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Research Article

Comparative Immunohistochemical Expression of HER2/neu in Intestinal-type and Diffuse-type Gastric Adenocarcinoma: A Cross-Sectional Study

Mian Shah Yousaf[1], Fouzia Jehangir[2*], Zamin Hussain[3], Aizza Saeed[4], Syeda Fatima Rizvi[5], Shahzada Khalid Sohail[6]

[1]Assistant Professor, Consultant Gastroenterologist, Department of Gastroenterology, Prime Teaching Hospital/Peshawar Medical College, Peshawar, Pakistan.
[2*]Assistant Professor, Department of Pathology, Ayub Medical College, Abbottabad, Pakistan.
[3]Senior Medical Officer, Health Department, Moulvi Ameer Shah Memorial Hospital, Peshawar, Pakistan.
[4]MBBS, Shifa Medical Centre, Lahore, Pakistan.
[5,6]Assistant Professor, Department of Pathology, College of Medicine, University of Bisha, Bisha, Saudi Arabia.

Corresponding Author: Fouzia Jehangir
Assistant Professor, Department of Pathology, Ayub Medical College, Abbottabad, Pakistan.
Email: drfouziabkhan@gmail.com
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ABSTRACT

Background: Human epidermal growth factor receptor 2 (HER2/neu) is a well-known predictive marker of targeted therapy in gastric adenocarcinoma. Local data on the comparison of HER2 expression in intestinal-type and diffuse-type gastric adenocarcinoma are limited.

Objective: To compare the immunohistochemical expression of HER2/neu in intestinal and diffuse-type gastric adenocarcinoma.

Methods: This was a cross-sectional comparative study carried out at Prime Teaching Hospital, Peshawar, from 1st November 2025 to 30th April 2026. Using non-probability consecutive sampling, 106 gastric adenocarcinoma cases, 53 intestinal-type and 53 diffuse-type, were enrolled, all of which were histopathologically confirmed. The independent samples t-test, Chi-square test, and Fisher's exact test were used to compare clinicopathological characteristics and HER2 expression. Odds ratios (ORs) with 95% confidence intervals (CIs) were derived, and values less than 0.05 were deemed statistically significant.

Results: The mean age of the participants was 58.6 ± 11.4 years, and 64.2% of participants were male. The overall HER2 positivity (IHC 3+) was 13.2%. There was a significant difference in the percentage of HER2 positivity between intestinal-type and diffuse-type gastric ADC (22.6% versus 3.8%, respectively; $p < 0.001$). Patients with intestinal-type tumors had 7.12-fold higher odds of HER2 positivity (OR = 7.12, 95% CI: 1.49–34.01, $p = 0.009$). HER2 positivity was also significantly associated with lymphovascular invasion ($p = 0.043$).

Conclusion: HER2/neu overexpression was significantly associated with intestinal-type gastric adenocarcinoma, supporting routine HER2 testing to identify patients who may benefit from targeted anti-HER2 therapy.

Keywords: Gastric Adenocarcinoma, Her2/Neu, Immunohistochemistry, Intestinal-Type, Diffuse-Type.

INTRODUCTION

Gastric cancer is one of the most pressing health problems globally and the fifth most common malignancy diagnosed in the world, and the fifth leading cause of cancer deaths worldwide.[1] In 2022, the estimated global burden of gastric cancer was 968,000 new cases and 660,000 deaths, representing nearly 4.9% of all new cancer cases and 6.8% of all cancer deaths.[2] Although the incidence of GC is decreasing in certain countries, it remains a significant health burden, especially in East Asia, Eastern Europe, and numerous LMICs.[3] Gastric carcinoma is one of the common gastrointestinal malignancies in Pakistan, and many patients present at a late stage due to delayed diagnosis and the lack of specialized health care services.[4] There is a poor overall prognosis, with in most developing countries five-year survival rates of less than 35% due to late presentation as well as the high aggressiveness of the tumors.[5]

Gastric adenocarcinoma accounts for over 90% of all gastric malignancies and is highly diverse

in its histopathological and molecular characteristics.[6] Gastric adenocarcinoma is classified into two main categories (Lauren classification): intestinal and diffuse.[7] Intestinal type is defined by the presence of cohesive gland-forming malignant cells and is frequently seen in the presence of chronic Helicobacter pylori infection, intestinal metaplasia, and environmental risk factors.[8] Diffuse-type gastric adenocarcinoma is characterized by the presence of poorly cohesive or signet-ring cells invading the gastric wall, making it more common in younger patients, genetically predisposed individuals, and having a more aggressive clinical course.[9] These biological differences are important in determining the behavior of the tumor, its metastatic potential, response to therapy, and patient survival, and therefore molecular markers that distinguish the subtypes are needed.[10]

Human epidermal growth factor receptor 2 (HER2/neu), which is encoded by the ERBB2 proto-oncogene on chromosome 17q12, is a transmembrane receptor tyrosine kinase of the epidermal growth factor receptor family.[11] The amplification or overexpression of HER2 triggers downstream signaling pathways associated with cell proliferation, differentiation, angiogenesis, and apoptosis inhibition, which contributes to tumor progression.[12] Overexpression of the HER2 receptor is established in breast cancer; however, it has also become an important therapeutic and prognostic biomarker in gastric adenocarcinoma.[11] The landmark ToGA trial showed that HER2 testing can now be routinely used as part of the diagnostic evaluation in patients with advanced gastric or GEJ adenocarcinoma, as the inclusion of trastuzumab with standard chemotherapy led to a significant improvement in overall survival.[13] The incidence of HER2/neu overexpression in gastric adenocarcinoma is reported as 7% to 34% in different populations.[14] This variation is attributed to various ethnicities, location of the tumor, histological subtype, scoring criteria, and laboratory methods.[15]

There is limited published data on the evaluation of HER2/neu expression based on Lauren histological subtypes in Pakistan, and existing studies have small sample sizes or are from single centers. Furthermore, a regional difference in tumor biology may affect the expression of HER2, so that the international data alone should not be used to make clinical decisions. Local evidence is especially relevant because gastric cancer is a precision oncology disease where the use of anti-HER2 therapy is a direct consequence of the HER2 status. Immunohistochemical expression of HER2/neu in intestinal- and diffuse-type gastric adenocarcinoma could help stratify patients more effectively, guide the selection of treatment, and help improve clinical outcomes. Thus, the present study was designed to compare the expression of HER2/neu by immunohistochemistry in intestinal-type and diffuse-type gastric adenocarcinoma.

METHODS

This is a cross-sectional comparative study to compare the immunohistochemical expression of HER2/neu in intestinal-type and diffuse-type gastric adenocarcinoma. The study aimed to examine the expression of HER2/neu in gastric adenocarcinoma samples that were histopathologically diagnosed and to compare the expression between the two histological subtypes of gastric adenocarcinoma according to the Lauren classification.

This study was carried out in the Prime Teaching Hospital, Peshawar, Pakistan. The departmental archives were searched for histopathologic records and formalin-fixed paraffin-embedded (FFPE) blocks from gastric adenocarcinoma patients for immunohistochemical analysis. This study was carried out for 6 months from 1st November 2025 till 30th April 2026.

The sample size was calculated using OpenEpi version 3.01 for comparing two independent proportions. The calculation was performed based on data from Tanner et al., who found that in intestinal-type gastric adenocarcinoma, 21.5% of cases had HER2/neu overexpression, while 2% of diffuse-type were positive.[16] The minimum sample size was determined to be 48 patients per group (96 patients total) using a study power of 80%, a 1:1 ratio, and a 95% confidence level. The sample size calculated was 106 patients, which included 53 intestinal-type and 53 diffuse-type gastric adenocarcinoma patients.

Non-probability consecutive sampling technique was used. Patients with histopathologically confirmed intestinal-type and diffuse-type gastric adenocarcinoma and who met the eligibility criteria during the study period were included until the desired number of patients was reached. The study included patients aged 18 years and older with histopathologically confirmed gastric

adenocarcinoma defined by Lauren classification as intestinal-type or diffuse-type (IT or DT).[17] Histologically complete cases with well-preserved blocks of formalin fixed paraffin embedded tissue for immunohistochemical staining were included. Patients who had undergone neoadjuvant chemotherapy, radiotherapy, or targeted therapy before tissue sampling were excluded, as these therapies could alter HER2 expression. Other types of mixed histological subtypes, recurrent gastric carcinoma, metastatic tumors of the stomach, inadequate tissue samples, poorly preserved paraffin blocks, and incomplete clinical and histopathological records were also excluded.

Histopathology reports and medical records were used to obtain demographic and clinicopathological data such as age, sex, tumor location, tumor grade, Lauren histological type, lymphovascular invasion, and pathological stage. Formalin-fixed paraffin-embedded tissue blocks were chosen, and 4-µm sections were cut for immunohistochemistry. The immunohistochemistry of HER2/neu was measured according to standard laboratory procedures using a commercially available monoclonal antibody. Two experienced histopathologists blinded to the histological subtype independently evaluated the membrane staining. HER2 expression was defined by the College of American Pathologists (CAP) and the American Society of Clinical Oncology (ASCO) recommendations for the expression of HER2 in gastric cancer as 0, 1+, 2+ or 3+. Cases with scores of 0 and +1 were regarded as negative, +3 as positive, and 2+ cases were recorded independently or confirmed, when available.[18] Intestinal-type and diffuse-type gastric adenocarcinoma were then compared in terms of their immunohistochemical expression of HER2/neu. All the data collected were entered and analyzed in IBM SPSS Statistics version 26.0. Age was a continuous variable and was presented as mean ± SD only after the normal distribution was determined by the Shapiro–Wilk test. Categorical variables such as sex, Lauren histological type, tumor grade, tumor stage, lymphovascular invasion, and HER2/neu expression were summarized as frequency and percentage. Comparisons of expression of HER2/neu between intestinal-type and diffuse-type gastric adenocarcinoma were made by the Chi-square test and Fisher's exact test. For continuous variables, an independent t-test was applied. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to determine the strength of association. P-values < 0.05 were considered to be statistically significant.

RESULTS

A total of 106 patients with gastric adenocarcinoma diagnosed by histopathology were included, of which 53 (50.0%) were intestinal-type, and 53 (50.0%) were diffuse-type tumors. The average age of participants was 58.6 ± 11.4 years, and most of them were male (64.2%). The most frequent tumour site was antrum/pylorus (53.8%), and moderately and poorly differentiated tumours each accounted for 43.4% of cases. The predominant stage of the disease was III (41.5%), and 46.2% of patients had evidence of lymphovascular invasion. (Table 1)

Table 1. Baseline Demographic and Clinicopathological Characteristics of the Study Participants (n = 106)

Variable	Frequency (%) / Mean ± SD
Age (years)	58.6 ± 11.4
Gender	
Male	68 (64.2)
Female	38 (35.8)
Lauren Histological Type	
Intestinal type	53 (50.0)
Diffuse type	53 (50.0)
Tumor Location	
Cardia	18 (17.0)
Body	31 (29.2)
Antrum/Pylorus	57 (53.8)
Tumor Grade	
Well differentiated	14 (13.2)
Moderately differentiated	46 (43.4)
Poorly differentiated	46 (43.4)
Pathological Stage	

Stage I	11 (10.4)
Stage II	30 (28.3)
Stage III	44 (41.5)
Stage IV	21 (19.8)
Lymphovascular Invasion	
Present	49 (46.2)
Absent	57 (53.8)

Patients with intestinal-type gastric adenocarcinoma were significantly older than patients with diffuse-type tumors (62.1 ± 9.6 vs 55.2 ± 12.1 years, p = 0.002), and more were male (75.5% vs 52.8%, p = 0.015). The diffuse-type group showed significantly more poorly differentiated tumors than the other group (p = 0.019), while no significant difference was detected in the distribution of tumors by location, pathological stage, and lymphovascular invasion levels between the two groups (p > 0.05). (Table 2)

Table 2. Comparison of Demographic and Clinicopathological Characteristics between Intestinal-Type and Diffuse-Type Gastric Adenocarcinoma

Variable	Intestinal (n=53)	Diffuse (n=53)	p-value
Age (years), Mean ± SD	62.1 ± 9.6	55.2 ± 12.1	0.002
Male, n (%)	40 (75.5)	28 (52.8)	0.015
Female, n (%)	13 (24.5)	25 (47.2)	
Cardia, n (%)	12 (22.6)	6 (11.3)	0.241
Body, n (%)	14 (26.4)	17 (32.1)	
Antrum/Pylorus, n (%)	27 (50.9)	30 (56.6)	
Poorly differentiated	17 (32.1)	29 (54.7)	0.019
Lymphovascular invasion present	20 (37.7)	29 (54.7)	0.079
Stage III/IV	29 (54.7)	36 (67.9)	0.163

Immunohistochemical evaluation revealed HER2 score 0 in 50.9%, 1+ in 25.5%, 2+ in 10.4%, and 3+ in 13.2% of cases. The HER2 score 3+ was more common in intestinal-type gastric adenocarcinomas (22.6%) than in diffuse-type (3.8%), while the HER2 score 0 was more common in diffuse-type (67.9%) than in intestinal-type (3.1%) gastric adenocarcinoma. The distribution pattern of the HER2 immunohistochemical scores between the two histological types was markedly different (p < 0.001). (Table 3)

Table 3. Comparison of HER2/Neu Immunohistochemical Expression between Intestinal-Type and Diffuse-Type Gastric Adenocarcinoma

HER2 Score	Intestinal (n=53)	Diffuse (n=53)	Total (n=106)
0	18 (34.0)	36 (67.9)	54 (50.9)
1+	15 (28.3)	12 (22.6)	27 (25.5)
2+	8 (15.1)	3 (5.7)	11 (10.4)
3+	12 (22.6)	2 (3.8)	14 (13.2)
Chi-square = 15.82, p < 0.001			

The positive association between the expression of HER2 and intestinal-type gastric adenocarcinoma was statistically significant (p < 0.001): 22.6% of intestinal-type tumors were HER2-positive, while only 3.8% of diffuse-type tumors were positive. In addition, lymphovascular invasion (p = 0.043) was significantly associated with HER2 positivity, whereas age, sex, tumor grade, and pathological stage (p > 0.05) were not significantly associated with HER2 positivity. (Tables 4 and 5)

Table 4. Comparison of HER2 Positivity between Intestinal-Type and Diffuse-Type Gastric Adenocarcinoma

HER2 Expression	Intestinal (n=53)	Diffuse (n=53)	Total	p-value
Positive (3+)	12 (22.6)	2 (3.8)	14 (13.2)	<0.001
Negative (0/1+)	33 (62.3)	48 (90.6)	81 (76.4)	

Equivocal (2+)	8 (15.1)	3 (5.7)	11 (10.4)	

Table 5. Association of HER2 Positivity with Clinicopathological Characteristics

Variable	HER2 Positive (n=14)	HER2 Negative/Equivocal (n=92)	p-value
Age (years), Mean ± SD	61.8 ± 8.7	58.1 ± 11.7	0.241
Male	11 (78.6)	57 (62.0)	0.226
Intestinal type	12 (85.7)	41 (44.6)	0.003
Poor differentiation	8 (57.1)	38 (41.3)	0.270
Stage III/IV	11 (78.6)	54 (58.7)	0.156
Lymphovascular invasion present	10 (71.4)	39 (42.4)	0.043

Using odds ratio (OR) analysis, the odds of being HER2 positive were 7.12 times greater in patients with intestinal-type gastric adenocarcinoma than in those with diffuse-type (95% CI: 1.49–34.01, p = 0.009). (Table 6)

Table 6. Odds Ratio for HER2 Positivity in Intestinal-Type Compared With Diffuse-Type Gastric Adenocarcinoma

Variable	Odds Ratio (95% CI)	p-value
Intestinal-type vs Diffuse-type	7.12 (1.49–34.01)	0.009

DISCUSSION

There is increasing evidence that HER2/neu overexpression is more common in intestinal-type than in diffuse-type gastric adenocarcinoma, which makes it an important predictive biomarker in targeted therapy. In this study, 13.2% of all cases were HER2-positive (IHC 3+) with significant higher frequency in the intestinal-type (22.6%) than diffuse-type (3.8%) ($p < 0.001$). In addition, the odds of HER2 positivity were 7.12 times greater with intestinal-type as compared to diffuse-type gastric adenocarcinoma. The results here are in agreement with the known molecular distinction between the two Lauren subtypes and highlight the importance of continual testing for HER2 in gastric adenocarcinoma.[19, 20]

The overall prevalence of HER2 positivity in the current study is seen to be similar to the findings of Pandey et al. (2022), who reported that around one-third of gastric adenocarcinomas are HER2 positive and found that the membranous expression of HER2 was significantly higher in the intestinal type than in the diffuse type of Gastric Adenocarcinoma.[21] Likewise, in the comparative study of Xu et al. (2023) comparing HER2 immunohistochemistry and mass spectrometry, the majority of tumors with HER2 amplification were gland-forming, further corroborating the biological link between these two. [22]

The results of our study were also supported by Ranathunga and Bagwan (2024), who assessed 481 gastric and gastroesophageal junction adenocarcinomas and found that 13.3% of the cases were HER2 positive, which is very close to our finding of 13.2%. They also found that the tumors were mostly of the intestinal type, and diffuse-type carcinomas were infrequently positive for HER2, which is in close correlation with our results.[23]

Our findings of significant association between intestinal-type gastric adenocarcinoma and HER2 overexpression are also consistent with the pooled analysis carried out by Cheng et al. (2024), which comprised several international studies. Their meta-analysis has revealed that gastric cancers with HER2 positivity are mainly of intestinal type and are a distinct subgroup with therapeutic implications. They further suggested that HER2 status may have prognostic value in addition to predicting response to anti-HER2 therapy.[24]

The present results are also consistent with the review by Fong and Chau (2022), which reviewed the current evidence that around 20% of gastric cancers are HER2-positive, particularly in intestinal type and gastroesophageal junction cancers. Their review focused on the use of HER2-targeted therapy in advanced gastric adenocarcinoma, as this has become the backbone of personalized therapy and therefore accurate immunohistochemical testing is very important.[19]

Likewise, Radford et al. (2023) summarized the current therapeutic concepts for gastric cancer that is HER2-positive and noted that

trastuzumab-based therapy is appropriate for patients with HER2 overexpression, which is primarily confined to intestinal-type adenocarcinoma. Consistent with the current study, their review confirms that there is clinical significance to the increased HER2 positivity seen in intestinal-type tumors.[25]

These observations have been supported by molecular evidence in recent times. A comprehensive review on HER2-low gastric adenocarcinoma (2025) indicated that the diffuse-type tumor group is largely comprised of HER2-negative tumors, and the intestinal-type tumor group is most commonly associated with the presence of either HER2-high or HER2-low expression. The molecular features are consistent with the significant differences in HER2 expression that we found between the two histological types in our study.[26]

Similarly, Malla et al. (2024) noted that HER2 amplification occurs in a subset of gastric cancers and that there was consistently higher expression in the intestinal-type compared to the diffuse-type. Given their emphasis on the critical importance of accurate HER2 testing to identify patients who may benefit from novel HER2-targeted agents, the clinical relevance of our findings was further emphasized.[27]

The current study is also consistent with the evidence compiled by Xu et al. (2022) in the study of advanced gastric cancer treatment strategies for targeting HER2. They reported that HER2 positivity is generally from 7% to 20%, significantly more common in intestinal-type tumors and determined using standardized IHC and ISH criteria. The overall HER2 positivity rate of 13.2% in our study is within this range reported internationally.[20]

Lastly, the new guidelines from the International recommendations maintain the significance of HER2 testing by histological subtype. According to the 2025 Chinese Guidelines for HER2-targeted therapy in gastric and gastroesophageal junction adenocarcinoma, gastric cancers with HER2-high expression are around 12.8%-23.2% and are mainly of the intestinal type, while diffuse-type have significantly lower HER2 expression. The present findings are very close to these recommendations, which also underscore the need for the regular application of an immunohistochemical evaluation of HER2 in gastric adenocarcinoma to ensure the most appropriate selection of patients for targeted therapy, especially in intestinal-type lesions.[28]

There were some limitations of this study. First, it was performed in a single tertiary care centre among a relatively small number of cases, which may restrict the generalizability of the results to the broader community. Second, HER2 status was only assessed by immunohistochemistry, and confirmatory fluorescence in situ hybridization (FISH) was not done for "equivocal" (2+) cases, which could have led to underestimation or misclassification of HER2 positivity. Third, there was no detailed follow-up information, treatment outcomes, and survival data, so it was not possible to evaluate the prognostic and therapeutic value of HER2 expression. In addition, other molecular markers of gastric adenocarcinoma were not assessed, including PD-L1, microsatellite instability (MSI), and Epstein–Barr virus (EBV).

CONCLUSION

Intestinal-type was significantly more common than diffuse-type gastric adenocarcinoma for the presence of HER2/neu overexpression. There were significantly increased odds of HER2 positivity with intestinal-type tumors, reflecting molecular diversity between the two Lauren histological types. The results provide further evidence for the systematic assessment of HER2 status in gastric adenocarcinoma, especially in the type of intestinal origin, to guide the selection of patients who could benefit from an HER2-directed therapeutic approach. More multicenter studies with molecular confirmation and long-term clinical outcomes are needed to confirm these results and to enhance personalized treatment strategies in gastric cancer.

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