

# Correlation of Narrow Band Imaging Endoscopy and Histopathology in the Diagnosis of Nonerosive Reflux Disease

Arul P, Vinoth B<sup>1</sup>, Thomas Alexander<sup>1</sup>, Manjiri Phansalkar<sup>2</sup>, Somanath Padhi<sup>2</sup>

Department of Pathology,  
Dhanalakshmi Srinivasan  
Medical College and Hospital,  
Siruvachur, Perambalur,  
Tamil Nadu, India, Departments  
of <sup>1</sup>Gastroenterology and  
<sup>2</sup>Pathology, Pondicherry  
Institute of Medical Sciences,  
Kalapet, Puducherry, India

**Address for correspondence:**

Dr. Arul P,  
Department of Pathology,  
Dhanalakshmi Srinivasan Medical  
College and Hospital,  
Siruvachur - 621 113,  
Perambalur, Tamil Nadu, India.  
E-mail: drarul3@gmail.com

## ABSTRACT

**Background/Aim:** Narrow band imaging (NBI) is a novel, innovative high-resolution endoscopic technique, which utilizes spectral narrow band filter for the visualization of mucosal patterns and microvasculature. Nonerosive reflux disease (NERD) is a type of gastroesophageal reflux disease (GERD) and it is characterized by reflux symptoms without mucosal breaks on white light endoscopy (WLE). Biopsies from distal esophagus of GERD patients show group of histologic features such as basal cell hyperplasia, elongation of lamina propria papillae, and inflammatory cells. The present study was undertaken to evaluate diagnostic utility of NBI endoscopy and biopsy study in NERD patients and also to correlate NBI endoscopy findings with histologic features of GERD. **Patients and Methods:** A total of 71 cases of NERD having symptom score more than 10 and those not having erosion on WLE were recruited prospectively and underwent NBI endoscopic examination. Two mucosal biopsies were taken at 3 cm above the squamocolumnar junction. **Results:** Histologic features of GERD were seen in 50 (70.4%) out of 71 cases. No significant correlation between NBI endoscopic findings with histologic features of GERD was found. **Conclusion:** The present study showed that histopathologic evaluation of distal esophageal mucosa has promising diagnostic value over NBI endoscopy in NERD patients. Use of newly introduced NBI technique requires tremendous familiarity for the detection of the cases of NERD, which show histologic features of GERD.

**Key Words:** Gastroesophageal reflux disease, narrow band imaging, nonerosive reflux disease

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Gastroesophageal reflux disease (GERD) is a common disorder in the West and it affects approximately 20%–50% of adults in Western countries, causing huge economic burden.<sup>[1-3]</sup> The prevalence of GERD symptoms occurring once a week is approximately 8% in Indian subjects.<sup>[4]</sup> Nonerosive reflux disease (NERD) and erosive reflux disease (ERD) are types of GERD. NERD is defined as white light endoscopy (WLE) negative patients with reflux symptoms with or without abnormal esophageal acid exposure during ambulatory 24-h esophageal pH monitoring.<sup>[5]</sup> WLE cannot visualize superficial and small esophageal lesions in GERD. In view of the need for more diagnostic accuracy, high-definition endoscopy

with narrow band imaging (NBI) was developed by Olympus Medical System in Japan.<sup>[6]</sup> It was first reported by Sano *et al.*, in 1999 and introduced commercially in 2005.<sup>[6,7]</sup> NBI endoscopy is said to be more sensitive in detecting mucosal abnormalities as it is an optical image technology that enhances structural mucosal patterns (pit-pattern), as well as mucosal/submucosal vessels by employing the characteristics of light spectrum.<sup>[8]</sup> It is based on the optical phenomenon that the depth of light penetration into tissues is dependent on the wavelength (415 and 540 nm). The 415 nm image channel analyzes the fine surface architecture of the mucosa and the superficial capillary network appear as brownish color; the 540 nm image channel analyzes the collecting vessels in the depth of the mucosa appearing as a bluish color.<sup>[6-10]</sup> NBI endoscopy may help to improve diagnostic accuracy compared with white light endoscopy in the diagnosis of GERD.<sup>[9,10]</sup> Reflux disease is associated with a group of histologic features, which represents changes from secondary to acid injury and mucosal healing,<sup>[11]</sup> and these histologic findings have been well defined for the diagnosis of GERD.<sup>[12]</sup> Hence

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histopathologic examination of distal esophageal mucosa may be considered as a diagnostic tool for NERD.<sup>[13]</sup> This study was undertaken to evaluate diagnostic utility of NBI endoscopy and biopsy study in NERD and also to correlate NBI endoscopy findings with histologic features of GERD.

## PATIENTS AND METHODS

### Overview of study design

The present prospective study was undertaken at the Departments of Pathology and Gastroenterology, Pondicherry Institute of Medical sciences, Puducherry, India, conducted during the period from February 2012 to May 2013, after obtaining approval from the Institutional Ethical Committee. Informed written consent was obtained from each patient before endoscopy and for biopsy.

### Study population

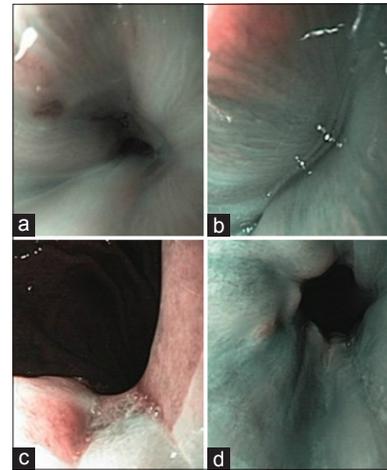
Subjects were enrolled if they met the following inclusion criteria: More than 18 years of age and ability to provide written informed consent with symptoms of GERD as defined by GERD health-related quality of life (HRQL) heartburn score<sup>[14]</sup> more than 10, but endoscopically negative for ERD on WLE. A total number of 71 cases were included in the study. Patients with one or more of the following criteria were excluded from this study: (1) Inability to provide written informed consent; (2) patients on acid suppression therapy and proton pump inhibitors for 4 weeks before endoscopy; (3) evidence of cancer or mass lesion in the esophagus; (4) gastric lesion, namely, ulcer, polyp, or cancer; (5) prior history of upper gastrointestinal surgeries, namely, gastrectomy, distal esophagectomy, gastro-jejunostomy, fundoplication; (6) severe gastroparesis; (7) esophageal varices; (8) severe uncontrolled coagulopathy; (9) inability to discontinue nonsteroidal anti-inflammatory drugs or aspirin prior to the study; and (10) history of pill use (doxycycline, quinidine, alendronate, and so on).

### Equipment and endoscopic procedure

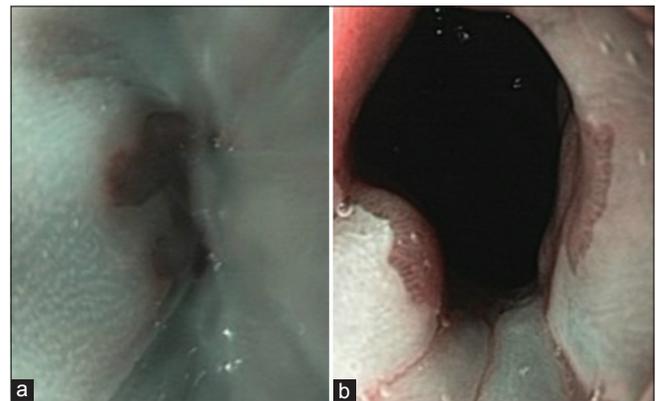
The endoscopic procedures of all 71 cases performed using the gastrointestinal videoscope (Olympus Evis Exera II GIF-H 180). NBI endoscopic findings such as microerosions [Figure 1a], increased vascularity above squamocolumnar junction (SCJ) [Figure 1b], increased vascularity below SCJ [Figure 1c], mucosal brownish areas [Figure 1d], round pit pattern [Figure 2a], straight pit pattern [Figure 2b], mucosal islands [Figure 3] were recorded by gastroenterologists. Two mucosal biopsies were taken at 3 cm above SCJ from each patient. Methodology of study is shown in Flow Chart 1.

### Histopathologic evaluation

Biopsy specimens fixed in 10% neutral buffered formalin, processed routinely, embedded in paraffin and 4 µm



**Figure 1:** Narrow band imaging endoscopy findings in nonerosive reflux disease. (a) Microerosion, (b) increased vascularity above squamocolumnar junction (SCJ), (c) increased vascularity below SCJ, and (d) mucosal brownish area



**Figure 2:** Narrow band imaging endoscopy findings in nonerosive reflux disease. (a) Round pit pattern, and (b) straight pit pattern



**Figure 3:** Narrow band imaging endoscopy showing mucosal island

thick sections stained with hematoxylin and eosin were evaluated. Periodic Acid Schiff stain was also done to

rule out fungal esophagitis. All biopsies were examined using a light microscope by pathologists blinded to the clinical characteristics, GERD–HRQL heartburn score and endoscopic findings.

The diagnosis of microscopic esophagitis was based on the presence of one or more of the following criteria:<sup>[15]</sup> (1) Basal cell zone exceeding 15% of the whole thickness of epithelium along with elongation of the connective tissue papilla from lamina propria to the upper third of the whole epithelial thickness [Figure 4], (2) focal or diffuse infiltration of the epithelium by polymorphonuclear (PMN) leukocytes (>2 PMN leukocytes per tissue section) or eosinophils [Figure 5] (>5 eosinophils per tissue section), (3) dense nonfollicular infiltration of mononuclear inflammatory cells and/or an easily recognized infiltrate of neutrophils in lamina propria.

**Statistical analysis**

Chi-square test and correlation coefficient (kappa) were used to assess the correlation of NBI endoscopic findings with histologic features of GERD. Statistical tests were performed using SPSS version 20. A *P* < 0.05 was considered statistically significant.

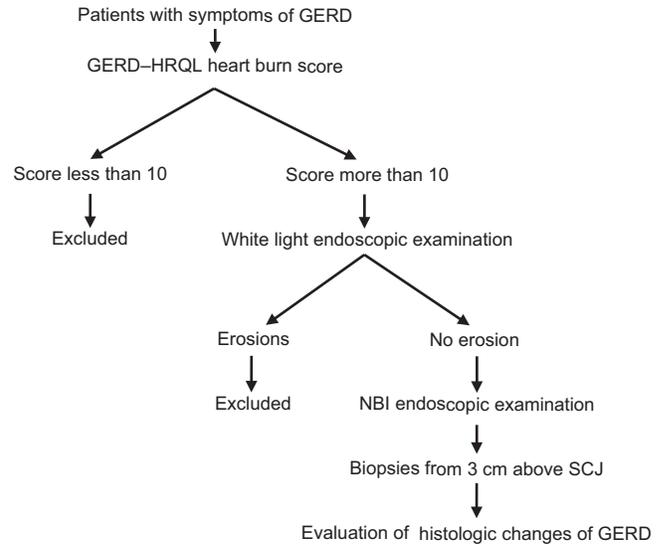
**RESULTS**

The mean age of the study population was 38.59 years, with a range from 18 to 63 years. Of these patients, 35 (49.3%) were males and 36 (50.7%) were females. Smokers were 12 (16.9%) and nonsmokers were 59 (83.1%). Fifty (70.4%) patients had evidence of histologic features of GERD.

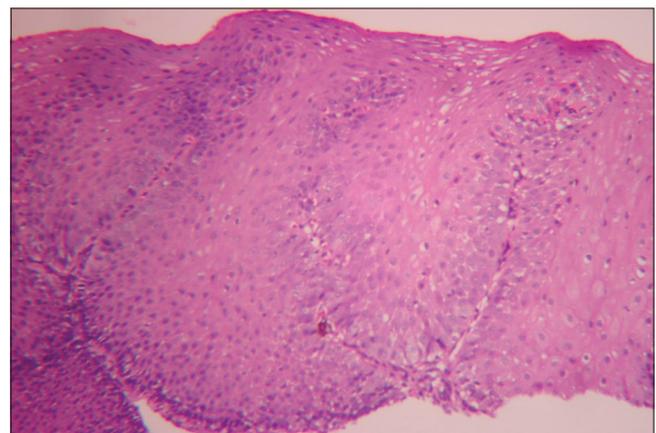
NBI endoscopic findings such as microerosions, increased vascularity above SCJ, increased vascularity below SCJ, round pit pattern, straight pit pattern, mucosal brownish areas, and mucosal islands in 71 NERD patients and in 50 cases of histologic GERD are summarized in Table 1. (More than one NBI endoscopic findings were noted in most of the cases.) These NBI endoscopy findings were analyzed for correlation with histologic features of GERD by Chi-square test and correlation coefficient (kappa). The *P* values of Chi-square test are shown in Table 2. The correlation coefficient (kappa) value for histologic features of GERD with microerosions was -0.058, increased vascularity above SCJ was 0.048, increased vascularity below SCJ was -0.075, round pit pattern was 0.116, straight pit pattern was -0.129, mucosal brownish areas was -0.117, and mucosal islands was 0.015.

**DISCUSSION**

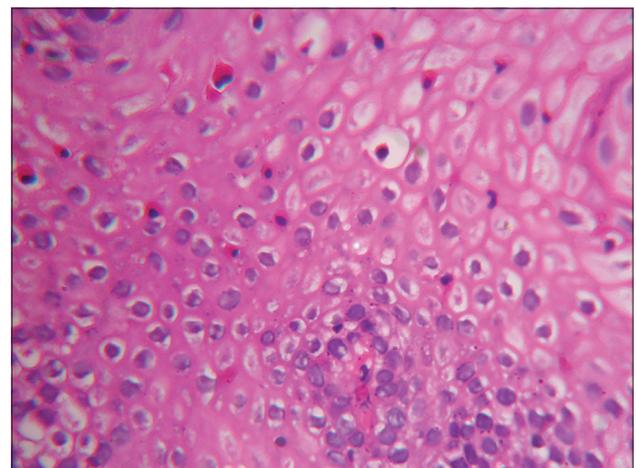
Our study showed that NBI endoscopy findings such as straight pit pattern (56.3%), increased vascularity at SCJ (46.47%) (considering together the increased vascularity



**Flow Chart 1:** Methodology of study



**Figure 4:** Photomicrographs of distal esophageal mucosa showing basal cell hyperplasia and papillary elongation (hematoxylin and eosin x100)



**Figure 5:** Photomicrographs of distal esophageal mucosa showing neutrophils and eosinophils (hematoxylin and eosin x400)

**Table 1: NBI endoscopic findings in NERD (n=71) and histologic GERD cases (n=50)**

NBI endoscopic findings	NERD cases N=71 (%)	Histologic GERD cases N=50 (%)
Microerosions	9 (12.7)	5 (10)
Increased vascularity above SCJ	17 (23.9)	13 (26)
Increased vascularity below SCJ	29 (40.8)	19 (38)
Round pit pattern	31 (43.7)	24 (48)
Straight pit pattern	40 (56.3)	26 (52)
Tubular pit pattern	0	0
Villous/ridge pit pattern	0	0
Mucosal brownish areas	15 (21.1)	8 (16)
Mucosal islands	18 (25.4)	13 (26)

NBI: Narrow band imaging; SCJ: Squamocolumnar junction;  
NERD: Nonerosive reflux disease; GERD: Gastroesophageal reflux disease.  
Note: More than one NBI endoscopic findings were noted in most of the cases

**Table 2: Correlation of NBI endoscopy findings with histologic findings among NERD patients (n=71)**

NBI findings	Histologic GERD (%)		P* value
	Present	Absent	
Microerosions			
Present	5 (10)	4 (19)	0.296
Absent	45 (90)	17 (81)	
Increased vascularity above SCJ			
Present	13 (26)	4 (19)	0.531
Absent	37 (74)	17 (81)	
Increased vascularity below SCJ			
Present	19 (38)	10 (47.6)	0.452
Absent	31 (62)	11 (52.4)	
Round pit pattern			
Present	24 (48)	7 (33.3)	0.255
Absent	26 (52)	14 (66.7)	
Straight pit pattern			
Present	26 (52)	14 (66.7)	0.255
Absent	24 (48)	7 (33.3)	
Mucosal brownish areas			
Present	8 (16)	7 (33.3)	0.102
Absent	42 (4)	14 (66.7)	
Mucosal islands			
Present	13 (26)	5 (23.8)	0.846
Absent	37 (74)	16 (76.2)	

NBI: Narrow band imaging; SCJ: Squamocolumnar junction;  
GERD: Gastroesophageal reflux disease. \*P value <0.05 was considered statistically significant

above and below SCJ, increased vascularity at SCJ was noted in 33 cases) and round pit pattern (43.7%) were common in NERD cases. A study done by Fock *et al.*<sup>[9]</sup> observed increased prevalence of increased vascularity at SCJ (91.7%), microerosions (52.8%), and lower prevalence of round pit pattern (5.6%) suggestive of NERD compared with controls. Sharma *et al.*<sup>[10]</sup> evaluated the utility of NBI in patients with symptoms of GERD, found that

NERD cases had more frequency of increased number and dilatation of intrapapillary capillary loops (IPCLs), microerosions, and increased vascularity at SCJ compared with the control subjects. Our results are partially similar to Fock *et al.*'s<sup>[9]</sup> and Sharma *et al.*'s<sup>[10]</sup> studies as we all noted increased vascularity at SCJ in NERD cases. In contrast to Fock *et al.*'s<sup>[9]</sup> and Sharma *et al.*'s<sup>[10]</sup> studies, we found more number of straight and round pit patterns and less number of microerosions as shown in Table 3. Studies done by Lundell *et al.*<sup>[16]</sup> and Bytzer *et al.*<sup>[17]</sup> suggested that endoscopic features of edema and increased vascularity were unreliable for the diagnosis of GERD. However, studies by Fock *et al.*,<sup>[9]</sup> Sharma *et al.*,<sup>[10]</sup> and our data suggest that increased vascularity at the SCJ noted by NBI may be one of the endoscopic feature of NERD. Similar to NERD patients ( $n = 71$ ), histologic GERD ( $n = 50$ ) also showed the same NBI endoscopic findings [Table 1]. NBI endoscopic findings were analyzed for correlation with histologic features of GERD. There is no study on NERD cases till date to correlate all the parameters of NBI endoscopy with histologic GERD. Hence, in the present study, we attempt to correlate the NBI endoscopic findings with histologic features of GERD. However, none of these NBI endoscopic findings, including increased vascularity above and below SCJ showed statistically significant correlation with histologic features of GERD [Table 2]. The correlation coefficient (kappa) showed that there was poor agreement between NBI endoscopic findings and histologic features of GERD. We could not characterize individual morphology of IPCLs as our endoscope had digital magnification and not an optical magnification. Hence we were unable to confirm the NBI endoscopic features such as more frequency of increased number and dilatation of IPCLs as markers of NERD.

The histologic parameters of GERD include squamous cell hyperplasia such as basal cell hyperplasia and papillary elongation, intraepithelial neutrophils and eosinophils, mucosal erosion/ulceration, and dilated intracellular spaces occur due to lower esophageal epithelial injury and repair. Endoscopic examination of ERD can reveal erosions, ulcers, strictures. However, approximately 50%–60% of symptomatic GERD patients show normal mucosa or only mild hyperemia at endoscopy. Furthermore, histologic GERD may appear normal endoscopically; conversely, hyperemia does not necessarily indicate the presence of histologic features of GERD. Because of these endoscopic and pathologic discrepancies, biopsies are always warranted in symptomatic patients to document the presence of tissue injury. The diagnostic biopsies should generally be obtained more than 2.0 cm above the SCJ, because the lower 1–2 cm of the esophagus, often reveal evidence of mild squamous hyperplasia even in asymptomatic subjects.<sup>[11,18-21]</sup> Hence we took biopsies from 3 cm above SCJ for the diagnosis of histologic GERD.

**Table 3: Comparison of NBI findings of present study with other studies**

NBI features	Fock <i>et al.</i> <sup>[9]</sup>		Sharma <i>et al.</i> <sup>[10]</sup>		Present study (NERD) n=71 (%)
	NERD n=36 (%)	Control n=30 (%)	NERD n=20 (%)	Control n=30 (%)	
Microerosions	52.8	23.3	30	0	12.7
Increased vascularity at SCJ	91.7	36.7	25	6.7	46.47
Round pit pattern	5.6	70	-	-	43.7
Straight pit pattern	19.4	20	-	-	56.3
Tubular pit pattern	52.8	10	-	-	0
Villous/ridge pit pattern	22.2	0	15	10	0
Mucosal brownish areas	-	-	-	-	21.1
Mucosal/columnar islands	38.9	50	50	33	25.4

NBI: Narrow band imaging; SCJ: Squamocolumnar junction; NERD: Nonerosive reflux disease

**Table 4: Learning curve effect in the use of NBI endoscopy in the diagnosis of histologic GERD (1-15 cases of NERD)**

NBI findings	Histologic GERD (%)		P* value
	Present	Absent	
Microerosions			
Present	4 (57.1)	3 (42.9)	0.782
Absent	4 (50)	4 (50)	
Increased vascularity above SCJ			
Present	4 (80)	1 (20)	0.146
Absent	4 (40)	6 (60)	
Increased vascularity below SCJ			
Present	6 (54.6)	5 (45.4)	0.876
Absent	2 (50)	2 (50)	
Round pit pattern			
Present	1 (50)	1 (50)	0.919
Absent	7 (53.8)	6 (46.2)	
Straight pit pattern			
Present	7 (53.8)	6 (46.2)	0.919
Absent	1 (50)	1 (50)	
Mucosal brownish areas			
Present	1 (25)	3 (75)	0.185
Absent	7 (63.7)	4 (36.3)	
Mucosal islands			
Present	2 (40)	3 (60)	0.464
Absent	6 (60)	4 (40)	

NBI: Narrow band imaging; NERD: Nonerosive reflux disease; GERD: Gastroesophageal reflux disease. \*P value <0.05 was considered statistically significant

In a prospective study by Zentilin *et al.*,<sup>[21]</sup> histologic evidence of reflux esophagitis was seen in 76% of cases of 59 NERD patients. Kasap *et al.*<sup>[22]</sup> showed that in 40 NERD cases, 57.5% patients had abnormal histology. Zuberi *et al.*<sup>[23]</sup> studied 109 NERD patients, of whom 64.2% showed abnormal histologic features. The present study showed that 70.4% of NERD patients had histologic features of GERD. The histologic GERD found in our study was higher than previous studies<sup>[22,23]</sup> and also highly specific, because we took biopsies from 3 cm above SCJ in contrast to those in Kasap *et al.*'s and Zuberi *et al.*'s studies in which biopsies

were taken from 2 cm above SCJ and at SCJ, respectively, as it often appears as mild squamous hyperplasia even in asymptomatic individuals.<sup>[18,19]</sup>

Kasap *et al.*<sup>[22]</sup> investigated 40 NERD patients by NBI endoscopy. Among the 40 cases, 28 (70%) had normal NBI endoscopy (NERD) and remaining 12 (30%) had mucosal brownish areas, which were considered as acid-related mucosal change in ERD. In this study, authors considered only mucosal brownish area as a feature of ERD, not of NERD. They did not study the other features of NERD on NBI such as microerosions, increased vascularity above and below SCJ, mucosal pit patterns, and mucosal islands. Authors found that NBI is more sensitive than WLE in the detection of esophageal lesions in GERD patients. However, histopathologic evaluation is the most sensitive method to diagnose NERD.

Lee *et al.*<sup>[24]</sup> investigated 230 patients with GERD symptoms by both WLE and NBI endoscopy. WLE was normal (NERD) in 65.6% of patients, whereas NBI endoscopy was normal in 59.1% of patients. Up to 6% of patients were reclassified from NERD to grade A esophagitis by the utilization of NBI.

Tseng *et al.*<sup>[25]</sup> assessed 62 NERD patients by NBI endoscopy. Out of the 62 NERD patients, only 18 (29%) showed normal NBI endoscopic findings, and the remaining cases 71% were reclassified as ERD. In our study only 9 (12.7%) patients showed microerosions.

Among the NERD (n = 71) cases, NBI endoscopic findings of first 15 and last 15 cases were analyzed to find out learning effect by correlating them with histologic features of GERD. There was no significant apparent learning effect in the use of NBI for diagnosis of histologic GERD as shown in Tables 4 and 5. Our study suggests that it required tremendous familiarity and a long learning curve for interpretation of NBI endoscopic findings in the diagnosis of NERD.

**Table 5: Learning curve effect in the use of NBI endoscopy in the diagnosis of histologic GERD (57-71 cases of NERD)**

NBI findings	Histologic GERD (%)		P* value
	Present	Absent	
Microerosions			
Present	0 (0)	0 (0)	-
Absent	14 (93.3)	1 (6.7)	
Increased vascularity above SCJ			
Present	3 (100)	0 (0)	0.605
Absent	11 (91.7)	1 (8.3)	
Increased vascularity below SCJ			
Present	5(83.3)	1 (16.7)	0.205
Absent	9 (100)	0 (0)	
Round pit pattern			
Present	7 (100)	0 (0)	0.333
Absent	7 (87.5)	1 (12.5)	
Straight pit pattern			
Present	7 (87.5)	1 (12.5)	0.333
Absent	7 (100)	0 (0)	
Mucosal brownish areas			
Present	0 (0)	0 (0)	-
Absent	14 (93.3)	1 (6.7)	
Mucosal islands			
Present	4 (100)	0 (0)	0.533
Absent	10 (90)	1 (10)	

NBI: Narrow band imaging; NERD: Nonerosive reflux disease; GERD: Gastroesophageal reflux disease. \*P value <0.05 was considered statistically significant

### Limitations of our study

Failure of correlation of NBI endoscopic findings with NERD and histologic features of GERD may be due to the following

- The present study was performed by using gastrointestinal videoscope (Olympus Evis Exera II GIF-H 180), which had NBI with 1.5× digital magnification. Hence we could not characterize the individual morphology of IPCLs
- It required tremendous familiarity and a long learning curve for interpretation of NBI endoscopic findings
- Lack of enrollment of control group was another important limitation, because histologic features of GERD can be seen in asymptomatic individuals and also for comparison of NBI endoscopic findings between NERD and controls
- To date, the research work concerning the use of NBI endoscopy in GERD is relatively scanty, and there is still a need for large scale studies to validate the endoscopic findings.

### CONCLUSION

Our study concluded that biopsy from distal esophageal mucosa has promising diagnostic utility over NBI endoscopy

in NERD patients who suffer from symptoms of GERD. Use of newly introduced NBI technique requires tremendous familiarity for the detection of cases of NERD, which show histologic features of GERD.

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