Pediatr Gastroenterol Hepatol Nutr. 2023 Jul;26(4):173-180
https://doi.org/10.5223/pghn.2023.26.4.173
pISSN 2234-8646·eISSN 2234-8840

Pediatric Gastroenterology, Hepatology & Nutrition
pghn

Original Article

Association Between Pediatric Gastroesophageal Reflux Disease Symptom and Quality of Life Questionnaire Score, Endoscopy and Biopsy in Children with Clinical Gastroesophageal Reflux Disease: A Prospective Study

Fatima Safira Alatas,[1] **Dian Wulandaru Sukmaning Pertiwi**,[1] **Muzal Kadim**,[1] **Pramita Dwipoerwantoro**,[1] **Hanifah Oswari**,[1] **Badriul Hegar**,[1] and **Yvan Vandenplas** [2]

[1]Department of Child Health, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusomo Hospital, Jakarta, Indonesia
[2]Vrije Universiteit Brussel, UZ Brussel, KidZ Health Castle, Brussels, Belgium

Received: Nov 9, 2022
Revised: Feb 19, 2023
Accepted: May 10, 2023
Published online: Jul 5, 2023

Correspondence to
Yvan Vandenplas
Vrije Universietit Brussel (VUB), UZ Brussel, KidZ Health Castle, Laarbeeklaan 101, Brussels 1090, Belgium.
Email: yvan.vandenplas@uzbrussel.be

ORCID iDs
Fatima Safira Alatas
https://orcid.org/0000-0003-1299-7154
Dian Wulandaru Sukmaning Pertiwi
https://orcid.org/0000-0002-8476-1696
Muzal Kadim
https://orcid.org/0000-0003-2512-255X
Pramita Dwipoerwantoro
https://orcid.org/0000-0003-3755-3808
Hanifah Oswari
https://orcid.org/0000-0003-4310-5841
Badriul Hegar
https://orcid.org/0000-0002-5924-1664
Yvan Vandenplas
https://orcid.org/0000-0002-1862-8651

Funding
None.

ABSTRACT

Purpose: Gastro esophageal reflux disease (GERD) is a burdensome disease affecting many children. A clinical examination is reported to be unreliable to diagnose GERD in children. This study aimed to investigate the relationship between the Pediatric Gastroesophageal Reflux Disease Symptom and Quality of Life Questionnaire (PGSQ) and endoscopic and histopathological findings in children with symptoms suggesting GERD. Changes in the PGSQ score in children with esophagitis as response to one month therapy were recorded as secondary outcome.

Methods: This is a prospective cohort study in the pediatric outpatient clinic in an Indonesian tertiary hospital. Children aged 2–17 years old with clinical symptoms suspected of GERD are included in the study. Blinded endoscopic and histopathological examination was performed in all patients before one month proton pump inhibitors (PPI) therapy. The PGSQ information was collected at inclusion and after one month PPI treatment.

Results: Fifty-eight subjects were included. Esophagitis was found in 60.9% of subjects according to endoscopy and 58.6% according to histology. There was no significant relationship between the PGSQ score and endoscopic (p=0.781) nor biopsy (p=0.740) examinations. The PGSQ showed a low diagnostic value compared to endoscopy and biopsy (area under the curve [AUC] 0.477, p=0.477, 95% confidence interval [CI] 0.326–0.629 and AUC 0.474, p=0.740 (95% CI 0.321–0.627 respectively). The PGSQ improved significantly post one month of PPI treatment.

Conclusion: The PGSQ cannot be used to diagnose esophagitis in children with clinical symptoms suggesting GERD. However, the PGSQ can be used to monitor the treatment response in children with esophagitis.

Pediatric Gastroenterology, Hepatology & Nutrition pghn

Conflict of Interest
The authors have no financial conflicts of interest.

Keywords: Gastro-esophageal reflux; Pediatric Gastroesophageal Reflux Disease Symptom and Quality of Life Questionnaire; Endoscopy; Gastroscopy; Histology; Esophagitis

INTRODUCTION

Gastro-esophageal reflux (GER) presenting with troublesome symptoms is referred as gastroesophageal reflux disease (GERD) [1]. Prolonged and/or frequent exposure to gastric acid during reflux episodes may irritate the esophageal luminal wall and will subsequently cause inflammation and esophagitis [2,3].

GER-symptoms affect 1.8–7.2% of 3 to 9 year-old and 5.2–8.2% of 10–17 year old children [4]. A study by Mulyani in Jakarta, Indonesia, found a prevalence of reflux esophagitis of 85.7% in children aged 1 to 5 years old who presented with feeding problems lasting for at least one month [5]. Similarly, the prevalence of reflux esophagitis in Indian children accounted for 78.8% of children undergoing endoscopy because of GERD symptoms [6]. Prompt diagnosis is imperative to prevent the development of complications. Up to 6–13% children with GERD ultimately may require surgery due to Barret's Esophagus [7-9].

The clinical diagnosis of GERD is challenging since the clinical presentation varies greatly. Commonly reported symptoms include persistent vomiting, hematemesis, failure to thrive, or other non-specific symptoms such as hoarseness, dysphagia/odynophagia, and sleep disturbance [10-12]. In older children and adolescents who are more capable of expressing complaints objectively, symptoms remain varied and non-specific [10-12].

The diagnosis of esophagitis is based on endoscopic and histopathological examination [5,10]. However, endoscopy causes discomfort, is invasive, can be quite expensive and is also operator-dependent [13]. In several countries, including Indonesia, endoscopy is limited to tertiary hospitals. This renders GERD screening in the clinical field crucial to avoid under- and over-diagnosis and unjustified empirical therapy. Since clinical screening plays a very important role, there is a need to study the relationship between the presenting clinical symptoms and findings upon endoscopy and histopathology.

A study by Kleinman et al. [14] validated the Pediatric Gastroesophageal Reflux Disease Symptom and Quality of Life (PGSQ) questionnaire to diagnose GERD in 231 subjects. The PGSQ questionnaires consist of 21 questions for GERD symptoms and 20 question on quality of life. The PGSQ-Cp questionnaire is used for children aged 2–8 years old and filled by the parents/guardians, while the PGSQ-A questionnaire is used for children aged 9–17 years old and is completed by the subjects themselves. However, the utility of this questionnaire to furtherdistinguish reflux esophagitis from non-esophagitis among GERD patients has never been reported. The primary objective of this study was to investigate the relationship between the PGSQ questionnaire and endoscopic and histopathological findings in children with clinical GERD. In addition, we also assessed the changes in the PGSQ questionnaire in response to therapy.

https://doi.org/10.5223/pghn.2023.26.4.173

Pediatric Gastroenterology, Hepatology & Nutrition pghn

MATERIALS AND METHODS

This prospective cohort study was performed in the pediatric outpatient clinic of the Cipto Mangunkusumo General Hospital. Pediatric patients aged 2–17 years old with clinical symptoms suggesting GERD such as hematemesis, recurrent vomiting, poor weight gain/failure to thrive, heartburn, globus pharyngeus, dysphagia/odinophagia, anemia, and reccurrent respiratory or ear, nose, and throat (ENT) symptoms that did not respond to standard therapy (for the respiratory tract or ENT symptomatology) and lasted at least for the past 4 weeks were candidates to be included in the study.

Patients with neurological and congenital abnormalities, history of esophageal surgery, contraindicated for endoscopy, malnutrition (actual body weight/ideal weight for height <−3 standard deviation), and patients with history of food allergy and receiving medications (proton-pump inhibitor, H2 antagonist, cisapride, domperidone, metoclopramide) within 2 weeks prior to recruitment were excluded.

Subjects were recruited via consecutive sampling. Upon obtaining informed consent, the subjects and/or parents were given a short instruction on how to fill in the PGSQ questionnaires and were given approximately 60 minutes. The questionnaires were translated into Indonesian and were validated [15].

Endoscopic examination was performed by pediatric gastroenterology and hepatology consultants who were blinded to the questionnaire score. Endoscopic findings were classified using the Los Angeles classification into four grades A to D (A: 1 or more mucosal breaks <5 mm; B: 1 or more mucosal breaks ≥5 mm; C: 1 or more mucosal breaks that is continuous between the tops of two or more mucosal folds but that involves <75% of the circumference; D: 1 or more mucosal breaks that involves ≥75% of esophageal circumference) [16]. Any abnormalities found which were milder than Los Angeles grade A classification, were then considered as "unclassified". The biopsies were examined by an independent pathologist blinded to the questionnaire and endoscopic results. Esophagitis was diagnosed using the classification by the Caris Research Institute and was further classified into 8 types: type 1 (normal esophageal mucosa), type 2 (minimal reactive esophagitis), type 3 (mild active esophagitis), type 4 (active esophagitis), type 5 (erosive esophagitis), type 6 (esophageal ulcer), type 7 (eosinophillic esophagitis pattern of injury), and type 8 (Barrett's mucosa). Subjects were categorized as esophagitis when the biopsy showed a minimum of type 3 Caris Research Institute classification. Furthermore, assessment for *Helicobacter pylori* infection was performed in all study participants.

All patients who had esophagitis and/or gastritis evident from endoscopic and/or histopathological findings were then treated with proton-pump inhibitors (PPI) 1–2 mg/kg/day (max 40 mg/day), once daily, for one-month, independent of the evolution of symptoms. Following completion of one-month regimen, the PGSQ questionnaires were reassessed. Untreated patients were not followed and had no second assessment. There was no second endoscopy performed after one month PPI treatment.

All data were analyzed using IBM SPSS Statistics for Windows (version 22.0; SPSS Inc.). Saphiro-Wilk test was used to assess the data distribution. Association between PGSQ-Cp, PGSQ-A, and esophagitis diagnosis (by endoscopy or biopsy) were analyzed using one-way ANOVA. Changes in PGSQ scores in response to treatment were analyzed using Wilcoxon-

https://doi.org/10.5223/pghn.2023.26.4.173

Pediatric Gastroenterology, Hepatology & Nutrition pghn

signed rank test. The receiver operating curve (ROC) was used to assess the diagnostic value of PGSQ score to diagnose esophagitis.

This study obtained approval from The Ethical Committee of Faculty of Medicine, Universitas Indonesia with approval number 773a/UN2.F1/ETIK/IX/2016. Written informed consent was obtained from the parents/legal guardians of subjects included in the study.

RESULTS

A total of 58 subjects were included: 32 subjects in the Cp group and 26 subjects in the A group. The most frequent symptoms were epigastric pain in 79.1%, recurrent vomiting in 67.2%, and poor weight gain/ failure to thrive in 39.7%. Hematemesis was seldom (**Table 1**).

The endoscopic and histologic characteristics of the study participants are presented in **Table 2**. No subject was diagnosed with *H. pylori* infection Based on LA classification, esophagitis was found in 40 subjects (60.9%), 22 subjects from the Cp group and 18 subjects from the A group. A total of 31.3% and 26.9% was grouped as Unclassified in the Cp and A group, respectively. Two of the Cp group (6.3%) had normal endoscopic findings. Meanwhile, the prevalence of histological esophagitis (Caris classification of type 3 and above) was 34/58 subjects (58.6%; 22

Table 1. Distribution of symptoms suspected of GERD according to age group

Symptoms suspected of GERD	Age group		
	Cp (n=32)	A (n=26)	Total (n=58)
Epigastric pain	28 (87.5)	18 (69.2)	46 (79.3)
Reccurent vomiting	17 (53.1)	22 (84.6)	39 (67.2)
Poor weight gain/failure to thrive	7 (21.9)	16 (61.5)	23 (39.7)
Heartburn	12 (37.5)	9 (34.6)	21 (36.2)
Poor intake	2 (6.3)	17 (65.4)	19 (32.8)
Globus pharyngeus	14 (43.8)	4 (15.4)	18 (31.0)
Recurrent respiratory or ENT symptoms	10 (31.3)	2 (7.7)	12 (20.7)
Dyspagia/odinophagia	4 (12.5)	6 (23.1)	10 (17.2)
Irritable/excessive crying	0 (0.0)	9 (34.6)	9 (15.5)
Hematemesis/melena	2 (6.3)	3 (11.5)	5 (8.6)
Anemia	1 (3.1)	0 (0.0)	1 (1.7)

Values are presented as number (%).
GERD: gastro esophageal reflux disease, ENT: ear, nose, and throat.

Table 2. Endoscopic and histologic characteristics based on age groups

Characteristics	Cp (n=32)	A (n=26)	Total (n=58)
Endoscopic LA classification			
Unclassified	10 (31.3)	8 (30.8)	18 (31.0)
A	8 (25.0)	3 (11.5)	11 (19.0)
B	8 (25.0)	11 (42.3)	19 (32.8)
C	5 (15.6)	4 (15.4)	9 (15.5)
D	1 (3.1)	0 (0.0)	1 (1.7)
Histologic Caris classification (biopsy)			
1	1 (3.1)	2 (7.7)	3 (5.2)
2	9 (28.1)	12 (46.2)	21 (36.2)
3	5 (15.6)	4 (15.4)	9 (15.5)
4	16 (50.0)	7 (26.9)	23 (39.7)
5	1 (3.1)	1 (3.8)	2 (3.4)
Esophagitis (endoscopic+biopsy)	22 (68.8)	16 (61.5)	38 (65.5)

Values are presented as number (%).

https://doi.org/10.5223/pghn.2023.26.4.173

Pediatric Gastroenterology, Hepatology & Nutrition pghn

subjects from Cp group and 12 subjects from A group). None of the subjects was classified as type 6–8 esophagitis; 65.5% had esophagitis according to endoscopic and biopsy results.

The median PGSQ score forboth groups was 16.0 (2–56). There was no significant association between the PGSQ score and the endoscopic diagnosis of esophagitis (p-value=0.781). The PGSQ score was also not associated with the histological diagnosis of esophagitis (p-value=0.740). Upon subgroup analysis, both PGSQ-Cp and PGSQ-A were neither associated with endoscopic nor histopathological diagnosis of esophagitis (**Table 3**). Furthermore, we could not identify a cut-off for an association between the PGSQ score and endoscopic or histological esophagitis. The PGSQ showed a low diagnostic value with area under the curve (AUC) of 0.477 (95% confidence interval [CI] 0.326–0.629) and p-value of 0.782 to diagnose endoscopic abnormalities. The ROC is shown in **Fig. 1A**. Similarly, diagnostic value analysis of the combined PGSQ score compared to biopsy diagnosis showed a weak diagnostic value with AUC of 0.474 (95% CI 0.321–0.627) and p-value of 0.740 was observed. The ROC is shown in **Fig. 1B**.

However, we found a significant decrease in the PGSQ score following one month PPI therapy (p<0.001). In addition, the subgroup analyses also showed significant change in both PGSQ-Cp score (p<0.001) and PGSQ-A score (p-value=0.002) (**Table 4**).

DISCUSSION

GERD is common among the pediatric population [11,15]. Unlike in adults, symptoms in children are aspecific. Currently, there are no gold standard diagnostic tools for pediatric GERD. However, several diagnostic tools are recommended in approaching children with GERD, including endoscopy with histology and esophageal pH metry [11]. Esophagitis is one of the most common complications of GERD in children [17].

Table 3. Association between PGSQ score and esophagitis diagnosis made by endoscopical and histopathological examination

Parameter	Median (range)	p-value
Combined PGSQ score		
Endoscopic diagnosis		0.781
Negative	16.5 (6–30)	
Positive	16.0 (2–56)	
Biopsy diagnosis		0.74
Negative	16.0 (4–34)	
Positive	15.5 (2–56)	
PGSQ-Cp		
Endoscopic diagnosis		0.528
Negative	19.5 (11–31)	
Positive	17.0 (2–56)	
Biopsy diagnosis		0.903
Negative	19.0 (4–32)	
Positive	18.5 (2–56)	
PGSQ-A		
Endoscopic diagnosis		0.521
Negative	12.0 (6–20)	
Positive	14.0 (4–34)	
Biopsy diagnosis		0.11
Negative	15.0 (4–34)	
Positive	11.5 (6–20)	

PGSQ: Pediatric Gastroesophageal Reflux Disease Symptom and Quality of Life Questionnaire.

https://doi.org/10.5223/pghn.2023.26.4.173

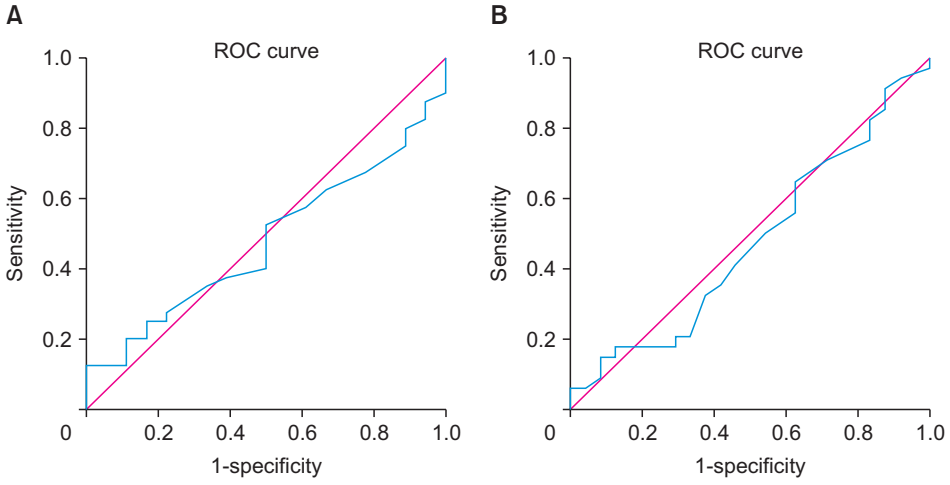

Fig. 1. (A) ROC curve of combined PGSQ score vs. endoscopic diagnosis of esophagitis in clinical GERD pediatric patients. (B) ROC curve of combined PGSQ score vs. histopathological diagnosis of esophagitis in clinical GERD pediatric patients.
ROC: receiver operating curve, PGSQ: Pediatric Gastroesophageal Reflux Disease Symptom and Quality of Life Questionnaire, GERD: gastro esophageal reflux disease.

Table 4. Changes in PGSQ scores post treatment in clinical GERD pediatric patients

PGSQ-score	Pre-treatment	Post-treatment	*p*-value
PGSQ-Cp (n=26)	12.5 (4–34)	2.5 (0–17)	<0.001*
PGSQ-A (n=32)	18.5 (2–56)	4.0 (0–21)	<0.001*
Combined PGSQ (n=58)	16.0 (2–56)	3.0 (0–21)	<0.001*

Non-parametric distribution presented as median (interquartile range).
PGSQ: Pediatric Gastroesophageal Reflux Disease Symptom and Quality of Life Questionnaire, GERD: gastro esophageal reflux disease.
*Wilcoxon signed-rank test, $p<0.05$.

Among 58 subjects with symptoms suggesting GERD, 69.0% had endoscopic esophagitis. This high prevalence is likely to be influenced by the selection of patients in a tertiary care hospital. Histological esophagitis was found in 58.6% of the study participants. Esophageal mucosal biopsies should be performed on endoscopic examination to enhance the accuracy of the diagnosis of esophagitis in the absence of severe inflammation (ulcers) [18]. A study by Genta compared the results of endoscopy and histological examination from 5,513 cases of suspected esophagitis, and found that normal endoscopy was confirmed by normal histology in 71% [19].

We found no correlation between PGSQ score and esophagitis diagnosed by endoscopy and/or biopsy examination. The PGSQ score includes symptoms directly associated with esophagitis, but also extraesophageal symptoms. Our study shows that the PGSQ score does not adequately predict endosocpic and/or histologic esophagitis. Hence, the PGSQ score cannot replace endoscopy and histopathology in diagnosing esophagitis. These data support the recommendation of European and North American Societies of Pediatric Gastroenterology and Nutrition and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, Hepatology and Nutrition, recommending esophago-gastro-duodenoscopy with biopsies to assess GERD complications.

A study by Artanti et al. [15] reporteda GERD prevalence of 32.9% among Indonesian children applying the proposed PGSQ cut-off score of 7. Moreover, the prevalence of GERD

https://doi.org/10.5223/pghn.2023.26.4.173

decreased with the increase of PGSQ score. Meanwhile, the findings of our study does not allow to propose a cut off of the PGSQ to predict esophagitis. The difference in sample size may be the reason for the different results obtained; their study accumulated data from 520 samples (without performing endoscopy), while this study is based on 58 children. Further studies with more samples are needed to provide a statistically significant result.

We found a statistically significant difference between PGSQ in both PGSQ-Cp and PGSQ-A before and after one month of omeprazole therapy. A study by Shaw et al. [20] in adult subjects presenting with presumed GERD have previously reported that the Reflux Disease Questionnaire score significantly declined in treatment groups compared to placebo after two weeks of treatment using esomeprazole. Similarly, our study demonstrated the strength of PGSQ questionnaires in measuring the treatment effect of clinical GERD children.

There were other limitations of this study. This study took place at a tertiary referral hospital. Hence, our patients were cases with moderate to severe symptomatology, resulting in a high percentage of esophagitis. Parental information may not accurately reflect their children's condition, especially in children under eight years old with limited communication skills; therefore, the use of PGSQ-Cp may pose a risk of bias.

In conclusion, this study was the first to assess the diagnostic ability of the PGSQ questionnaire (PGSQ-A and PGSQ-Cp) compared to endoscopic and histopathological diagnosis of esophagitis in children with suspected clinical symptoms of GERD. This study found a high prevalence of esophagitis among children with suspected clinical symptoms of GERD. However, the PGSQ questionnaire could not be used to discriminate between those with and without esophagitis. However, the PGSQ questionnaire is useful to monitor treatment response in pediatric patients with reflux esophagitis.

REFERENCES

1. Omari TI, Barnett CP, Benninga MA, Lontis R, Goodchild L, Haslam RR, et al. Mechanisms of gastro-oesophageal reflux in preterm and term infants with reflux disease. Gut 2002;51:475-9.
PUBMED | CROSSREF
2. Vandenplas Y. Reflux esophagitis in infants and chidren: a report from the working group on gastroesophageal disease of the European Society of Paediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 1994;18:413-22.
PUBMED | CROSSREF
3. Black DD, Haggitt RC, Orenstein SR, Whitington PF. Esophagitis in infants. Morphometric histological diagnosis and correlation with measures of gastroesophageal reflux. Gastroenterology 1990;98:1408-14.
PUBMED | CROSSREF
4. Nelson SP, Chen EH, Syniar GM, Kaufer Christoffel K. Prevalence of symptoms of gastroesophageal reflux during childhood: A pediatric practice-based survey. Arch Pediatr Adolesc Med 2000;154:150-4.
PUBMED | CROSSREF
5. Mulyani L, Hegar B, Tumbelaka AR, Krisnuhoni E. Reflux esofagitis in children with feeding problems: A preliminary study. Paediatri Indones 2010;50:284-90.
CROSSREF
6. Dadhick SK, Yachha SK, Srivastava A, Sikora SS, Pandey R. Endoscopic and histologic evaluation of reflux esophagitis. Indian Pediatr 2000;37:1111-4.
PUBMED
7. Salvatore S, Vandenplas Y. Gastro-esophageal reflux disease and motility disorder. Best Pract Res Clin Gastroenterol 2003;17:163-79.
PUBMED | CROSSREF

8. El-Serag HB, Bailey NR, Gilger M, Rabeneck L. Endoscopic manifestation of gastroesophageal reflux disease in patients between 18 months and 25 years without neurological deficits. Am J Gastroenterol 2002;97:1635-9.
PUBMED | CROSSREF
9. Salvatore S, Hauser B, Vandenplas Y. The natural course of gastro-esophageal reflux. Acta Paediatr 2004;93:1063-9.
PUBMED | CROSSREF
10. Vandenplas Y, Salvatore S, Hauser B. The diagnosis and management of gastro-esophageal reflux in infants. Early Hum Dev 2005;81:1011-24.
PUBMED | CROSSREF
11. Rosen R, Vandenplas Y, Singendonk M, Cabana M, Dilorenzo C, Gottrand F, et al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 2018;66:516-54.
PUBMED | CROSSREF
12. Rybak A, Pesce M, Thapar N, Borrelli O. Gastro-esophageal reflux in children. Int J Mol Sci 2017;18:1671.
PUBMED | CROSSREF
13. Salvatore S, Hauser B, Vandemaele K, Novario R, Vandenplas Y. Gastroesophageal reflux disease in infants: How much is predictable with questionnaires, pH-metry, eodoscopy and histology? J Pediatr Gastroenterol Nutr 2005;40:210-5.
PUBMED | CROSSREF
14. Kleinman L, Nelson S, Kothari-Talwar S, Roberts L, Orenstein S, Mody R, et al. Development and psychometric evaluation of 2 age-stratified versions of the pediatric GERD Symptom and Quality of Life Questionnaire. J Pediatr Gastroenterol Nutr 2011;52:514-22.
PUBMED | CROSSREF
15. Artanti D, Hegar B, Kaswandani N, Soedjatmiko , Prayitno A, Devaera Y, et al. The gastroesophageal reflux disease questionnaire in adolescents: What is the best cutoff score? Pediatr Gastroenterol Hepatol Nutr 2019;22:341-9.
PUBMED | CROSSREF
16. Lundell LR, Dent J, Bennett JR, Blum AL, Armstrong D, Galmiche JP, et al. Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. Gut 1999;45:172-80.
PUBMED | CROSSREF
17. Shub MD, Ulshen MH, Hargrove CB, Siegal GP, Groben PA, Askin FB. Esophagitis: A frequent consequence of gastroesophageal reflux in infancy. J Pediatr 1985;107:881-4.
PUBMED | CROSSREF
18. Leape LL, Bhan I, Ramenofsky ML. Esophageal biopsy in the diagnosis of reflux esophagitis. J Pediatr Surg 1981;16:379-84.
PUBMED | CROSSREF
19. Genta RM, Spechler SJ, Kielhorn AF. The Los Angeles and Savary-Miller systems for grading esophagitis: Utilization and correlation with histology. Dis Esophagus 2011;24:10-7.
PUBMED | CROSSREF
20. Shaw M, Dent J, Beebe T, Junghard O, Wiklund I, Lind T, et al. The reflux disease questionnaire: A measure for assessment of treatment response in clinical trials. Health Qual Life Outcomes 2008;6:1-6.
PUBMED | CROSSREF