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Relationship between HER2 and clinicopathological data in gastric adenocarcinomas

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Ethics Committee Approval
The study was approved by the Inönü University Scientific Research and Publication Ethics Committee (No: 2022/2914, Date: February 8, 2022).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: The impact of human epidermal growth factor receptor 2 (HER2) overexpression on the surveillance of gastric cancer remains uncertain. Typically, HER2 status is assessed in both locally advanced and metastatic diseases, and targeted therapies are applied to cases with HER2-positive status. Our objective was to investigate the correlation between HER2 receptor status, clinicopathological characteristics, and prognosis in gastric cancers across all stages. Based on the results from this investigation, we aim to provide clinicians with insights into the clinicopathological conditions that warrant HER2 investigation.
Methods: In this retrospective study, we conducted a comprehensive analysis of clinicopathological data from a cohort of 169 patients who underwent surgical treatment for gastric cancer between 2014 and 2022. The HER2 status was determined based on results from immunohistochemistry (IHC) and fluorescent in situ hybridization (FISH) techniques applied to gastric cancer pathology samples. Based on the HER2 positivity, the patients were classified into two distinct groups: (1) HER2-positive and (2) HER2-negative. The relationship between the clinicopathological variables, HER2 status, and overall survival (OS) was evaluated using chi-squared and Kaplan–Meier analyses. A statistical significance level of P <0.05 was applied to determine significant associations.
Results: According to the IHC analyses performed in our study population, 33 among 169 patients were HER2-positive (19.53%). Statistically significant factors related to HER2 positivity, such as male gender (P=0.009), pathological stage, N category, lymphovascular invasion status ([LVI] P=0.046), and proximal tumor location (P=0.015) were observed. In addition, OS was 40.49 (6.21) months in HER2-positive gastric cancer patients and 57.43 (3.48) months in HER2-negative gastric cancers (P=0.045).
Conclusion: Irrespective of the pathological stage, gastric cancer exhibited HER2 positivity at a ratio of 5:1. Among the clinicopathological findings, a significant correlation was observed between HER2 expression and gastric cancers characterized by aggressive features. Moreover, HER2 positivity was associated with an unfavorable prognosis in gastric cancer patients.

Keywords: clinicopathological features, gastric cancer, HER2, immunohistochemistry, prognostic factor

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Introduction

Gastric cancer, along with colorectal cancer, is among one of the most prevalent malignancies affecting the gastrointestinal tract. Despite a recent decrease in its incidence and associated mortality rates, GC continues to be associated with a dismal prognosis [1]. The advent of targeted therapies in clinical practice has shed light on their potential efficacy in the treatment of gastric cancers. Notably, anti-human epidermal growth factor receptor 2 (HER2) therapies, which are widely employed in breast cancer treatment, have emerged as a crucial component of targeted therapy options [2].

HER2, also known as ErbB2, belongs to the family of epidermal growth factor receptors (EGFR) located on *chromosome 17 (17q21)* [3]. HER2 mediates signal transduction that is involved with regulation of cell proliferation, differentiation, adhesion, and migration via tyrosine kinase autophosphorylation, a process that leads to the activation of downstream pathways [4].

HER2 overexpression and amplification have been extensively observed in various cancers, particularly breast cancer [5]. Its presence in gastric cancer was initially identified in 1986 [6]. The incidence of HER2 positivity in gastric cancer ranges from 7% to 34% [7,8]. Immunohistochemistry (IHC) is the primary method for assessing HER2 expression with fluorescence in situ hybridization (FISH) performed for confirmation when necessary. The association between HER2 status and prognosis in gastric cancer remains incompletely elucidated. Nonetheless, multicenter studies have consistently demonstrated that patients with HER2-positive gastric cancer (HPGC) exhibit lower overall survival (OS) rates compared to those with HER2-negative gastric cancer [9]. Furthermore, trastuzumab, one of the therapies used in the targeted approach, has shown efficacy in producing improvements in OS in advanced HER2-positive gastric and esophagogastric junction cancers [10]. In this study, we aimed to investigate HER2 positivity, which has a significant impact on survival and is a treatment target in gastric cancer patients. Also, we aimed to explore the association between HPGC and its clinicopathologic characteristics.

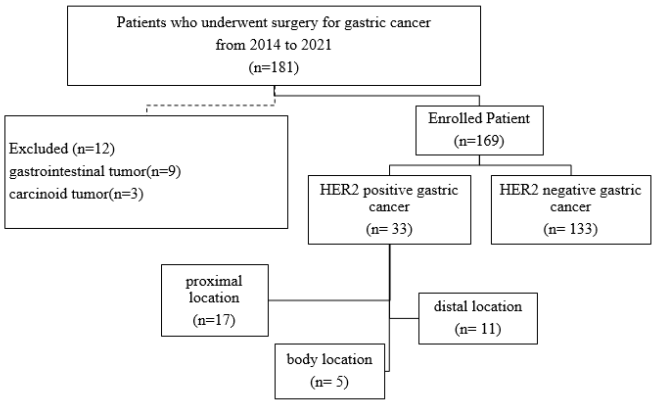
Materials and methods

Patient selection and study design

This study received approval from the Scientific Research and Publication Ethics Committee of İnönü University based on the established ethical guidelines. The approval was granted on February 8, 2022, and the assigned reference number for the study is 2022/2914. We retrospectively reviewed the data from 181 patients with gastric cancer who underwent total, completion total, or proximal gastrectomy between January 2014 and July 2021. Inclusion criteria were patients with histologically proven primary gastric adenocarcinoma regardless of pathological stage. Patients with limited electronic medical records were excluded from the study.

Among these, a total of 12 patients (nine gastrointestinal tumors, three carcinoid tumors) were excluded. Finally, 169 patients were eligible for the analysis (Figure 1).

Figure 1: Flowchart of the patient selection process.



Patient management

Following their surgical procedures, patients received either fluoropyrimidine-based or platinum-based chemotherapy with or without trastuzumab. Regular follow-up visits were conducted at 3, 6, 9, and 12 months after surgery. During these follow-up visits, patients underwent thoracoabdominal computed tomography (CT) scans every six months to screen for any signs of recurrence or metastasis. Additionally, endoscopy examinations were performed annually to monitor patients' conditions.

Another outcome measure in this study was the evaluation of the influence of HER2 status on OS. OS was defined as the period starting from the surgical intervention and ending with death from any cause. To ascertain the survival status of the patients, they were followed until July 2017.

Clinicopathological and survival data were retrieved from hospital medical records.

Evaluation of clinicopathological findings

Categorical and continuous clinicopathological data were collected and analyzed. Data on age (years), sex (male, female), Lauren's classification (intestinal type, diffuse type), tumor histology (differentiated, undifferentiated), T-stage (I–IV), N stage (0–3), pathological stage (1–4), tumor location (proximal, body, distal), lymphovascular invasion status (LVI) (absence, presence), perineural invasion status ([PNI] absence, presence), and HER2 status (positive, negative) were collected for each patient.

The World Health Organization (WHO) classification criteria and the eighth edition of the American Joint Committee on Cancer were used for pathological staging of gastric cancer [11].

Initially, the specimens were tested for HER2 expression based on IHC. IHC 3+ was defined as HER-2 positive. Those with IHC 0/1 were defined as HER-2 negative. Those with IHC 2+ were then evaluated based on FISH, and HER-2 expression was determined.

Statistical analysis

The sample size was determined using power analysis with the G-Power 3.1 software. Based on a power (1-β) of 0.80 and a confidence level of 95%, it was calculated that each group should have a sample size of 32. Therefore, the minimum total sample size for both groups was determined to be 64. Compliance of numerical data with normal distribution was checked using the Kolmogorov–Smirnov test. Continuous numerical variables were analyzed with the Mann–Whitney U test. The median, minimum, and maximum values of these variables were presented. A chi-squared analysis was performed for categorical variables. The

frequency and percentage values of these variables were presented. Univariate logistic regression analysis was performed for each variable by taking the variables with statistically significant p values in similar variables. Survival for HER2 status was calculated using the Kaplan–Meier method and log-rank test. *P*-value <0.05 was considered statistically significant. Analyses were performed using SPSS v23 (SPSS Inc., Chicago, IL, USA).

Results

Patient and sample characteristics

The median patient age was 63 (19–96) years, and the male-to-female ratio was 1.6:1. Thirty-three (19.53%) cases of HER-2 positivity gastric cancer were identified for which 17 (51.5%), 5 (15.2%), and 11 (33.3%) were found in proximal, body, and distal locations, respectively (Table 1, 2).

Based on the univariate analysis, statistically significant factors related to HER2 positive status, such as gender, pathological stage, N category, LVI, and tumor location, were found (Table 2). HER2 predominance in men (78.79%, 26/33) was detected. In addition, HER2 positivity was more commonly detected in proximal tumors (51.52%, 17/33). Most patients 84.02% (n=142) presented with advanced (T2 and above) tumors, and 21.83% (n=31) were HER2 positive. Additionally, among the 27 patients with early-stage GC, 7.41% (n=2) were HER2 positive, but this finding was not statistically significant (*P*=0.664) as shown in Table 2.

The differences between the two groups in terms of age, tumor size, PNI, Lauren's classification, tumor histology, and T category were not statistically significant (Table 2).

Survey analysis results

During follow-up, 59 of 169 (34.9%) patients died. The mean OS in all patients was 54.78 (3.18) months (95% CI: 48.55–61.01). The 3-year and 5-year survival rates were 27.2% and 12.4%, respectively. The mean OS in HER2-positive gastric cancer patients was 40.49 (6.21) months (95% CI: 28.32–52.05). However, the mean OS for HER2-negative gastric cancers was 57.43 (3.48) months (95% CI: 50.61–64.25). When survival rates were compared among groups, it could be observed that OS was better in HER2-negative gastric cancers (log-rank *P*=0.045, Hazard ratio [HR]=1.808 [1.004–3.255]) as shown in Table 3 and Figure 2.

Table 1: Patients demographics and tumor characteristics

Characteristics	Value n=169 n(%)
Gender	
Male	105(62.13)
Female	64(37.87)
Age(year)	
Median (range)	63(19–96)
Mean (SD)	62 (13)
Tumor Location	
Proximal	59(34.92)
Body	26(15.38)
Distal	84(49.70)
Histology	
Differentiated	104(61.54)
Undifferentiated	65(38.46)
Lymphovascular invasion	
Presence	135(79.88)
Absence	34(20.12)
Perineural Invasion	
Presence	108(63.9)
Absence	61(32.1)
T category	
1a	10(5.92)
1b	17(10.06)
2	9(5.32)
3	67(39.65)
4a	63(37.27)
4b	3(1.78)
N category	
0	41(24.26)
1	24(14.2)
2	27(15.98)
3a	38(22.49)
3b	39(23.07)
Pathological Stage	
1a	18(10.65)
1b	12(7.1)
2a	13(7.69)
2b	30(17.75)
3a	23(13.6)
3b	21(12.43)
3c	47(27.81)
4	5(2.97)
Tumor Size(cm)	
Median (range)	5.5(0.7-20)
Mean (SD)	5.85 (3.62)
Lauren's Classification	
Intestinal type	102(60.4)
Diffuse type	67(39.6)
HER2	
Positive	33(19.53)
Negative	136(80.47)

SD: standard deviation

Table 3: Surveillance analysis results in gastric cancers

	Mean (SD) OS (month)	HR	95%CI	*P*-value
HER2 Status		1.808	1.004-3.255	0.045
HER2-negative GC	57.43 (3.48)			
HER2-positive GC	40.49 (6.21)			
Total	54.78 (3.18)			

OS: Overall Survival, SD: standard deviation, HR: Hazard Ratio, CI: Confidence Interval, HER2: human epidermal growth factor receptor 2, GC: Gastric Cancer. *P*-value <0.05 was considered statistically significant.

Figure 2: Effect of human epidermal growth factor receptor 2 (HER2) on overall survival in gastric cancer.

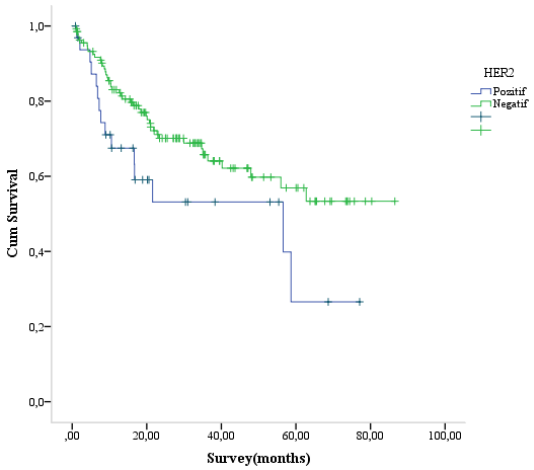


Table 2: Univariate analysis of risk factors for human epidermal growth factor receptor 2 (HER-2) positivity

	Characteristics	All patients n=169 n(%)	HER2-positive n=33 n(%)	OR	95% CI	*P*-value
Gender	Female	64(37.87)	7(21.21)	Reference		
	Male	105(62.13)	26(78.79)	2.486	1.088-6.601	0.009
Age(year)	<60	72(42.60)	12(36.36)	Reference		
	≥60	97(57.40)	21(63.64)	1.382	0.630-3.032	0.420
Tumor Location	Distal	84(49.70)	11(33.33)	Reference		
	Body	26(15.38)	5(15.15)	1.870	0.607-5.758	0.275
	Proximal	59(34.92)	17(51.52)	2.859	1.222-6.692	0.015
Histology	Differentiated	104(61.54)	7(78.79)	Reference		
	Undifferentiated	65(38.46)	26(21.21)	1.961	0.792–4.855	0.145
Lymphovascular Invasion	No Invasion	34(20.12)	7(21.21)	Reference		
	Invasion	135(79.88)	26(78.79)	4.769	1.082–21.031	0.046
Perineural Invasion	Invasion	108(63.9)	10(30.30)	Reference		
	No Invasion	61(32.1)	23(69.70)	1.380	0.608–3.132	0.441
T category	1a	10(5.92)	0(0)	Reference		
	1b	17(10.06)	2(6.06)	3.750	0.224–62.764	0.358
	2	9(5.32)	3(9.09)	1.000	0.063–15.988	1.000
	3	67(39.65)	15(45.45)	1.733	0.147–20.456	0.662
	4a	63(37.27)	12(36.36)	2.125	0.178–25.412	0.552
	4b	3(1.78)	1(3.03)	2.000	0.168–24.382	0.571
N category	0	41(24.26)	6(18.18)	Reference		
	1	24(14.2)	4(12.12)	3.646	1.238–10.735	0.019
	2	27(15.98)	2(6.06)	3.125	0.893–10.934	0.075
	3a	38(22.49)	6(18.18)	7.812	1.612–37.859	0.011
	3b	39(23.07)	15(45.45)	3.333	1.127–9.861	0.03
Pathological Stage	1a	18(10.65)	1(3.03)	Reference		
	1b	12(7.1)	4(12.12)	68.000	3.460–1336.268	0.005
	2a	13(7.69)	1(3.03)	8.000	0.658–97.311	0.103
	2b	30(17.75)	4(12.12)	48.000	2.404–958.237	0.011
	3a	23(13.6)	6(18.18)	26.000	2.287–295.637	0.009
	3b	21(12.43)	3(9.09)	11.333	1.048–122.549	0.046
	3c	47(27.81)	10(30.30)	24.000	1.952–295.061	0.013
	4	5(2.97)	4(12.12)	14.800	1.484–147.611	0.022
Tumor Size(cm)	≤5	87(51.48)	15(45.45)	Reference		
	>5	82(48.52)	18(54.55)	1.457	0.668–3.179	0.344
Lauren's Classification	Intestinal type	102(60.4)	20(60.60)	Reference		
	Diffuse type	67(39.6)	13(39.40)	0.987	0.453–2.149	0.974
Early Stage	Yes	27(15.98)	2(6.06)	Reference		
	No	142(84.02)	31(93.94)	1.261	0.443–3.589	0.664

OR: Odds Ratio, CI: Confidence Interval. *P*-value <0.05 was considered statistically significant.

Discussion

In many recent studies, several different factors have been revealed to be relevant to the relationship between HPGC and clinicopathological parameters (tumor location, LVI, hepatic metastasis, Lauren's Classification, age, gender, higher lymph node stage, and advanced staging) [9,12,13]. Although conditions such as hepatic metastasis and advanced stage can be explained by HER2 overexpression and amplification, intestinal histological type, low grade, and predominant localization of the cancer to the proximal stomach cannot be explained.

In this study consisting of a total of 169 gastric cancer patients, we identified several clinicopathological factors that were associated with HPGC based on the analysis: (1) male gender, (2) proximal tumor location, (3) higher lymph node stage, and (4) advanced staging. In addition to HER2 positive status is a poor factor for predicting survival in gastric cancer.

A meta-analysis demonstrated a significant association between HER-2 overexpression and overall survival in patients [14]. However, a study by Grabsch et al. [15] reported no relationship between HER-2 expression and prognosis. The role of HER2 expression as a prognostic factor has been confirmed in advanced gastric cancer, but it does not appear to affect disease-free survival and OS in early-stage gastric cancers [16]. Another study found no association between HER-2 status, clinical-pathological characteristics, and OS in early-stage gastric cancer [17]. In our study, we did not observe a correlation between HER2 and early-stage gastric cancers. However, regardless of the pathological stage, HPGC patients exhibited poorer survival. In conclusion, the impact of HER2 on overall survival remains controversial.

The Lauren classification categorizes gastric cancer into intestinal, diffuse, and mixed subtypes, and this classification has been recognized as an important prognostic factor in previous studies [18]. Specifically, patients with the intestinal subtype were found to have a higher likelihood of HPGC.

Several studies have reported a predominance of the intestinal subtype among HER2-positive patients [19,20]. However, in our study, we did not observe a significant relationship between HPGC and the intestinal subtype.

In a study conducted in South Korea, the rate of HER2 was 7.3%. As in our study, male gender, proximal tumor location, higher lymph node stage, and advanced pathological stages were found to be correlated with HPGC in the South Korean study [21]; however, no correlation was found between older age and the intestinal subtype in our study. In addition, the HPGC in our study was found to be 19.53%.

In addition to being a poor prognostic factor in many malignancies, LVI is also associated with metastatic disease, recurrence, and poor prognosis in gastric cancers [22]. Laboissiere et al. [23] found that LVI correlated with HER2 overexpression in their gastric cancer study. In our study, it was shown that LVI and HER2 were correlated.

Limitations

The primary limitation of our study is the lack of consensus regarding the determination of HER2 receptor status. As a result, HER2 positivity rates vary significantly across the existing literature. Another limitation is the retrospective nature of our study, which inherently carries potential biases and limitations. However, to overcome these limitations, it is crucial

to establish a pathology-related consensus regarding HER2 determination and gather data from well-designed randomized prospective studies for further validation and confirmation.

Conclusion

Similar to results from other studies in the literature, our study revealed an HER2 incidence rate of 19.53% in gastric cancers. Furthermore, HER2 positivity was found to be associated with unfavorable prognostic indicators, including high lymph node ratios, advanced stage, and LVI. Additionally, HER2 positivity was more commonly observed in males and proximal tumors. Surveillance analysis demonstrated that HER2-positive gastric cancer patients had a shorter OS, indicating that HER2 serves as a negative prognostic marker for gastric cancers. Given the availability of targeted therapy, assessing HER2 receptor status is recommended to guide clinicians in line with the identified factors.

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