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ORIGINAL ARTICLE

Barrett's Esophagus and Human Epidermal Growth Factor 2 Status in patients with Gastroesophageal Reflux Disease

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ABSTRACT

Background: Gastroesophageal reflux disease (GERD) is a common upper gastrointestinal condition and a key risk factor for Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC). Identifying reliable biomarkers, such as Human Epidermal Growth Factor 2 (HER2), could improve early detection and management. This study aimed to determine the frequency of Barrett's esophagus among GERD patients and evaluate HER2 expression in relation to dysplasia and carcinoma.

Methods: This cross-sectional study included 193 patients with chronic GERD symptoms who underwent clinical evaluation, laboratory testing, upper GI endoscopy with biopsies, and histopathological examination. HER2/neu expression was assessed immunohistochemically and scored per standardized criteria.

Results: Barrett's esophagus was diagnosed in 5.7% of GERD patients, predominantly short-segment (72.7%). BE was significantly associated with age ≥50 years (81.8%, p = 0.033), obesity (81.8%, p = 0.034), smoking (90.9%, p = 0.047), hiatal hernia (90.9%, p = 0.004), and H. pylori infection (63.6%, p = 0.009). Male sex showed a higher frequency, but the difference was not statistically significant (p = 0.085). HER2/neu overexpression was found in all EAC cases (100%), 63.6% of BE cases, but only in 5.4% of erosive reflux disease (ERD) and 4.6% of non-erosive reflux disease (NERD) cases (p<0.001). HER2 demonstrated a sensitivity of 63.6% and specificity of 95% for detecting BE (AUC = 0.793).

Conclusion: Endoscopic surveillance in GERD patients is critical for early detection of BE and EAC. High HER2 expression correlates with advanced dysplasia and EAC, supporting its utility as an early biomarker and potential therapeutic target.

Keywords: Barrett's Esophagus, Human Epidermal Growth Factor 2, Gastroesophageal Reflux Disease.

INTRODUCTION

Gastroesophageal reflux disease (GERD) remains one of the most prevalent diseases that affects the upper gastrointestinal tract, caused by the backward flow of stomach acid into the esophagus. This process often irritates the esophageal lining, and patients present with symptoms such as heartburn, retrosternal pain, difficulty swallowing, and occasionally persistent coughing [1]. Importantly, GERD is recognized as one of the major risk factors for the development of Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC), with additional risks associated with obesity, hiatal hernia, and smoking [2].

A longstanding complication of GERD is Barrett's esophagus, a premalignant condition in which the squamous epithelium of the lower

esophagus is replaced by intestinal-type cells. This change could be a result of chronic exposure to gastric acid and bile. While the initial triggers are not well understood, the specific molecular steps that drive BE to dysplasia and eventually to EAC remain unclear [3]. The clinical concern is increased by the poor prognosis associated with EAC, especially when the diagnosis occurs late throughout the disease course.

The BE can be categorized into four main types: non-dysplastic, low-grade dysplasia, high-grade dysplasia, and invasive carcinoma [4]. Dysplasia is the most significant indicator of risk for malignant transformation. The annual risk of progressing from low-grade dysplasia (LGD) to high-grade dysplasia (HGD) or EAC varies widely in the literature and research trials but is estimated to be around 0.5–13% [5]. The international guidelines recommend regular endoscopic surveillance and biopsy for BE patients, aiming to detect dysplasia early [2].

Management strategies for BE are tailored according to dysplasia grade. Non-dysplastic and low-grade dysplasia patients are usually monitored with periodic endoscopy, whereas high-grade dysplasia and early EAC could be managed with endoscopic resection or ablation. More advanced EAC typically requires surgery or palliative therapy [4]. Researchers suggest that cancers detected during BE surveillance are at an earlier stage and are associated with improved survival compared to those found or discovered late after symptoms first appear [6]. However, early detection remains challenging, as most EAC cases are diagnosed at advanced stages, which contributes to a five-year survival rate of less than 25% [7].

Currently, dysplasia remains the only established clinical biomarker for EAC risk. There is a growing interest in identifying more precise biomarkers, particularly immunohistochemical (IHC) markers, which are more practical for clinical use compared to genetic or molecular techniques [6]. Among these, the human epidermal growth factor receptor 2 (HER2) has drawn attention. HER2 is a receptor tyrosine kinase involved in several cancers, including breast and gastric malignancies. Overexpression of HER2 has been documented in about one-fifth of advanced gastric cancers, and therapies targeting this pathway have demonstrated improved outcomes [8]. The role of HER2 in BE and its progression toward dysplasia or EAC is still not fully uncovered, with varying results reported in different studies [9].

Despite extensive research into BE and its malignant transformation, data on the prevalence and significance of HER2 expression in BE, especially in relation to dysplasia and carcinoma development, are limited and sometimes conflicting. This lack of clarity highlights an increasing need for further study. This work aimed to assess the frequency of Barrett's esophagus among patients with GERD and to evaluate HER2 expression and its association with dysplasia and carcinoma.

METHODS

This cross-sectional study was conducted at the Departments of Hepatology, Gastroenterology, Infectious Diseases, and Pathology, Zagazig University Hospitals. The research was performed from February 2024 to October 2024.

Institutional Review Board (IRB #11176-3-10-2023) clearance was obtained, and informed consent was obtained from all patients who participated in the study.

A total of 193 patients, presenting chronic symptoms suggestive of GERD, were included from both inpatients and outpatients who required upper GI endoscopy. The sample size was determined using an expected prevalence of 15%, a 95% confidence level, and an estimated population size of 10,000 patients, resulting in 193 cases [9].

The inclusion criteria of the study involved patients who were above 18 years old, regardless of sex, and had clinical manifestations of GERD, including those who had received the optimal duration and dose of GERD therapy. Patients presenting with alarm symptoms like dysphagia, unexplained weight loss, anemia, evidence of gastrointestinal

bleeding, or a history of prior endoscopy were also included, provided they agreed to follow-up and consented to participation. Exclusion criteria were patients below 18 years old, those diagnosed with other tumors, and pregnant women.

Each participant underwent a comprehensive evaluation, which started with a detailed medical history covering demographic information, symptoms related to liver or cardiac disease, history of comorbidities such as diabetes and hypertension, medication use (including NSAIDs or anticoagulants), and special emphasis on GERD-related symptoms like heartburn, dysphagia, vomiting, GI bleeding, smoking, and rapid health deterioration suggestive of esophageal carcinoma.

A thorough clinical examination was conducted for all patients, including assessments for anemia, vital signs, and an abdominal examination for the detection of organomegaly or masses. Abdominal ultrasonography was performed using Sonoscape S11 with a 3.75 MHz probe to check for metastasis, lymphadenopathy, or peritoneal involvement.

Routine laboratory investigations included a complete blood count (CBC), liver function tests (serum albumin, bilirubin, ALT, and AST), renal function tests (serum urea and creatinine), a coagulation profile (PT and INR), and viral markers for HIV, hepatitis B, and hepatitis C. All assays were performed using standardized equipment as per the manufacturer's instructions.

For all cases, upper GI endoscopy was performed after the initial patient had stabilized and coagulopathies were corrected, following standard protocols. Patients received sedation with midazolam and were placed in the left lateral position. Endoscopy was done using a Pentax EG-3840 Gastroscope, with continuous monitoring of vital signs, and particular attention to the identification of Barrett's esophagus or features suggestive of adenocarcinoma. Endoscopic biopsies were taken from the gastroesophageal junction for histopathological and immunohistochemical examination. Four-quadrant biopsies were taken every 2 cm along the columnar-lined esophagus, and additional samples were obtained from suspected adenocarcinoma lesions and adjacent mucosa.

Diagnosis of Barrett's esophagus required endoscopic evidence of columnar epithelium extending above the gastroesophageal junction, confirmed by histological findings of intestinal metaplasia. Barrett's segments were classified as short (<3 cm) or long (≥3 cm) based on the extent of columnar lining.

Histopathological evaluation included examination of hematoxylin and eosin (H&E)-stained sections for changes consistent with GERD (basal cell hyperplasia, elongation of papillae, intraepithelial inflammation), Barrett's esophagus (intestinal metaplasia with goblet cells), dysplasia (low and high grade), and carcinoma. Tumors were classified and graded according to the WHO and Laurens criteria [10]. All slides were reviewed and assessed by a Professional experienced Pathology Doctor.

Immunohistochemical analysis for HER2/neu was performed on all biopsies using the peroxidase-antiperoxidase method. [11]. Briefly, paraffin-embedded sections were processed, and the HER2/neu primary antibody was applied. Slides were evaluated for HER2/neu expression using the scoring system recommended by Hofmann et al. [12], comparing the staining patterns with those of positive controls. HER2/neu staining was interpreted as membranous positivity and scored accordingly.

The Hofmann scoring system categorizes HER2 membranous staining intensity and completeness as 0 (no reactivity or <10% of tumor cells), 1+ (faint or barely perceptible incomplete staining in ≥10% of cells), 2+ (weak to moderate complete or basolateral staining in ≥10% of cells), and 3+ (strong complete or basolateral staining in ≥10% of cells). Scores of 0 and 1+ are considered negative, 2+ equivocal, and 3+ positive [12].

Statistical analysis

Data were collected through clinical evaluations and laboratory tests, coded in

Excel, and analyzed using SPSS v21. Qualitative data were reported as frequencies and percentages, while quantitative data were presented as means, standard deviations, and ranges. One-way ANOVA or Kruskal-Wallis tests compared groups as appropriate. Categorical associations were assessed by the chi-square test, and correlations by Spearman's coefficient. ROC analysis determined diagnostic cut-off values, with sensitivity, specificity, and predictive values calculated. Statistical significance was set at $p < 0.05$.

RESULTS

Among 193 GERD patients, the majority were overweight or obese (85.5%), male (58%), and over 40 years of age (77.2%). High-risk features included a striking prevalence of smoking (62.7%) and diabetes mellitus (30%). The regurgitation was the most prevalent symptom in the studied patients, representing 90.16%, followed by heartburn, which was 84.46%. In contrast, vomiting, upper GIT bleeding, unexplained anemia, and dysphagia represented 7.25%, 3.11%, 12.44% and 9.84% respectively (Table 1).

Among the 193 GERD patients, erosive reflux disease (ERD) was identified in 48.1%, with the majority classified as grade A (73.1%). Non-erosive reflux disease (NERD) accounted for 45.1% of cases. Endoscopically suspected Barrett's esophagus was found in 5.7% of patients (as in Figure 1 B), predominantly presenting as short-segment disease (72.7%). Histopathologically, classic features of GERD (NERD + ERD) were confirmed in 93.3% of cases. Barrett's esophagus was histologically diagnosed in 5.7% of patients, mirroring endoscopic findings, with most showing no dysplasia (72.7%) (as in Figure 1 D) and only a minority exhibiting low (18.2%) or high-grade (9.1%) dysplasia, 2 cases of cancer (1.1%) (as in Figure 1 C) (Table 2)

Barrett's esophagus in GERD patients was significantly associated with age ≥50 years (81.8%, p=0.033), obesity (81.8%, p=0.034), smoking (90.9%, p=0.047), hiatal hernia (90.9%, p=0.004), and H. pylori infection (63.6%, p=0.009). Male sex also showed a higher frequency (81.8%), but did not reach statistical significance ($p = 0.085$) (Table 3).

Histological findings of the stomach revealed that gastritis was present in 58 cases (30.05%) and gastric ulcers in 5 cases (2.59%). H. pylori was diagnosed in 57 cases (29.53%). In contrast, no cases of gastric cancer were detected; histological findings of the duodenum of the studied patients revealed that 9.84% of them were diagnosed as duodenitis. Only 2 cases (1.036) had a duodenal ulcer, and no cases of duodenal cancer were reported (Table 4).

Table 6 shows that using HER2 neu for the detection of esophageal adenocarcinoma, it was positive in 100% of cases (2 cases), as shown in Figure 1F. Also, it was positive in 63.64% of patients with Barrett's Esophagus (7/11). In comparison, it was positive in only 5.38% of patients with ERD and 4.6% of patients with NERD (as shown in Figure 1E), with a highly significant difference ($P < 0.001$).

HER2 neu positivity demonstrated a sensitivity of 63.6% and a high specificity of 95% for detecting Barrett's esophagus among patients with GERD. The test showed a positive predictive value (PPV) of 43.8%, a negative predictive value (NPV) of 97.7%, and an overall diagnostic accuracy of 93.2% (AUC = 0.793) (Table 6, Supplementary Figure 1).

Table 1: Demographic, Clinical, and Symptom Profile of Studied Patients (N = 193)

Parameter	Subcategory / Statistic	Number (N = 193)	%
Age (years)	**Mean ± SD**	**44.58 ± 9.49**	
	Max	**60.0**	
	Min	**18.0**	
	Median	**46**	
	IQR	**11**	
Age Distribution	**< 30**	**19**	**9.84**
	30 – <40	**25**	**12.95**

Parameter	Subcategory / Statistic	Number (N = 193)	%
	40 – <50	72	37.31
	≥ 50	77	39.90
Sex	Female	81	41.97
	Male	112	58.03
Smoking	Negative	72	37.31
	Positive	121	62.69
Diabetes Mellitus (DM)	Negative	135	69.95
	Positive	58	30.05
Hypertension (HTN)	Negative	143	74.09
	Positive	50	25.91
Body Mass Index (BMI)	Mean ± SD	28.51 ± 3.88	
	Max	35.0	
	Min	18.5	
	Median	28	
	IQR	5.1	
BMI Categories	Normal	28	14.51
	Overweight	80	41.45
	Obese	85	44.04
Regurgitation	Negative	19	9.84
	Positive	174	90.16
Heartburn	Negative	30	15.54
	Positive	163	84.46
Vomiting	Negative	179	92.75
	Positive	14	7.25
Upper GIT Bleeding	Negative	187	96.89
	Positive	6	3.11
Unexplained Anemia	Negative	169	87.56
	Positive	24	12.44
Dysphagia	Negative	174	90.16
	Positive	19	9.84

DM: Diabetes mellitus, HTN: Hypertension, BMI: Body mass index, SD: Standard deviation, IQR: Interquartile range, GIT: Gastrointestinal tract. Statistical summary: Data are presented as mean ± SD, median (IQR), or number and percentage.

Table 2: Endoscopic and Histopathological Findings in Patients with GERD and Barrett's Esophagus

Parameter / Classification	Number (n)	Percentage (%)
Total Patients	193	100
Endoscopic Findings		
ERD (Erosive Reflux Disease)	93	48.1
ERD A	68	73.12
ERD B	20	21.50
ERD C	3	3.23
ERD D	2	2.15
NERD (Non-Erosive Reflux Disease)	87	45.1
Barrett's Esophagus (Endoscopic)	11	5.7
Long Segment	3	27.27

Parameter / Classification	Number (n)	Percentage (%)
Short Segment	**8**	**72.73**
Esophageal Adenocarcinoma (Endoscopic)	**2**	**1.1**
Hiatal Hernia (H.H.)		
Negative	**98**	**50.78**
Positive	**95**	**49.22**
Histopathological Findings		
GERD (NERD + ERD)	**180**	**93.26**
Barrett's Esophagus (Histopathology)	**11**	**5.7**
Esophageal Adenocarcinoma (Histopathology)	**2**	**1.04**
Histological Features in GERD (n = 180)		
Basal Cell Hyperplasia		
Negative	**93**	**51.67**
Positive	**87**	**48.33**
Elongation of Papillae		
Negative	**142**	**78.89**
Positive	**38**	**21.11**
Intraepithelial Lymphocytes		
Negative	**156**	**86.67**
Positive	**24**	**13.33**
Combination of 3 Main Features		
Negative	**149**	**82.78**
Positive	**31**	**17.22**
Spongiosis		
Negative	**177**	**98.32**
Positive	**3**	**1.68**
Intraepithelial Neutrophils		
Negative	**179**	**99.44**
Positive	**1**	**0.56**
Intraepithelial Eosinophils		
Negative	**179**	**99.44**
Positive	**1**	**0.56**
Barrett's Esophagus by Histopathology (n = 11)		
No Dysplasia	**8**	**72.73**
Low Grade Dysplasia	**2**	**18.18**
High Grade Dysplasia	**1**	**9.09**

GERD: Gastroesophageal Reflux Disease; NERD: Non-Erosive Reflux Disease; ERD: Erosive Reflux Disease; H.H.: Hiatal Hernia; n: number in subgroup; Percentage (%): of subgroup or category; Barrett's Esophagus: Replacement of the normal squamous epithelium by specialized intestinal metaplasia in the esophagus.

Table 3: Association between Barrett's esophagus and patient characteristics.

	Barrett's esophagus		X2	P- value
	Negative (180)	Positive (11)		
Sex				
Female (80)	**78 (43.33%)**	**2 (18.18%)**	**2.69**	**0.085**
Male (111)	**102 (56.67%)**	**9 (81.82%)**		
Age				
< 30 (19)	**19 (10.56%)**	**0 (0.0%)**		
30 - <40 (24)	**24 (13.33%)**	**0 (0.0%)**	**8.74**	**0.033**
40 - <50(71)	**69 (38.33%)**	**2 (18.18%)**		
≥ 50 (77)	**68 (37.78%)**	**9 (81.82%)**		
Smoker				
Negative (71)	**70 (38.89%)**	**1 (9.09%)**	**3.94**	**0.047**
Positive (120)	**110 (61.11%)**	**10 (90.91%)**		
BMI				
Normal (28)	**27 (15%)**	**1 (9.09%)**		
Overweight (78)	**77 (42.78%)**	**1 (9.09%)**	**6.78**	**0.034**
Obese (85)	**76 (42.22%)**	**9 (81.82%)**		
Hiatus hernia				
Negative (98)	**97 (53.89%)**	**1 (9.1%)**	**8.32**	
Positive (93)	**83 (46.11%)**	**10 (90.9%)**		**0.004**
H pylori				
Negative (136)	**132 (73.33%)**	**4 (36.36%)**	**6.91**	**0.009**
Positive (55)	**48 (26.67%)**	**7 (63.64%)**		

Table 4: Histological Findings of Stomach and Duodenum Among Studied Patients (N = 193)

Histological Finding & Site	Status	Number (%)
Gastritis (Stomach)	**Negative**	**135 (69.95%)**
	Positive	**58 (30.05%)**
Gastric Ulcer (Stomach)	**Negative**	**188 (97.41%)**
	Positive	**5 (2.59%)**
H. pylori (Stomach)	**Negative**	**136 (70.47%)**
	Positive	**57 (29.53%)**
Gastric Cancer (Stomach)	**Negative**	**193 (100%)**
Duodenitis (Duodenum)	**Negative**	**174 (90.16%)**
	Positive	**19 (9.84%)**
Duodenal Ulcer (Duodenum)	**Negative**	**191 (99.96%)**
	Positive	**2 (1.04%)**
Duodenal Cancer (Duodenum)	**Negative**	**193 (100%)**

H. pylori: Helicobacter pylori; N: Number of patients; %: Percentage.

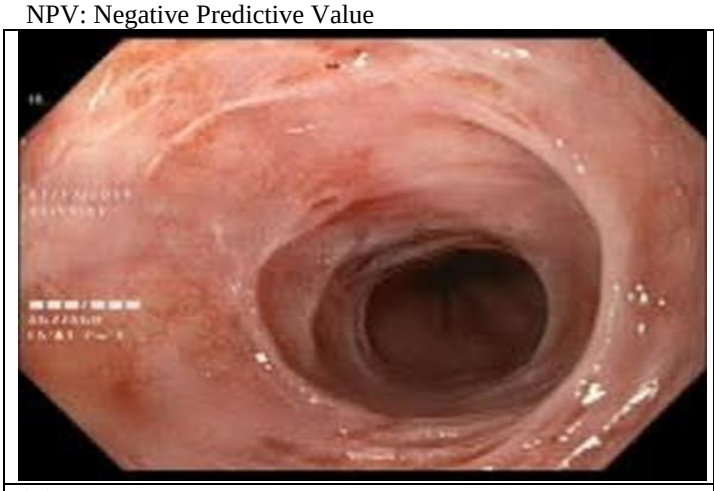
Table 5: Relation between HER2 neu and Endoscopic Finding

Endoscopic Finding	HER2 neu		X2	P- value
	Negative	Positive		
NERD (87)	83 (95.4%)	4 (4.6%)	23.82	<0.001
ERD (93)	88 (94.62%)	5 (5.38%)	25.72	<0.001
Barrette (11)	4 (4.6%)	7 (63.64%)	12.23	<0.001
Esophageal adenocarcinoma (2)	0 (0.0%)	2 (100.0%)	31.82	<0.001

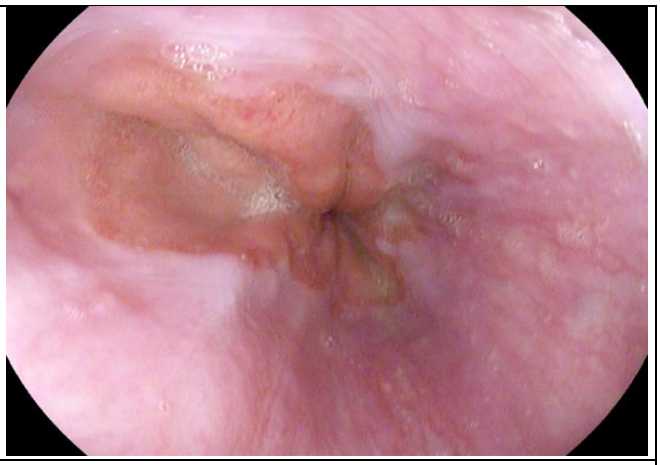
Table 6: Diagnostic Performance of HER2 neu in Detecting Barrett's Esophagus

HER2 neu Result	Barrett's Esophagus Positive	Barrett's Esophagus Negative	Total	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	AUC
Positive	7	9	16	63.63	95	43.75	97.71	93.19	0.793
Negative	4	171	175						
Total	11	180	191						

HER2 neu: Human Epidermal Growth Factor Receptor 2, AUC: Area under the curve, PPV: Positive Predictive Value, NPV: Negative Predictive Value



(A)



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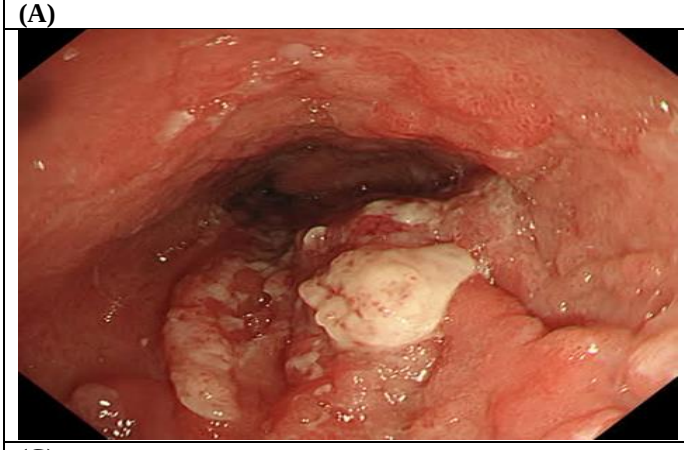

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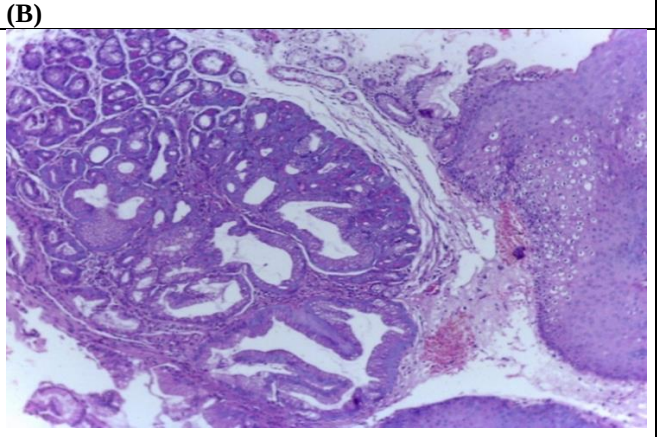

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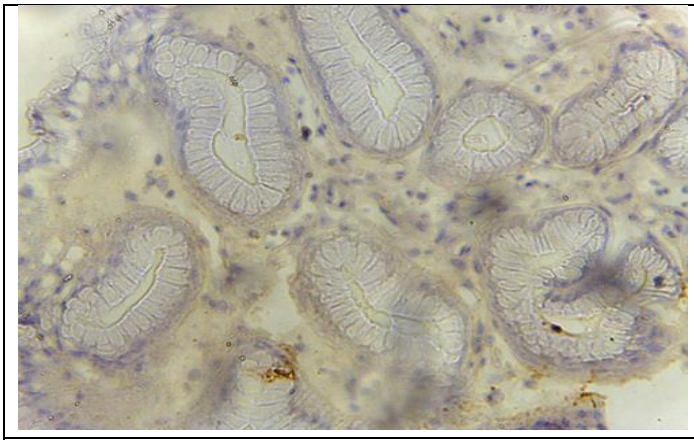

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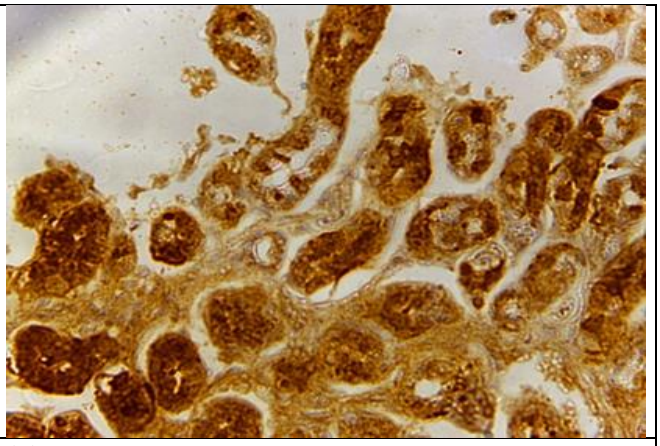

(F)

Figure 1: (a): Normal esophagogastroduodenoscopy, (b): Barrett's esophagus with tongue like projections of dark reddish brown mucosa at the distal esophagus near the gastroesophageal junction., (c): Esophageal adenocarcinoma with a mass at the distal esophagus near the gastroesophageal junction., (d): photographic image showing squamous covering of esophagus with area of intestinal metaplasia and goblet cells (Barrett's esophagus) no dysplasia,(X200, H&E), (e): negative expression of HER2 IHC in barrettes with no dysplasia (X200, HER2NEU IHC), (f): severe expression of her2neu IHC in barrettes with adenocarcinoma (X200, HER2NEU IHC)

DISCUSSION

The current study findings showed that Barrett's esophagus (BE) was present in 11 out of 193 Egyptian patients with chronic GERD (5.7%), with most cases (72.7%) presenting as short-segment BE and only a minority showing low-grade (18.2%) or high-grade dysplasia (9.1%). These figures are highly consistent with recent global studies, such as the work of Maret-Ouda et al. [13], who found a BE prevalence of around 7% in large GERD cohorts, and Kinra et al. [14], who described similar frequencies in high-risk symptomatic patients. This supports the idea that BE is an important but not exceedingly common complication among GERD patients, and reinforces the clinical value of targeted endoscopic surveillance, especially in symptomatic or high-risk individuals.

When considering age distribution, the current study revealed a clear predilection for older patients, with 81.8% of BE cases found in individuals aged 50 or older. This finding aligns with Januszewicz and Fitzgerald [15] and Maslyonkina et al. [16], who both highlighted the cumulative effect of reflux exposure with age and reported that the mean age of BE diagnosis clusters is in the sixth decade of life. In addition, Kim et al. [17] described a similar shift in BE prevalence after the fifth decade in a South Korean population, while Spechler et al. [18] found that advanced age is a significant risk factor for progression from BE to dysplasia and esophageal adenocarcinoma, likely reflecting the effects of chronic mucosal injury and long-standing reflux. However, some studies from the Middle East and Asia have reported a relatively higher proportion of BE among younger adults, which may be related to early and sustained exposure to dietary or environmental risk factors, differing population age structures, or genetic backgrounds [19]. This suggests that while age is a universal risk factor, the threshold for BE screening might need to be adapted according to local epidemiology.

A male predominance was observed, with 81.8% of BE cases occurring in males in the current study. This trend is well-documented in large Western and international series, where male-to-female ratios for BE often approach 4:1, as noted by Shaheen et al. [20] and Sharma et al. [21]. Men are thought to have higher rates of abdominal obesity, and differences in hormonal milieu—such as lower estrogen exposure—may contribute to their greater

susceptibility. Furthermore, Cook et al. [22] demonstrated that not only is BE more common in males, but the progression to high-grade dysplasia and adenocarcinoma is also more aggressive. Gatenby et al. [23] similarly demonstrated higher rates of neoplastic progression in men, possibly due to greater central adiposity, longer reflux exposure, or less robust mucosal defense mechanisms. Nevertheless, the current study did not find male sex to be an independent statistical risk factor, which could be related to limited power or confounding by obesity and smoking, as discussed by Oh and Bang [24]. Some meta-analyses [25] have questioned whether male predominance persists after adjusting for obesity and smoking, suggesting that lifestyle factors may partially explain the observed sex gap.

Obesity was found to be highly prevalent in our GERD population (85.5% overweight or obese), and 81.8% of BE patients were obese. These match reports by Bennett and Mashimo [26] and Corley et al. [27] emphasized the pivotal role of increased BMI, particularly abdominal adiposity, in the development of BE. The mechanisms are multifactorial and likely include increased intra-abdominal pressure, chronic low-grade inflammation, and the impact of dietary and metabolic factors. Multiple meta-analyses confirm that the risk of BE rises in a dose-dependent fashion with BMI, and even modest weight gain can elevate both GERD and BE risk substantially [28]. For example, El-Serag et al. [29] estimated a 20% risk increase for each 5-unit rise in BMI, with the effect being more pronounced in those with central obesity. Some have suggested that waist circumference may be a more accurate marker of risk than BMI alone, especially in Asian populations where body composition differs [30]. Interestingly, in Asian cohorts where obesity is less common, BE prevalence is also generally lower, further supporting the role of adiposity in BE pathogenesis [31].

Smoking also emerged as a prominent risk factor in our study, with 90.9% of BE cases being current or former smokers. This aligns with Andrici et al. [32], who found that smoking increased BE risk in a dose-response manner, likely through chronic inflammation, impaired mucosal defense, and direct epithelial injury. Similar findings were seen in a recent Egyptian series by Mohamed et al. [33], where tobacco use was a consistent predictor of BE among GERD patients. Pandeya et al. [34] and Lagergren et al. [35] have also shown, in large prospective studies, a clear gradient of risk with higher cumulative tobacco exposure, particularly in males and those with coexisting obesity. However, Hofmann et al. [36] reported weaker associations for smoking after adjusting for obesity and alcohol consumption, suggesting possible effect modification or residual confounding. Differences in how smoking is assessed (current vs. ever, pack-years) and population genetics may partly explain these discrepancies.

Helicobacter pylori infection was identified in 63.6% of BE cases in the present study higher than among GERD patients overall (29.5%). The literature on this association is mixed: Verma et al. [37] and Rodrigues et al. [30] have reported that chronic H. pylori gastritis may increase the risk of metaplastic transformation in some individuals, particularly those with long-standing infection or atrophic gastritis. In contrast, Hofmann et al. [36] and Xie et al. [38] highlighted that certain H. pylori strains, especially those that are CagA-positive, may have a protective effect by reducing gastric acid secretion and thereby decreasing esophageal acid exposure. A recent meta-analysis by Xie et al. [38] found that while H. Helicobacter pylori was associated with a reduced risk of BE and esophageal adenocarcinoma in Western populations; results were inconsistent in Asia and Africa, underscoring the importance of local factors such as bacterial strain, antibiotic use, host immunity, and environmental exposures.

Endoscopically, 48.1% of GERD patients in this study had erosive reflux disease (ERD), and 45.1% had non-erosive reflux disease (NERD). The BE was diagnosed in 5.7%, and esophageal adenocarcinoma in 1%. These rates

closely reflect those observed in recent high-risk populations by Westhoff et al. [28], who reported BE prevalence between 6% and 8% and a predominance of short-segment BE in GERD patients. Tan et al. [29] similarly noted that most BE cases at diagnosis were short-segment, with dysplasia rates below 20%, highlighting the importance of regular surveillance rather than immediate intervention in most cases. Fonseca et al. [30] and Odze [31] also reported that the progression to dysplasia or carcinoma is infrequent at initial diagnosis, underscoring the value of risk stratification and endoscopic follow-up.

On histology, basal cell hyperplasia (48.3%), papillary elongation (21.1%), and intraepithelial lymphocytes (13.3%) were the most common findings in GERD biopsies, reflecting the classic features of reflux esophagitis, as detailed by Mastracci et al. [32]. The detection of goblet cells in BE and the grading of dysplasia were performed using established international criteria. However, Grin and Streutker [33] highlight the significant challenge of interobserver variability—particularly in low-grade dysplasia, which remains a source of diagnostic uncertainty in both routine and research practice.

A particularly remarkable finding in this study was the frequency of HER2/neu overexpression: HER2/neu was positive in all esophageal adenocarcinoma cases (2/2), in 63.6% of BE cases (7/11), but only in 5.4% of ERD and 4.6% of NERD cases. These findings are in line with Oh and Bang [24] and Bennett and Mashimo [26], who noted HER2 positivity rates in BE and adenocarcinoma of 20–40%, particularly in dysplastic lesions or advanced metaplasia. The relatively high rate of HER2 positivity in our BE cohort may reflect a higher proportion of dysplastic or at-risk cases, or technical differences in immunohistochemical staining, as suggested by Shi et al. [34]. Multiple studies agree that HER2 is rarely expressed in non-dysplastic or benign reflux, supporting its utility as a marker of neoplastic progression. Parra et al. [35] and Stoss et al. [36] further confirm HER2's value as a particular marker for high-risk BE, though sensitivity is moderate, indicating it should be used in combination with other risk stratification tools.

The diagnostic performance of HER2/neu in this study, a sensitivity of 63.6% and specificity of 95% for BE, matches recent international data and demonstrates that while HER2 can help identify higher-risk lesions, it cannot reliably rule out lower-risk disease. Incorporating HER2/neu status into BE surveillance protocols, as recommended by Januszewicz and Fitzgerald [15], may help to refine risk stratification and focus intensive surveillance or early intervention on those most likely to progress. Recent studies also suggest a possible role for targeted HER2 therapies in selecting BE and esophageal adenocarcinoma patients, particularly those with strong membranous overexpression [24].

Some disagreement with previous research is apparent. The higher H. pylori rate in BE seen in this cohort differs from reports in Europe and North America, likely due to regional differences in H. pylori epidemiology, strain distribution, and treatment patterns [37]. The high HER2 positivity rate in BE may reflect a small sample size, referral bias, or methodological differences, underscoring the need for standardized protocols for immunohistochemistry. Moreover, studies from East Asia often report lower rates of HER2 overexpression, which may be due to ethnic and molecular differences in BE biology [38].

The main strength of this study is its cross sectional design and relatively large sample size of patients with chronic GERD evaluated at a university hospital, allowing for systematic endoscopic and histological assessment. The inclusion of immunohistochemical evaluation of HER2/neu adds a novel aspect and may provide valuable insight into risk stratification of Barrett's esophagus in an Egyptian population. Additionally, all samples were assessed by senior pathologists, which enhances diagnostic reliability.

This study has some limitations. The study was conducted in a single center, so the findings

may not be representative of all GERD patients in Egypt or other regions. The number of patients with Barrett's esophagus and esophageal adenocarcinoma was relatively small, which limits the power of subgroup analysis. Additionally, referral bias may have influenced the results, as more severe or complicated cases may have been overrepresented. Finally, interpretation of HER2/neu immunohistochemistry may vary due to technical factors, and follow-up data on long-term outcomes were not included.

CONCLUSION

Close endoscopic follow-up in GERD patients is essential for early detection of Barrett's esophagus and esophageal adenocarcinoma. High HER2 expression was associated with advanced dysplasia and cancer risk, indicating its value as a potential early biomarker and therapeutic target. HER2 expression may play a crucial role in esophageal carcinogenesis and can be regarded as a valuable target for elucidating the molecular mechanisms underlying cancer.

Data Availability: Requests for access to the underlying data that substantiate the results of this study may be directed to the corresponding author, who will consider providing them in accordance with institutional policies and applicable ethical guidelines.

Author Contributions: E.A.M. played a central role in formulating the research idea, outlining the methodology, and overseeing the progress of the study. M.A.G. carried out the pathological examinations and offered detailed analysis of the microscopic findings, which were crucial to the work. M.A.M.D. contributed by gathering patient data, handling clinical aspects, and assisting in writing the preliminary draft. N.E.E. revised the manuscript thoroughly, ensured accuracy of the scientific content, and added valuable guidance throughout the work. Each author contributed significantly and approved the final draft before submission.

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SUPPLEMENTARY MATERIAL

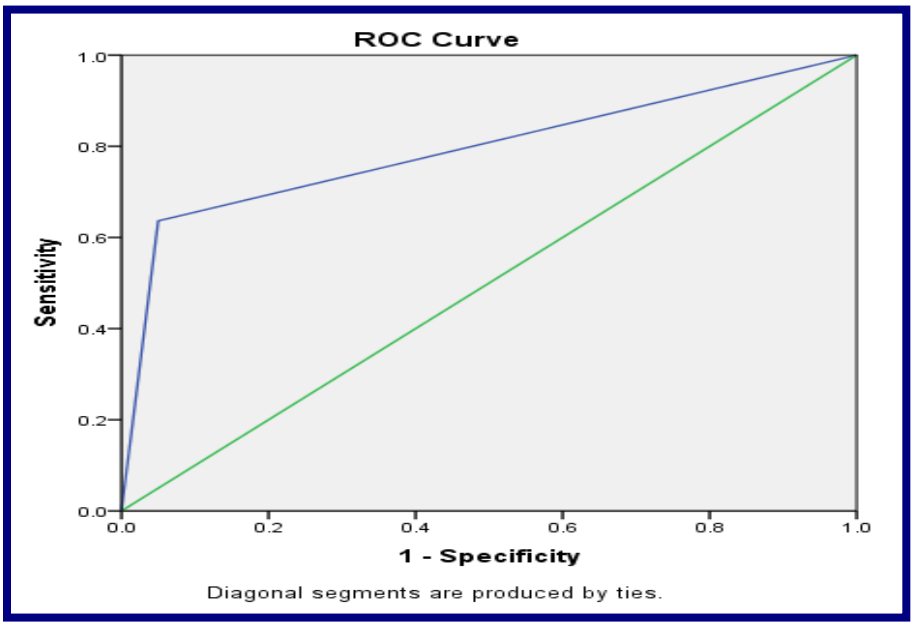

Figure (S1): Receiver-operating characteristic (ROC) curve for HER2 neu in detecting Barrett's Esophagus.

Citation

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