Prevalence of HER2 expression and its association with clinicopathological parameters in gastric and gastroesophageal junction adenocarcinoma: A 10-year experience of an academic center

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Abstract. HER2 overexpression is a marker for targeted therapy in adenocarcinoma of the gastroesophageal junction (GEJ) and stomach. The present study aimed to evaluate the frequency of HER2 overexpression with reference to clinicopathological characteristics in subjects from King Abdulaziz University Hospital, Jeddah, Saudi Arabia over a 10-year period. A retrospective cross-sectional study was conducted on all biopsy and resection specimens diagnosed with either gastric cancer (GC) or GEJ adenocarcinomas from patients between January 2014 and December 2023 that had a final pathology report. Demographic characteristics of 122 patients, including age and sex, were collected, along with pathological details such as tumor grade, histological subtype and HER2 status. χ^2 test was used to analyze the association between collected clinicopathological characteristics and HER2 status of the tumor. Most patients were aged 40-60 years. Males constituted 66% of the patients, and the ethnic distribution between Saudi and non-Saudi was almost equal. The most common subtype of cancer was the intestinal type (49%), and the majority of cases were poorly differentiated (64%). HER2 status was assessed in only 61% of cases, with 13.5% showing gene amplification. There was no significant association found between HER2 status and clinicopathological features.

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Abbreviations: GEJ, gastroesophageal junction; GC, gastric cancer; NCCN, National Comprehensive Cancer Network; IHC, immunohistochemistry; ISH, *in situ* hybridization; ToGA, trastuzumab for gastric cancer

Key words: clinicopathological characteristic, gastric cancer, gastroesophageal adenocarcinoma, HER2 expression, prevalence, retrospective study

Introduction

Gastric cancer (GC) is a notable global health issue that continues to rank as the fifth most prevalent cancer worldwide, with 968,784 new cases identified globally in 2022. It is also the fifth most common fatal cancer globally; ~0.6 million individuals succumb to stomach cancer annually and it accounts for 7.1% of all cancer-associated deaths in Western Asia. Although it is the 11th most common cancer in both sexes in Saudi Arabia, it is the 7th most common cause of cancer-associated fatalities in the country (1).

From 2004 to 2017, GC represented 3.7 and 2.1% of all cancer cases in males and females, respectively, in Saudia Arabia, with a notable increase in cases recorded among individuals aged ≥50 years, with males representing 83.3 and females 70.9% of the cases in this age group (2). In developed countries, the 5-year survival rate for advanced stage GC is <30%, while it is ~20% in developing countries (3). Surgery serves as the primary treatment modality for early-stage disease, while chemotherapy enhances survival rates in patients with advanced GC. Recent research focuses on potential molecular targets for treatment in GC and gastroesophageal junction (GEJ) adenocarcinomas (4-6). Although GEJ adenocarcinoma is not as common as GC, its incidence is increasing globally. In 2020, an estimated 604,100 new cases of esophageal cancer were reported worldwide, with esophageal adenocarcinoma comprising ~14% of these cases (7).

HER2 (ERBB2) is a proto-oncogene situated on chromosome 17, encoding a 185-kDa tyrosine kinase receptor that is part of the epidermal growth factor receptor family. Its phosphorylation triggers signalling pathways that promote cell division, proliferation, differentiation and apoptosis (8-10). The HER2 gene product is present in normal epithelial cells, with amplification observed in GC and GEJ adenocarcinomas. According to the National Comprehensive Cancer Network (NCCN) guidelines, the rates of HER2 positivity in patients with GC range from 12 to 23% (11). Additionally, the College of American Pathologists, American Society for Clinical Pathology and the American Society of Clinical Oncology joint guidelines indicate that the frequency of HER2 upregulation in gastroesophageal adenocarcinoma is 7-38%, with a slightly

higher prevalence in GEJ cancer compared with GC (12). This upregulation is influenced by histological subtype, with the intestinal type exhibiting greater levels than the diffuse type, and by differentiation, where moderately differentiated tumours show higher expression compared with poorly differentiated ones (11). Tumor site may also influence HER2 upregulation, as proximal GC, particularly those located in the cardia or near the gastroesophageal junction, exhibit higher rates of HER2 overexpression compared to distal gastric cancers involving the antrum or pylorus (12,13).

The NCCN recommends assessing tumour HER2 expression through immunohistochemistry (IHC) or *in situ* hybridization (ISH) for patients with inoperable locally advanced, recurrent, or metastatic adenocarcinoma of the stomach or GEJ who are being considered for trastuzumab therapy (11). Results from a 2010 open-label, international, phase 3 randomized controlled trial [Trastuzumab for Gastric Cancer (ToGA)] demonstrated that the anti-HER2 humanized monoclonal antibody trastuzumab significantly prolongs survival in patients with HER2-positive adenocarcinoma of the stomach and GEJ compared with chemotherapy alone. Therefore, trastuzumab and chemotherapy are commonly used together as the first line treatment for HER2-positive metastatic GC and GEJ adenocarcinomas (14). Trials are currently underway for other substances targeting HER2 (15,16). HER2 is also a significant prognostic factor in GC; however, the existing literature presents conflicting evidence, with not all studies demonstrating an association between HER2 expression and adverse prognosis (5,17-19).

The present study aimed to assess the prevalence of HER2 gene amplification in patients with GC and GEJ adenocarcinoma and its association with clinicopathological factors.

Materials and methods

Study design. The present cross-sectional analytic study was conducted at Pathology Laboratory of the Department of Clinical Laboratories in King Abdulaziz University Hospital in Jeddah, Saudi Arabia. The study was approved by the Unit of Biomedical Ethics of the Faculty of Medicine at King Abdulaziz University (Institutional Review Board approval no. 337-24). The internal database was searched for all cases diagnosed as GC or GEJ adenocarcinoma between January 2014 and December 2023. The clinicopathological data were gathered from the electronic health records and pathology reports. Inclusion criteria were endoscopic biopsy and surgical resection specimens. A total of 122 patients were included, with an age range of 24-90 years. The cohort consisted of 81 males and 41 females. Duplicate specimens from the same individual were excluded.

Clinicopathological parameters. Clinicopathological parameters included age, sex, nationality, tumor histological subtype (intestinal, diffuse or mixed), grade (G1, well; G2, moderately or G3, poorly differentiated), as well as its location [GEJ, gastric cardia, fundus, body, antrum, pylorus and overlapping location (proximal, distal, and whole stomach) or unknown]. In addition, the status of background gastric mucosa and presence or absence of *Helicobacter pylori* and intestinal metaplasia was recorded. Typing and grading of the carcinomas were performed based on the latest World Health Organization guidelines at the time of diagnosis (20). In cases of uncertainty, a second independent pathologist reviewed the case to reach a consensus diagnosis. Age was categorised based on commonly used epidemiological thresholds in GC and gastroesophageal cancer studies, which considered non-linear relationships between age and HER2 status (21-23).

HER2 testing. The status of HER2 expression determined by IHC and gene amplification by fluorescence ISH (FISH) were also recorded, if performed. HER2 IHC staining was performed on paraffin-embedded tissue sections, 4 μm in thickness, fixed in 10% neutral-buffered formalin for 24-48 h at room temperature. Sections were deparaffinized in xylene and rehydrated in descending ethanol concentrations. Antigen retrieval was carried out using Tris-EDTA buffer (pH 9.0) at 95˚C on the Ventana BenchMark XT automated immunostainer (Ventana Medical Systems, Inc.), according to the manufacturer's protocol. The primary antibody used was Ventana PATHWAY anti-HER2/neu (4B5) rabbit monoclonal antibody (ready-to-use; Ventana, cat. no. 790-2991), and detection was performed with the UltraView Universal DAB Detection Kit (Ventana, cat. no. 760-500). Hematoxylin counterstaining was performed at 37˚C. Slides were analyzed under a light microscope. IHC for both GC and GEJ adenocarcinoma was scored according to the criteria used in the ToGA trial (14). Equivocal cases (IHC score, 2+) are usually further assessed by an outside lab for ISH. In the present study, HER2 results were extracted from pathology reports. No new reassessment of HER2 status was performed. As the study was designed to collect pre-recorded data without reassessment of HER2 status, no intra- or inter-observer variability analysis was conducted. HER2 status was defined by combining IHC and FISH results. HER2-positive adenocarcinomas were defined as IHC 3+ or 2+ and FISH-positive cases as the United States Food and Drug Administration has approved trastuzumab in association with chemotherapy for treatment of metastatic GC only for cases with these results according to the eligibility criteria of the ToGA trial. Cases with HER2 IHC 0 or 1+ were counted as HER2-negative. Cases with incomplete HER2 status were included and missing HER2 values were analyzed separately. No imputation was performed.

Statistical analysis. Descriptive statistics were employed to describe the characteristics of the patient population. Nominal variables such as tumor grade are presented as frequencies and percentages. χ^2 was used to determine the association between HER2 positivity and histopathological subtype with patient demographics, tumor location, and tumor grade. The association between the quantitative non-parametric variables (expressed as mean ± SD) was examined using the Mann Whitney test. Since no significant association was found in bivariate analysis, multivariate analysis was not performed to avoid overfitting and misinterpretation. $P<0.05$ was considered to indicate a statistically significant difference. SPSS version 26 (IBM Corp.) was used for all statistics performed. Normality of continuous variables was assessed using the Shapiro-Wilk test.

Results

The present study recruited 122 patients with GC and GEJ. Of patients, 84 (68.9%) were aged >50 years, with a mean age of 58.2±14.9 years. The majority (81; 66.4%) were male, and 62 (50.8%) were Saudis. More than half (63; 51.6%) had a body/distal stomach tumor location, and 60 (49.2%) and 58 (47.5%) had an intestinal and diffuse histological subtype, respectively. Of patients, 78 (63.9%) had grade 3 tumor and 73 (59.8%) had unremarkable background gastric mucosa. A total of 37 (30.3%) had intestinal metaplasia, 16 (13.1%) had *H. Pylori* infection and 10 (8.2%) had a HER2 positive status (Table I).

A total of 39% of cases had missing HER2 status data. Tumor location was documented in 109 of 122 cases (89.3%). As the present study relied on retrospective data collection, missing data were not imputed, and only available records were analyzed. Reactive gastropathy, reported in three cases, refers to non-inflammatory gastric mucosal injury caused by various factors such as bile reflux, non-steroidal anti-inflammatory drugs or chemical irritants.

There was no significant association between the HER2 status and all the demographic and the clinicopathological characteristics (P>0.05; Table II). The mean age of HER2-negative and -positive patients was 56.9±14.3 and 53.6±11.4 years, respectively (P=0.495). When analyzed by histological subtype, patients with intestinal-type tumors had a mean age of 62.7±15.3 years, compared to 53.8±15.1 years in diffuse-type and 56.3±20.0 years in mixed-type tumors (P=0.01). The prevalence of mixed histological subtype was significantly higher among younger patients (≤50 years), males, those with a body/distal stomach tumor locations and those having grade 2 tumors (P<0.05; Table III).

Table I. Distribution of patients according to demographic and clinicopathological characteristics.

Variable		n (%)
Age, years	≤50	38 (31.1)
	>50	84 (68.9)
Sex	Female	41 (33.6)
	Male	81 (66.4)
Nationality	Non-Saudi	60 (49.2)
	Saudi	62 (50.8)
Tumor location	Body/distal stomach	63 (51.6)
	GEJ	24 (19.7)
	GEJ/body/distal stomach	2 (1.6)
	GEJ/whole stomach	2 (1.6)
	GEJ/proximal stomach	4 (3.3)
	Whole stomach	6 (4.9)
	Proximal stomach	8 (6.6)
	Not reported	13 (10.6)
Histological subtype	Adenosquamous	1 (0.8)
	Diffuse	58 (47.5)
	Intestinal	60 (49.2)
	Mixed	3 (2.5)
Tumor grade	1	7 (5.7)
	2	37 (30.3)
	3	78 (63.9)
Background gastric mucosa	AIG with ECL hyperplasia	1 (0.8)
	Chronic active gastritis	22 (18)
	Chronic inactive gastritis	23 (18.9)
	Unremarkable	73 (59.8)
	Reactive gastropathy	3 (2.4)
Intestinal metaplasia	Not present	85 (69.7)
	Present	37 (30.3)
Helicobacter pylori	Not present	106 (86.9)
	Present	16 (13.1)
HER2 status	Negative	60 (49.2)
	Positive	10 (8.2)
	Unknown	52 (42.6)

GEJ, gastroesophageal junction; AIG, autoimmune gastritis; ECL, enterochromaffin-like cells.

Discussion

HER2 expression in GC and gastroesophageal cancers has been recognized for its crucial role in cancer pathogenesis and targeted therapy (24,25). The efficacy of trastuzumab in patients with breast cancer has generated increasing interest in its application for HER2-positive gastric carcinoma, with numerous studies exploring its role in treating GC and gastroesophageal cancer (26-28).

Though the incidence of GC and GEJ adenocarcinoma in Saudi Arabia is relatively low compared with other countries, there is a lack of data regarding HER2 expression. The aim of the present study was to provide an insight into the rate of HER2-positivity in GC and GEJ adenocarcinoma and clinicopathological characteristics of patients.

Consistent with prior studies, the present study identified a male predominance in GC, with male-to-female ratio of ~2:1 (2,29). The body/distal stomach was the most prevalent location of involvement, consistent with previous studies (30,31). The low *H. pylori* positivity rate (13.1%) may be attributed to multiple factors. Prior antibiotic use could have eradicated the bacteria before histological examination, leading to false-negative results. Additionally, variations in detection methods, such as differences in sensitivity between histological assessment, serological tests and molecular techniques, may contribute to discrepancies in reported prevalence rates. Sample type may also serve a role, as biopsy specimens may yield different detection rates compared with resection specimens (32,33). Furthermore, regional differences in *H. pylori* prevalence, lifestyle changes and improved hygiene have contributed to a declining global trend in *H. pylori* infection, particularly in populations from high-income and urbanized regions such as Western Europe, North America, and parts of East Asia. The widespread use of eradication therapy has decreased the detection rate of active infections (34,35). Therefore, future studies should incorporate standardized detection methods and assess additional risk

Table II. Association between the HER2 status and demographic and clinicopathological characters of patients.

Variable		HER2 status (%)		χ^2	P-value
		Negative	Positive		
Age, years	≤50	18 (30.0)	4 (40.0)	0.4	0.816
	>50	42 (70.0)	6 (60.0)		
Sex	Female	23 (38.3)	4 (40.0)	1.8	0.402
	Male	37 (61.7)	6 (60.0)		
Nationality	Non-Saudi	28 (46.7)	5 (50.0)	0.3	0.856
	Saudi	32 (53.3)	5 (50.0)		
Tumor location	Body/distal stomach	39 (65.0)	6 (60.0)	16.8	0.266
	GEJ	9 (1.5)	0 (0.0)		
	GEJ/body/distal stomach	1 (1.7)	0 (0.0)		
	GEJ/whole stomach	1 (1.7)	0 (0.0)		
	GEJ/proximal stomach	1 (1.7)	1 (10.0)		
	Proximal/body/distal stomach	3 (5.0)	0 (0.0)		
	Proximal stomach	2 (3.3)	1 (10.0)		
	Missing data	4 (6.7)	2 (20.0)		
Histological subtype	Diffuse	34 (56.7)	5 (50.0)	6.0	0.424
	Intestinal	25 (41.7)	5 (50.0)		
	Mixed	1 (1.7)	0 (0.0)		
Tumor grade	1	3 (5.0)	0 (0.0)	3.1	0.534
	2	15 (25.0)	3 (30.0)		
	3	42 (70.0)	7 (70.0)		
Background gastric mucosa	AIG with ECL hyperplasia	1 (1.7)	0 (0.0)	6.9	0.731
	Chronic active gastritis	12 (20.0)	2 (20.0)		
	Chronic inactive gastritis	15 (25.0)	1 (10.0)		
	Gastropathy	1 (1.7)	0 (0.0)		
	Unremarkable	30 (50.0)	7 (70.0)		
	Reactive gastropathy	1 (1.7)	0 (0.0)		
Intestinal metaplasia	Not present	38 (63.3)	7 (70.0)	2.4	0.296
	Present	22 (36.7)	3 (30.0)		
Heliobacter pylori	Not present	53 (88.3)	8 (80.0)	0.5	0.766
	Present	7 (11.7)	2 (20.0)		

GEJ, gastroesophageal junction; AIG, autoimmune gastritis; ECL, enterochromaffin-like cells.

factors to understand the true burden of *H. pylori* in gastric carcinogenesis.

An analysis of 122 cases of GC/gastroesophageal adenocarcinomas biopsy and resection specimens revealed an overall HER2 positivity rate of 13.5%, consistent with the previously reported rate of 4.4-53.4% (24). The differences in HER2-positivity rates across countries and populations may be partially attributed to the prevalence of carcinoma exhibiting characteristics associated with HER2-positivity, such as intestinal-type histology, well to moderately differentiated tumors and proximal tumor location. Accordingly, HER2 overexpression has been correlated in previous studies with various clinicopathological parameters in patients with GC (13,27,28). Lei *et al* (27) found HER2 upregulation in GC to be correlated with male sex, proximal location of tumor, advanced stage, lymph node metastasis, distant metastasis, well-differentiated tumors and intestinal subtype (27). There is also a higher HER2 expression rate in Asians than in Europeans (27). The present study found no significant association between HER2 upregulation and clinicopathological variables such as age, sex, tumor location and histological grade.

HER2 overexpression was observed more frequently in individuals aged >50 years and males, but without a significant association. A previous study has also showed that older age and male sex are associated with HER2 gene expression (31). Roy *et al* (36), on the other hand, discovered that the rate of HER2 positivity was not substantially greater in males or those aged >60 years.

Although HER2-positivity was more frequent in distal (60%) than proximal GC (40%), the difference was not significant, possibly due to sample size limitations rather than true biological variability. Roy *et al* (36) reported that proximally located gastric tumors alone constituted 38% of cases, while GEJ adenocarcinoma accounted for 21% of all cases.

Table III. Relationship between histological subtype and demographic and clinicopathological characteristics.

Variable		Histological subtype (%)			χ^2	P-value
		Diffuse	Intestinal	Mixed		
Age, years	≤50	24 (41.4)	11 (18.3)	2 (66.7)	11.4	0.01
	>50	34 (58.6)	49 (81.7)	1 (33.3)		
Sex	Female	27 (46.4)	14 (23.3)	0 (0.0)	9.2	0.027
	Male	31 (53.4)	46 (76.7)	3 (100)		
Nationality	Non-Saudi	32 (55.2)	25 (41.7)	3 (100)	6.3	0.100
	Saudi	26 (44.8)	35 (58.3)	0 (0.0)		
Tumor location	Body/distal stomach	40 (69.0)	21 (35.0)	2 (66.7)	16.6	0.019
	GEJ	3 (5.2)	20 (33.3)	0 (0.0)		
	GEJ/body/distal stomach	2 (3.4)	0 (0.0)	0 (0.0)		
	GEJ/whole stomach	1 (1.7)	1 (1.7)	0 (0.0)		
	GEJ/proximal stomach	2 (3.4)	2 (3.3)	0 (0.0)		
	Whole stomach	4 (6.9)	1 (1.7)	1 (33.3)		
	Proximal stomach	2 (3.4)	6 (10.0)	0 (0.0)		
	Missing data	4 (6.9)	9 (15.0)	0 (0.0)		
Tumor grade	1	0 (0.0)	7 (11.7)	0 (0.0)	10.9	<0.001
	2	1 (1.7)	32 (53.3)	3 (100)		
	3	57 (98.3)	21 (35.0)	0 (0.0)		
Background gastric mucosa	AIG with ECL hyperplasia	1 (1.7)	0 (0.0)	0 (0.0)	12.3	0.655
	Chronic active gastritis	8 (18.8)	14 (23.3)	0 (0.0)		
	Chronic inactive gastritis	13 (22.4)	8 (13.3)	1 (33.3)		
	Gastropathy	0 (0.0)	1 (1.7)	0 (0.0)		
	Unremarkable	36 (62.1)	35 (58.3)	2 (66.7)		
	Reactive gastropathy	0 (0.0)	2 (3.3)	0 (0.0)		
Intestinal metaplasia	Not present	46 (79.3)	36 (60.0)	2 (66.7)	5.7	0.130
	Present	12 (20.7)	24 (40.0)	1 (33.3)		
Heliobacter pylori	Not present	50 (86.2)	52 (86.7)	3 (100)	0.6	0.89
	Present	8 (13.8)	8 (13.3)	0 (0.0)		

GEJ, gastroesophageal junction; AIG, autoimmune gastritis; ECL, enterochromaffin-like cells.

Counting both GEJ and gastric cardia tumors together in the aforementioned study may explain the higher HER2 positivity rate of proximal tumors overall, as both sites are individually associated with relatively higher HER2 expression compared to distal gastric locations (36).

Poorly differentiated histology was more frequently observed in HER2 positive cases. In a study by Shan *et al* (28), HER2-positivity was more common in well- or moderately differentiated histology (50 and 26%, respectively) than in poorly differentiated carcinomas (23%). Another study discovered considerably increased HER2 expression in low grade tumors (37). Roy *et al* (36) discovered that the rate was higher in patients with well differentiated histology, however this was non-significant, similar to the findings in the present analysis.

The present study observed an association between the mixed histological subtype of GC and factors such as younger age, male sex, body/distal tumor location and grade 2 differentiation. While these findings suggest that the mixed histological subtype may have distinct biological characteristics, the small sample size (three out of 122 cases) limits the validity of comparisons and precludes definitive conclusions. Mixed-type gastric carcinomas exhibit more aggressive features compared with intestinal and diffuse types, including larger tumor size, deeper invasion and higher rates of lymph node metastasis (38). The association of the mixed histological subtype with younger age and male sex, however, aligns with the findings in the aforementioned study. However, due to the absence of staging data, direct comparison with previous literature could not be made. Future studies incorporating tumor stage, alongside HER2 expression in mixed-type GC, are needed to clarify the behavior and clinical relevance of this subtype. Elucidating the molecular and genetic profiles of mixed-type gastric carcinoma may provide insights into its unique biology and inform potential targeted treatment strategies.

The present findings suggest that HER2 expression may be influenced by molecular mechanisms beyond conventional clinicopathological parameters. Prior studies highlight the roles of genetic and epigenetic alterations, as well as the tumor microenvironment, in HER2 overexpression (39,40).

This underscores the need for further molecular and genetic profiling studies to understand the determinants of HER2 expression in gastric and GEJ adenocarcinomas. The lack of significant results may also be attributed to several factors, including limited sample size, potential selection bias and the retrospective nature of the study. A larger cohort with prospective data collection may identify associations that were not detected in the present analysis.

The present study also did not adjust for potential confounding factors such as tumor stage, lymphovascular invasion, lymph node metastasis and molecular subtype. These factors could play a key role in determining HER2 expression and its association with clinicopathological parameters. Multivariate analyses should control for these confounders to provide a clearer understanding of independent associations. Future research with more comprehensive data collection and multivariate analysis is recommended to account for these potential confounders and improve the robustness of findings.

The generalizability of the present findings is limited due to the relatively small sample size and the single-center nature of the study. The study also may contain some intrinsic bias because of the retrospective design. Furthermore, the absence of clinicopathological data-such as family history, tumor size, stage, lymphovascular invasion and lymph node metastasis, highlights the need for future studies to investigate the relevance of these factors. HER2 testing was selectively performed at the discretion of treating clinicians, rather than being systematically applied to all cases, introducing a potential selection bias that may have affect the reported HER2 positivity rate. Additionally, the lack of HER2 testing in 39% of cases represents a further limitation, potentially reducing the statistical power and leading to an underestimation of HER2 prevalence. The findings should be interpreted with caution, and future studies should implement uniform and systematic HER2 testing protocols to minimize selection bias and improve reliability. Another limitation of the present study is the absence of an intra- and inter-observer agreement analysis for HER2 scoring, as interpretation was performed by a single pathologist at the time of diagnosis. Future prospective studies should incorporate multiple reviewers and statistical concordance measures, such as κ statistics, to ensure reliability and reproducibility of HER2 assessment. While the data provide insights into HER2 expression trends in a specific population, caution should be exercised in making broader conclusions. Given the potential regional variability in HER2 expression and demographic, a nationwide database with multi-center studies is recommended to provide a more representative understanding of HER2 prevalence and its association with clinicopathological factors.

The present study found a significant 13.5% HER2 positivity rate among patients with GC/GEJ cancer, which is consistent with global data (41). No significant association was found between HER2 status and clinicopathological characteristics. However, HER2 status evaluation should be performed in accordance with established clinical guidelines and the availability of testing, particularly in patients for whom targeted therapy may be beneficial. Data pooling at the national level is required to gain a better understanding of which demographic, clinical and histological features have the best predictive value for HER2 overexpression in gastric and gastroesophageal junction adenocarcinomas. A prospective randomized multi-center trial is required to provide the prevalence of HER2 positivity. Further studies incorporating molecular markers such as microsatellite instability and tumor mutational burden are warranted to elucidate potential interactions with HER2-positive pathways and their implications for treatment response.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

RB conceptualized the study, developed the methodology, collected and analyzed the data, wrote and reviewed and edited the manuscript. All authors read and approved the final version of the manuscript.

R.B. confirms the authenticity of all the raw data.

Ethics approval and consent to participate

The Institutional Review Board of Faculty of Medicine of King Abdulaziz University approved (approval no. 337-24) the present study. The present study was in line with the Declaration of Helsinki (1995; as revised in Edinburgh in 2000). Written informed consent was not required as it is a retrospective study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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