form of assessment for the degree of severity of the disease based on symptoms, response to therapy and effect on the patients' quality of life. This diagnostic tool is then formulated in the form of a questionnaire (GERD questionnaire). Response to treatment with proton pump inhibitor (PPI) drugs is also often used to support the diagnosis of this disease.

Diamond study is a large study which aim to assess the accuration of the questionnaire and use of PPI test. Diagnostic method with questionnaire modality and followed by PPI test have sensitivity and specificity value, which are relatively similar to the symptoms-based diagnoses performed by general practitioners or gastroenterologist, as well as when compared to endoscopy and esophageal pH monitoring. Although the diagnosis by methods of questionnaires and PPI test is not the most ideal test in term of accuracy, but these tests are not expensive, readily available and worked mainly on primary health care. These test methods are favored compared to other tests.

Keywords: *gastroesophageal reflux disease (GERD), GERD questionnaire (GERDQ), proton pump inhibitor (PPI) test*

ABSTRAK

Penyakit refluks gastroesofagus, menurut American College of Gastroenterology (ACG), yaitu kerusakan mukosa yang diakibatkan oleh refluks abnormal dari isi lambung ke esofagus. Penyakit refluks gastroesofagus (gastroesophageal reflux disease/GERD) pada sebagian besar pasien tidak memperlihatkan kelainan pada gambaran endoskopinya. Hal inilah yang mendasari pentingnya sebuah alat diagnostik berupa penilaian derajat keparahan berdasarkan gejala, respon terhadap terapi dan pengaruhnya terhadap kualitas hidup pasien. Alat diagnostik ini kemudian dirumuskan dalam bentuk sebuah kuesioner (GERD questionnaire). Respon terhadap pengobatan dengan obat-obatan dari golongan inhibitor pompa proton (proton pump inhibitor/PPI) juga sering digunakan untuk mendukung diagnosis penyakit ini.

Studi Diamond yaitu sebuah studi besar yang dikerjakan untuk menilai akurasi kuesioner dan penggunaan tes PPI. metode diagnostik dengan modalitas kuisoner dan diikuti oleh PPI test memiliki angka sensitivitas

dan spesifisitas yang relatif sama dengan diagnosis berbasis gejala yang dilakukan oleh dokter umum maupun gastroenterologis, begitupun jika dibandingkan dengan pemeriksaan endoskopi dan pemantauan pH esofagus. Meskipun penegakan diagnosis dengan cara kuesioner dan PPI test bukan merupakan uji dengan akurasi yang paling ideal, akan tetapi pemeriksaan ini tidak mahal, pilihan yang mudah didapatkan dan dikerjakan terutama pada pelayanan kesehatan primer. Hal inilah yang diunggulkan dibandingkan pemeriksaan lainnya.

Kata kunci: penyakit refluks gastroesofagus, kuesioner gastroesophageal reflux disease, tes proton pump inhibitor

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a gastrointestinal disease which fairly common but the prevalence very diverse worldwide.¹ This disease is very common in Western Countries which occurs in 10-30% of population. In Singapore, the prevalence of gastroesophageal reflux disease's symptoms increased sharply from 1,6% of population in 1994 to 10,6% in 2001.¹ In Indonesia, there has been no representative data to describe the incidence of this disease, but data from Rumah Sakit Cipto Mangunkusumo (RSCM) showed that there is increased of prevalence from 6% in 1997 to 26% in 2002 on patients which undergone upper gastrointestinal endoscopy. This increasing trend is predicted caused by many things, which one of them is the increased use of endoscopic modalities.

The increasing prevalence due to the use of endoscopic modalities is very helpful in describing the actual conditions, especially in big cities, but it became a distinctive obstacle for regions with less advanced health facilities. These conditions need to be addressed with a more simple modalities which able to reach all areas, validated and reliable. Of course, use of gastroesophageal reflux disease questionnaire (GERDQ) and PPI test are expected to solve this problem. This paper will be presented the role and position of GERDQ and PPI test in diagnosis of gastroesophageal reflux disease.

The purpose of this literature review is to know the position of GERDQ and PPI test use in the diagnosis of gastroesophageal reflux disease. This brief paper also aims to provide a basis for the primary health care providers to not hesitate in diagnosing the gastroesophageal reflux disease.

GASTROESOPHAGEAL REFLUX DISEASE

Definition of Gastroesophageal Reflux Disease

Definition of gastroesophageal reflux disease based on the consensus of international experts group which known as Montreal definition. Gastroesophageal

disease defined as a condition that arises due to reflux of stomach contents which caused irritating symptoms and/or its complications.¹ What referred to irritating symptoms are any symptoms that lower the quality of life of patients. These symptoms need to be confirmed in order to differentiate the symptoms of gastroesophageal reflux disease from episodic burning sensation in the chest.

Another definition of gastroesophageal reflux disease are based on American College of Gastroenterology (ACG), is symptoms or mucosal damage produced by abnormal reflux of gastric contents into the esophagus.² The latter definition can refer to the findings at endoscopy, but it is also need to keep in mind that not all gastroesophageal reflux disease required endoscopy.

Definition of gastroesophageal reflux disease	
Genval Workshop Report (1999)	Individuals exposed to the risk of physical complications from gastroesophageal reflux or those who experience clinically significant impairment of health-related well-being (quality of life) because of reflux-related symptoms, after adequate reassurance of the benign nature of their symptoms
Canadian Consensus Conference(2004)	The reflux of gastric contents into the esophagus causing symptoms sufficient to reduce quality of life or cause injury. Endoscopy negative reflux disease and normal endoscopy findings
American College of Gastroenterology (2005)	Symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus
Montreal Definition (2006)	A condition that develops when reflux of gastric contents causes troublesome symptoms or complications
American Gastroenterological Association (2008)	Montreal definition adopted

Figure 1. Definitions of gastroesophageal reflux disease³

Clinical Manifestations of Gastroesophageal Reflux Disease

Most typical clinical manifestations of gastroesophageal reflux disease are burning sensation in the chest and regurgitation. Burning sensation in the

chest defined as a burning sensation in the retrosternal area, while regurgitation defined as perception of flow or reflux of stomach contents into the mouth or hypopharynx. These two symptoms are assessed fairly descriptive to diagnose GERD. Dysphagia symptom is generally more often to appears if a burning sensation occurs long enough and in patients with erosive esophagitis. Dyspeptic symptoms mostly can be resolved with the administration of proton pump inhibitor (PPI). Slowly progressive dysphagia, especially for solid food with obstructive esophageal obstruction are suggestive for peptic stricture. Symptoms outside the esophagus which can be categorized as gastroesophageal reflux disease are chest pain, sleep disorders, cough, hoarseness and asthma.^{4,5}

Diagnosis of Gastroesophageal Reflux Disease

Based on Montreal definition and the acceptance of empiric therapy, there is no specific diagnostic test in the management of patients with gastroesophageal reflux disease. Diagnostic tools which needed must meet these two things: (1) Identification of complications of the disease; (2) Evaluating patients who have failed to be treated with empiric therapy.² Signs which make health practitioners should evaluated the empirical therapy in patients with suspected gastroesophageal reflux disease called alarm signs.⁴ Those alarm signs are vomiting, upper gastrointestinal bleeding, weight loss, dysphagia, anemia, and epigastric mass. Nevertheless, the evidence to support this, is very little. Another perspective found in a meta-analysis found that alarm signs in patients with upper gastrointestinal malignancy has 67% sensitivity and 66% specificity. This prompted the need of endoscopic examination for follow-up alarm signs.

Endoscopic and 24-hour esophageal pH probe examination initially recommended as the gold standard for the diagnosis of gastroesophageal reflux disease.¹ However, it is estimated that more than 70% of patients with typical symptoms of gastroesophageal reflux disease have a normal esophageal mucosa with endoscopic examination. 24-hour esophageal pH probe examination is not sensitive enough to be one of the diagnosis criteria. One study in China found that 63 of 102 patients with this disease is endoscopically positive, and 84 patients of the 115 patients who had a positive result on a 24-hour esophageal pH probe.¹ Furthermore, these two modalities are quite expensive and not readily available in small hospitals or clinics. Because of there are no gold standard

for gastroesophageal reflux disease diagnosis, valid assessment of symptoms is very important.

Endoscopy

Endoscopy is a diagnostic test which first considered in GERD diagnosis because of its capabilities to showed Barret metaplasia, stricture or diagnosis of another upper gastrointestinal diseases in patients.⁴ However, correlation between endoscopic findings and severity of symptoms is very weak. Endoscopy must be considered in patients which already have gastroesophageal reflux disease patients for more than 5 years, have alarm signs, and to search Barret esophagus.

Esophageal pH Monitoring Examination

Esophageal pH monitoring examination are invasive procedure which can be done after endoscopic and histopatologic examination showed normal result in patients with typical reflux symptoms. Applications of this examination is varied, probe can be placed 1 cm or 5 cm from gastric sfingter and duration of probe placed also varied (some said it can be done momentarily, but others said 24 hours examination is better). As with endoscopy, this modality also not readily available in primary health care centers so its use is very limited.

GERD Questionnaire

Some diagnostic tools have been tried to use in helping physicians in diagnose GERD. Dent et al reported a study entitled "Accuracy of the diagnosis of GERD by questionnaire, physicians and a trial of PPI treatment: The Diamond Study", the result is gastroesophageal reflux disease diagnosis based on symptoms with questionnaire have the same accuracy as diagnosis based on symptoms by a general practitioner or gastroenterologist.⁶

Proton Pump Inhibitor (PPI) Test

This test is one of the modalities to be considered when endoscopic diagnostic resources not available. Patients with typical symptoms will be given a double dose PPI for two weeks then the clinical response assessed. This test usually follow GERDQ or used alone as a diagnostic modality in places with limited resources. If this PPI test done after GERDQ, then the evaluation also use GERDQ. Administration of PPI will be continued with the usual doses if the patient had clinical improvement, and the patients will be considered have gastroesophageal reflux disease.⁴

ROLE OF GERD QUESTIONNAIRE AND PPI TEST

GERD Questionnaire

As previously described, gastroesophageal reflux disease occurs quite often, but most patients do not show abnormalities in the endoscopic findings. This is what underlies the importance of a diagnostic tool based on assessment for the degree of severity of the disease based on symptoms, response to therapy and effect on the patients' quality of life.⁷ This diagnostic tool is then formulated in the form of a questionnaire (GERD Questionnaire).

In general, symptom based questionnaire can be used as a discriminatory, predictive, or evaluative instrument. Discriminatory instrument is intended to distinguish this group of patients and to classify patients into a few degrees of severity and frequency of the disease. If used as a diagnostic instrument, the discriminatory questionnaire must have very specific questions, can rule out other diseases, and has high probability prediction. Questionnaire as a predictive instrument is used if there is a gold standard examination. Evaluative questionnaire with a scale used to assess the magnitude of change in the degree

of severity at certain times on individual and group. Of the three types of the questionnaire, GERDQ expected to meet three types.

There are several requirements that must be met for a good questionnaire, which are: (1) Sensitive to detect GERD patients; (2) Includes data on the frequency and intensity of symptoms of typical and atypical GERD; (3) Multidimensional (not only includes medical problems); (4) Have psychometric characteristics that can be proven (validity, level of confidence, reliability); (5) Practical and economical; (6) Can be done by the patient itself, without having to be accompanied (*self-assessed*); (7) Use language that easily understood by patients; (8) Provide a fast response to a change in the short term; (9) Can be used in daily settings to provide assessments during and after therapy; (10) Valid in different languages, for use on an international scale.¹¹

Some questionnaires have been made to answer some of these requirements. In general, the questionnaires are divided into symptomatology questionnaires (based on symptoms), questionnaires based on effect of the disease on quality of life, and serto questionnaire that combines both. The grouping of the questionnaires can be seen in the following table 1.

Table 1. Various questionnaires used to aid diagnose GERD¹¹

Symptomatology questionnaires (based on symptoms)	Questionnaires based on effect of the disease on quality of life	Questionnaire that combines both
Specific for GERD	Specific for GERD	Questionnaires by Colwell et al and Mathias et al
GERD specific esophageal symptom questionnaire	Gastroesophageal reflux disease health-related quality of life (GERD-HRQL)	HRQoL batteries
GERD specific questionnaire by Mold et al	Heartburn - specific quality of life instrument (HBQOL)	Domestic/International Gastroenterology Surveillance Study (DIGEST)
GERD specific questionnaire by R��ih�� et al	GERD specific QoL questionnaire by Jasani et al	Reflux questionnaire (ReQuest)
GERD questionnaire	QOL questionnaire in gastroesophageal reflux (Reflux-Qual)	Nocturnal GERD symptom severity and impact questionnaire (N-GSSIQ)
Infant gastroesophageal reflux questionnaire (I-GERQ)	Reflux-qual short-form (RQS)	
Gastroesophageal reflux questionnaire (GERQ)	Work Productivity and Activity Impairment Questionnaire for GERD (WPAI-GERD)	
GERD Activity Index (GRACI)	QoL questionnaire for patients undergoing antireflux surgery (QOLARS)	
GERD specific questionnaire by Carlsson et al	GERD-QOL	
GERD specific questionnaire by Manterola et al	Specific for Gastrointestinal	
GERD score	Gastrointestinal quality of life index (GIQLI)	
GERD Symptom Assessment Scale (GSAS)	Quality of life in reflux and dyspepsia (QOLRAD)	
GERD screener	Patient assessment of upper gastrointestinal disorders (PAGI-QOL)	
Questionnaire used by Vigneri et al		
Reflux disease diagnostic questionnaire (RDQ)		
Chinese GERD Questionnaire (Chinese GERDQ)		
Score related to GERD		
Standardized esophageal symptom questionnaire		
Questionnaire by Andersen et al		
Gastrointestinal Symptoms Rating Scale (GSRS)		
Questionnaire by Ruth et al		
Ulcer esophagitis subjective symptoms scale (UESS)		
Digestive health status instrument (DHSI)		
Modified bowel disease questionnaire (BDQ)		

Tabel 2. Results of systematic review on various GERD questionnaires⁷

Name	GERD-specific	Multidimensional	Self-assessed	Daily assessed	Available in different languages	Psychometrically validated
GERD Score	✓	-	-	-	-	✓
UESS	-	✓	✓	-	-	✓
GSAS	✓	✓	✓	-	-	✓
GSRS	-	-	✓	-	✓	✓
GRACI	✓	-	(✓)*	(✓)*	-	-

GERD: gastro-esophageal reflux disease; GRACI: GERD activity index; GSAS: GERD symptom assesment scale; GSRS: gastrointestinal symptoms rating scale; UESS: ulcer oesophagitis subjective symptom scale

*only parts of the scale

From many questionnaires which successfully documented, no one can be taken as the gold standard questionnaire.³ A systematic review conducted in 2004 showed that there are 5 pieces questionnaire that almost meets all the criterias of an ideal GERD questionnaire, but this study too long that a more contemporary study need to be conduct. Those five questionnaires can be seen in the following table 2.

The big question is which questionnaire that can be widely or generally used and how to choose the most appropriate questionnaire for the clinical situation in Indonesia, and how the actual role of this questionnaire in diagnosing gastroesophageal reflux disease. To answer some of these questions, there is a recent large study on the role of GERD questionnaire in 2009 which quite helpful to help answering doubts about the use of questionnaires as an approach in diagnosing gastroesophageal reflux disease. Details of the study will be discussed later.

Proton Pump Inhibitor (PPI) Test

Response to treatment with drugs from class of proton pump inhibitor (PPI), often used to support the diagnosis of gastroesophageal reflux disease, however the accuracy of this strategy is often questioned.⁸ Among some of the questions is whether this test can be applied in all cases, and whether this test can be used to replace other tests that are invasive and uncomfortable. Rationalization of the use of high-dose PPI drugs with a short duration as a diagnostic modality is its effect on gastric acid secretion to cope with erosive esophagitis and improve the symptoms of GERD.⁹ In general, PPI drugs can provide the acid suppressive effect within 1-28 days, because it is used to help diagnosis, then high dose of PPI is used to boost the effects supresinya and immediately improve patient complaints. The high doses expected to give effect before 28 days. The dose used in several large studies are double-dose PPI, which are 40-80 mg omeprazole, 30-60 mg lansoprazole, and 40 mg rabeprazole.¹⁰ Duration which widely used is 7-14 days. There is no definite strategy regarding this test procedure.

The type of PPI used varied, the most common is omeprazole, so this test once regarded as omeprazole test. New classes of drugs that are often used for research is omeprazole, but its effectiveness was similar to other drugs, if intended for PPI test. Large studies on this test using oral PPI, no one was using intravenous PPI with consideration of the application in the field, and this research subjects is intended for outpatients. The strategy for increasing the role of doctors in primary cares in improving diagnosis of GERD because the scope of this strategy is very simple and well tolerated by patients.

Disadvantages of this test is the absence of a standard test or the definitive gold standard for diagnosing GERD. In some studies, the PPI test is often compared to endoscopy and pH examination, by the fact that these two examinations also has many limitations. Because of these difficulties, the methods vary between studies, and the populations are different, therefore a lot of research data difficult to be compared. Sensitivity and specificity value became very wide, which are 27-89% for sensitivity and 35-73% for specificity. Schindlbeck et al showed that 40 mg omeprazole per day for 7 days resulted in a sensitivity of 27% and will be increased to 83% when the drug dose was increased to 40 mg twice daily. Fass et al stated that the omeprazole dose lower than previous studies (60 mg); which are 40 mg before breakfast, 20 mg before dinner; for 7 days will result in 80% for sensitivity of 80%. Study by Fass use 50% symptoms reduction as a positive limit value, if the value of this limit was increased to 75% symptoms reduction (clinical improvement) then the sensitivity value will increased to 86% with 91% positive predictive value and accuracy of 81%.¹⁰

A large study in India who studied algorithms diagnosis of gastroesophageal reflux disease stated that combination of a PPI test, endoscopy and histology examination can identify all cases of gastroesophageal reflux disease in the study, but not if the three tests stand on their own.¹¹ From the previous decription, it can be

concluded that the PPI test provides real benefits in diagnosing GERD, especially if the test is combined with other diagnostic.

Economic analysis test has also been used to determine the position of the PPI test in terms of efficiency of health cost. Economic analysis have stated that this test proven to reduce the cost of health expenditure because it can prevent the use of other diagnostic methods which are more expensive with high sensitivity and specificity that is not much different. This test saves 64% expenditure when compared to endoscopy, and saves 53% expenditure when compared to the 24-hour pH measurement.¹⁰

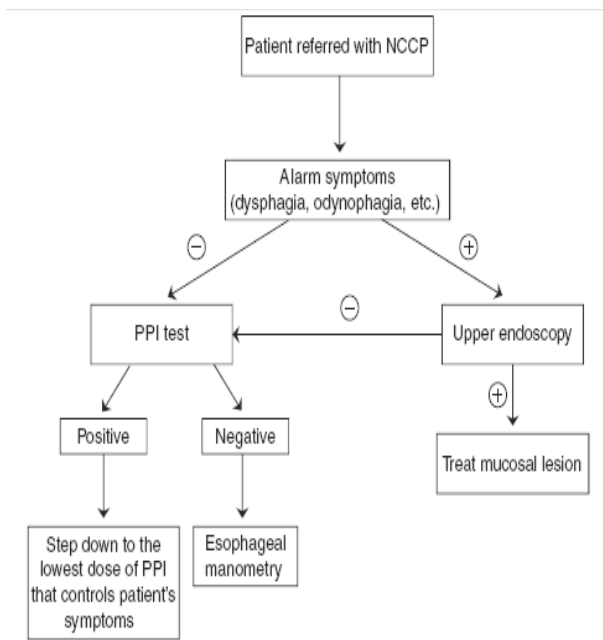


Figure 3. Position of PPI test at GERD diagnosis algorithm with non-cardiac chest pain symptoms

The algorithm showed above was proposed in clinical review conducted in 2008. The main approach of the diagnostic flow is patients with symptoms of with symptoms of heartburn or non-cardiac chest pain which is a classic symptom of GERD beside regurgitation. This algorithm showed that the position of the PPI test is quite useful and economically efficient.

The diagnostic algorithm illustrated above can also describe the role of PPI test in everyday clinical practices. The more specific symptoms the patient complained of, and if accompanied by signs of alarm, then the possibility of erosive esophagitis pathological features can be found is more likely. If the histological features is so clear then PPI test is not needed, but on the contrary, the more unspecific symptoms of GERD, the PPI test is more necessary to help establish the diagnosis.

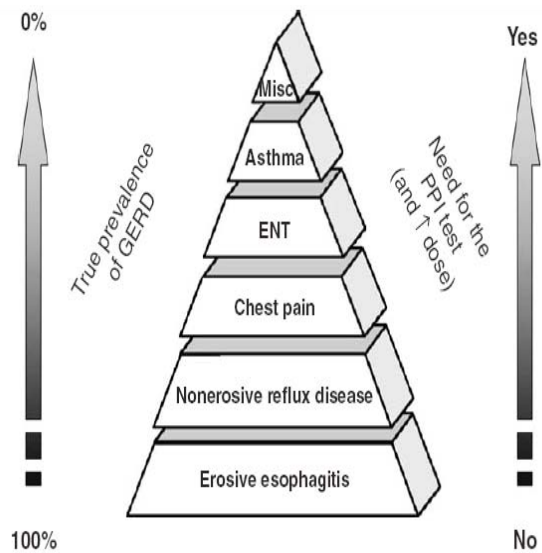


Figure 4. Correlations PPI test with frequency of symptoms

DIAMOND STUDY AND ITS APPLICATION IN INDONESIA

In 2009, there is a large study was done to assess the accuracy of the questionnaire and the use of PPI test, which expected to help the problem in diagnosing gastroesophageal reflux diseases. Report of this study was released in 2010, and often used as a basis for adopting a new questionnaire which easier, simpler and validated in various countries, including in Indonesia. This study was named the Diamond study.

Diamond study was conducted in many centers in various countries, which Germany, Sweden, Canada, Denmark, Norway, and the United Kingdom. This study 73 family physicians, 22 specialist clinics and 308 patients. Patients who entered the inclusion criteria requested previously to fill out three questionnaires, which have been validated, which are reflux disease questionnaire (RDQ), gastrointestinal symptom rating scale (GSRS), and gastro-oesophageal reflux disease impact scale (GIS).¹² Based on input from these three questionnaires, some questions which are considered best describes the symptoms and the effect on quality of life are made. These set of questions compiled in a questionnaire known as gastro-esophageal reflux disease questionnaire (GERDQ). This study also combined the questionnaire with PPI test to assess its role in assisting the diagnosis and simultaneously evaluating patients with of gastroesophageal reflux disease symptoms.

Table 3 . GERDQ from result of Diamond study

Question	Frequency score (points) for symptom			
	0 day	1 day	2-3 days	4-7 days
1. How often did you have a burning feeling behind your breastbone (heartburn)?	0	1	2	3
2. How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	0	1	2	3
3. How often did you have a pain in the centre of the upper stomach?	3	2	1	0
4. How often did you have nausea?	3	2	1	0
5. How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	0	1	2	3
6. How often did you take additional medication for your heartburn and/or regurgitation, other than what the physician told you to take? (such as Tums, Rolaid, Maalox?)	0	1	2	3

Eventually, this study mentioned that the sensitivity and specificity of gastroesophageal reflux disease diagnosis based on symptoms by questionnaire are 62% and 67% if filled out by patients, 63% and 63% if filled out by family physicians, 67% and 70% if filled out gastroenterologist, 54% and 65% if followed by PPI test for two weeks.¹² Therefore, it can be concluded that the diagnostic method with questionnaire modality which followed by PPI test has the sensitivity and specificity which relatively similar with symptoms based diagnosis which done by general practitioners and gastroenterologist, as well as when compared with endoscopy and esophageal pH monitoring examination.

Although GERD diagnosis with questionnaire and PPI test are not tests with the most ideal accuracy, but these tests are not expensive, readily available options and can be done especially in primary health care centers. These tests are favored compared to more invasive and uncomfortable examinations, especially in cases of gastroesophageal reflux disease without any alarm sign.

In Indonesia alone, the two diagnostic methods have been incorporated into the diagnostic algorithm of gastroesophageal reflux disease. GERDQ in English have been translated into Indonesian and validation test have been done. This validation test is done in 2009, and named as Virginia study.¹ Result from this study is all questions in GERD questionnaire are valid and reliable in Indonesian GERD patients.

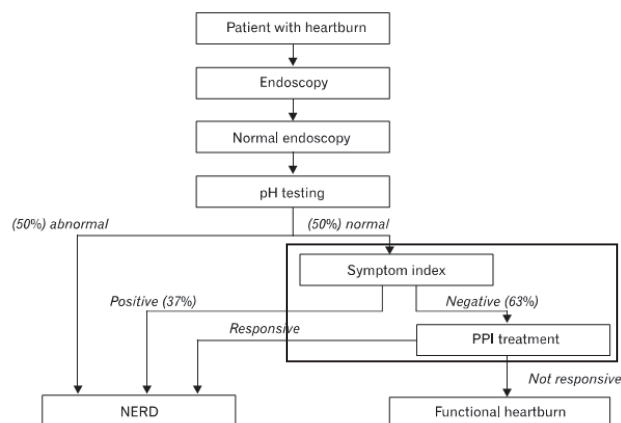


Figure 5. GERD diagnostic algorithm according to the ACG

Table 5. GERDQ in Indonesian have been proven to be valid dan reliable

Questions	Frequency score (points) for symptom in last 7 days					Point
	0 day	1 day	2-3 days	4-7 days		
1. How often did you have a burning feeling behind your breastbone (heartburn)?	0	1	2	3		+
2. How often did you have stomach contents (liquid or food) moving upwards to your throat or mouth (regurgitation)?	0	1	2	3		+
3. How often did you have a pain in the centre of the upper stomach?	3	2	1	0		+
4. How often did you have nausea?	3	2	1	0		+
5. How often did you have difficulty getting a good night's sleep because of your heartburn and/or regurgitation?	0	1	2	3		+
6. How often did you take additional medication for your heartburn and/or regurgitation, other than what the physician told you to take? (such as Tums, Rolaid, Maalox?)	0	1	2	3		+

CONCLUSION

Gastroesophageal reflux disease is one of the most common gastrointestinal diseases. Prevalences of this disease are varied, while in Indonesia there has been no representative data to describe the magnitude of the problem in this disease. Diagnostic modality which known to be very helpful in diagnose gastroesophageal reflux disease is upper gastrointestinal endoscopy. Weakness of this modality is the incapacibilities to

explain the correlation of abnormal findings with degree of severity of symptoms which affected patients' quality of life and this examination is not readily available in all health care centers in periphery areas. Initially, this examination became diagnostic gold standard of GERD, but because of its weakness until now there is no diagnosis standard in gastroesophageal reflux disease.

Some modalities which introduced recently are GERD questionnaire and PPI test. These two modalities usually simultaneously used, but sometime used separately. Some studies have shown similar validities when used by general practitioners or gastroenterologist. However, these test also have many limitations. Translation of questionnaire must be done carefully and the questionnaire must be revalidated at every place it was translated.¹ However, these two modalities very helpful to diagnose GERD, especially in remote areas.

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