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Estimation of Human Epidermal Growth Factor Receptor 2 (HER2) Expression in Colorectal Adenocarcinoma for HER2 Targeted Therapy

Faryal Javaid,[1] Shifa Basharat,[2] Ayesha Sajjad,[1] Raazia Mehmood,[1] Ayesha Safdar,[1] Maria Tasneem Khattak,[3] Iqbal Muhammad Khan[1]

1. Rehman Medical Institute, Peshawar, KP Pakistan.
2. Rehman Medical College, Peshawar, KP Pakistan.
3. Rehman College of Dentistry/Rehman Medical Institute, Peshawar, KP Pakistan.

ABSTRACT

Background: Colorectal carcinoma (CRC) ranks among the top cancers globally, with high mortality rates despite treatment advancements. Emerging therapeutic targets, including HER2, well-studied in breast and gastric cancers, are less explored in CRC literature.

Objectives: To determine the frequency of HER2 expression in colorectal adenocarcinoma for HER2-targeted therapy and its association with various clinic-pathological variables.

Materials and Methods: This cross-sectional study was conducted at the Department of Histopathology, Rehman Medical Institute (RMI), Peshawar, from November 15, 2022, to April 30, 2023. A total of 110 cases were included through consecutive sampling. The study included patients of both genders and all age groups who had undergone colectomy (right or left hemicolectomy, extended right hemicolectomy, abdominoperineal resection) and were previously diagnosed with CRC based on colonoscopic biopsies. Colonoscopic biopsy specimens and patients who had undergone neoadjuvant therapy were excluded. Immunohistochemistry assay for HER2 was performed, and the results were interpreted.

Results: The mean age (SD) of study sample was 45 (6.12) years. There was a predominance of male patients. Out of the total 110 patients, HER2 expression was positive in 69 (62.73%) and negative in 41 (37.27%) patients. The lesions were predominantly located in the rectum and left colon in 77 (70.00%) of the patients. Histologically, 92 (83.64%) patients had non-mucinous tumor variants. Among the 69 positive cases, 32 (29.09%) were scored as 1+, 24 (21.82%) as 2+, and 13 (11.82%) as 3+. Tumor grade, tumor stage, HER2 expression, and score were statistically significantly associated with IHC staining intensity ($p < 0.001$). Similarly, tumor grade, tumor stage, and HER2 score were statistically significantly associated with positivity status ($p < 0.001$). Furthermore, statistically significant relationship between the degree of differentiation (tumor grade), tumor stage, IHC staining intensity and the score of HER2 overexpression was observed ($p < 0.001$).

Conclusion: In our study, HER2 expression was observed in a significant number of patients. The findings indicate that HER2 expression correlates with specific tumor characteristics suggesting its potential as a biomarker in management for this disease. Further research with larger sample sizes and broader geographical diversity is recommended to better understand HER2's biological role in cancer.

Keywords: Colorectal adenocarcinoma, Gastrointestinal system, HER2, Immunohistochemistry, Targeted therapy.

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INTRODUCTION

Gastrointestinal malignancies, including colorectal cancer, rank among the most prevalent oncological concerns globally with slow increase in its incidence. Colorectal adenocarcinoma (CRC) is the third most common cancer in females and the fourth most frequent cancer in males worldwide.[1] It imposes a significant burden on the healthcare system due to its high mortality and morbidity, despite the significant advancements in treatment modalities over the years.[2]

Each year, the incidence of CRC rises by 2%,[3] and Asian people are more likely to have gastric cancer than any other group. In Pakistan, there has been a low but increasing incidence of CRC at a young age with advanced stages consistently observed in recent years.[4] The incidence of GI cancer in Pakistan is 6.9% in males and 4.9% in females.[5]

Several epithelial malignancies, such as breast, ovarian, lung, prostate, bladder, pancreatic, gastric, esophageal, and colorectal adenocarcinomas, have been documented to overexpress a protein called Human Epidermal Growth Factor Receptor 2 (HER2).[6,7] It is an integral part of the tyrosine kinase genes similar to epidermal growth factor and is responsible for a 185 kD transmembrane protein that lacks a natural ligand. Its activation initiates a signal transduction pathway, including the MAPK and PI3K/AKT pathways, which are essential for cellular proliferation, evasion from apoptosis, survival in ectopic sites, and metastatic spread.[8] Tyrosine kinase family receptors are normally present on healthy cells, but their overexpression can lead to significant oncogenesis and tumor mass formation.[9] According to reports, the frequency of HER2 overexpression in colorectal cancers varies from 0% to 83%.[10] HER2 positivity status in GI cancer also observed to be related with more aggressive disease, a poorer prognosis, and shorter duration of survival. Nonetheless, HER2/neu protein overexpression and

Correspondence: Dr. Maria Tasneem Khattak
Associate Professor,
Rehman Medical Institute/Rehman College of Dentistry,
Peshawar, KP Pakistan.
Email: accesstomaria@yahoo.com

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its relation with clinic-pathological characteristics like Dukes classification and survival is conflicting.[11]

Over the years, numerous novel therapeutic regimens have been tested in pursuit of the most precise and targeted methods for eliminating cancerous cells. Consequently, identifying molecular markers for targeted therapy remains a primary objective in cancer research. Patients with advanced CRC who harbor wild-type Kirsten rat sarcoma virus oncogene homolog (KRAS) mutations have shown benefit from treatment with anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies such as panitumumab and cetuximab.[12,13] However, a notable proportion of cancer patients do not respond well to therapy, and predicting treatment outcomes remains challenging despite significant therapeutic advancements.

Identifying molecular biomarkers that can predict prognosis, treatment response, and potential therapeutic targets for individuals with colorectal cancer is critical. The extracellular domain of the HER2/neu receptor is targeted by the monoclonal antibody trastuzumab, which has been humanized and has demonstrated therapeutic efficacy in patients with HER2/neu-positive breast cancer.[13,14] The Human Genome Organization (HUGO) Nomenclature Committee (HGNC) has designated ERBB2 as the approved symbol, with CD340, HER-2, HER2, and NEU as synonyms.[15]

While several studies have documented the occurrence and clinical implications of HER2/neu status in CRC patients, its precise clinical significance remains unclear. To date, no study has explored the expression of HER2 in CRC in our setting. Numerous ongoing clinical trials are investigating the potential for effective therapeutic targeting. Therefore, this study aimed to assess the expression of HER2 in colorectal adenocarcinoma in our region to explore the possibility of introducing targeted therapies like Herceptin for cases refractory to radiotherapy, ERBB targeted therapy, or metastatic adenocarcinoma of the colon.

MATERIALS AND METHODS

This cross-sectional study was conducted at the Histopathology Department of Rehman Medical Institute over a six-month period from November 15, 2022, to April 30, 2023. Approval for the study was obtained from the institutional ethical review committee under certificate number RMI/RMI-REC/Article approval/84 dated November 10, 2022. Informed consent was obtained from all patients undergoing surgery. The sample size of n=110 was determined using the WHO sample size calculator, based on a population of 152, with a confidence level of 95% and a margin of error of 5%.

The study included patients of both genders and all age groups who had undergone colectomy (including right hemicolectomy, left hemicolectomy, extended right hemicolectomy, and abdominoperineal resection) and were previously diagnosed with colorectal adenocarcinoma based on colonoscopic biopsies. Patients who had undergone colonoscopic biopsy specimens or neoadjuvant therapy (chemotherapy, radiotherapy) were excluded from the study.

Demographic and background characteristics of the patients were recorded, and specimen grossing was conducted following the guidelines of the College of American Pathologists. After grossing, specimens underwent formalin fixation and paraffin embedding, followed by Hematoxylin and Eosin staining according to the protocol. Tumor grades were categorized as "well-differentiated (Grade 1), moderately differentiated (Grade 2), poorly differentiated (Grade 3), and undifferentiated (Grade 4)," based on the 8th edition of the AJCC tumor manual, which includes assessment of gland formation and cytologic atypia of tumor cells.[16-18]

The tested samples underwent preparation for HER2 immunohistochemical staining using the Rabbit Monoclonal Primary antibody EP3 and the labeled streptavidin biotin (LASB) kit for antigen detection. A positive control consisted of a previously diagnosed breast cancer case scored as HER2 3+ on IHC, while a negative control lacked primary antibodies. Each section was reviewed by two expert histopathologists.

Various criteria are currently employed to define HER2-positivity in colorectal cancers. For instance, the HERACLES trial defines positivity as a staining intensity of 3+ in =50% of tumor cells on immunohistochemistry or HER2 gene amplification in =50% of tumor cells initially scored as 2+ by IHC. Other trials, such as My Pathway and DESTINY, align with CAP/ASCP/ASCO HER2 guidelines, which are broader in scope. The My Pathway trial includes cases showing increased HER2 copy numbers or activating mutations confirmed by molecular analysis. Notably, no significant difference was observed between NGE and IHC results.[19,20]

The scoring criteria for HER2 follow those used in the TOGA trial for evaluating HER2 immunohistochemical scores in gastric and gastroesophageal cancers.[21] Scores range from 0 to 3+: Score 0 indicates faint or barely perceptible staining in <10% of tumor cells, while score 1+ denotes faint/barely perceptible membrane staining in >10% of tumor cells, where staining occurs only partially on the membrane. Score 2+ represents weak to moderate staining of the entire membrane in >10% of tumor cells, while score 3+ indicates strong diffuse staining of the entire membrane in >10% of tumor cells. A score of 0 is considered negative, while scores of 1+, 2+, and 3+ are considered positive expressions, with a 2+ score requiring in situ hybridization correlation using FISH analysis.[21]

Data analysis was performed using SPSS version 21. Both qualitative and quantitative data were summarized using descriptive statistics. Means and standard deviations were calculated for numerical variables, while frequencies and percentages were calculated for categorical variables. Comparisons of categorical variables were made using the Chi-square or Fisher's exact test, where applicable. Differences in numerical variables were assessed using the Student's independent t-test or One-way ANOVA, as appropriate. Statistical significance was set at 5% with a 95% confidence level.

RESULTS

A total of 110 patients with colorectal adenocarcinoma were included in the study. The patients' ages ranged from 32 to 62.50 years, with a mean age of 45.00 ± 6.03 years. Of all the patients in the study, 60 (54.55%) were males while 50 (45.45%) were females. The lesions were present in the right colon in 33 (30.00%) patients, and in the rectum and left colon in 77 (70.00%) patients. Histologically, 18 (16.36%) tumors were mucinous, and 92 (83.64%) were non-mucinous variants.

Of the 110 cases, 34 cases (30.91%) were well-differentiated (grade I) tumors, 49 cases (44.55%) were moderately differentiated (grade II) tumors, and 27 cases (24.55%) were poorly differentiated (grade III) tumors as illustrated in figure 01. Lymph node involvement was positive in 64 (58.18%) patients and negative in 46 (41.82%) patients. Based on the stage of tumors, stage I & II tumors were observed in 39 (35.45%) patients, stage II & III tumors in 25 (22.73%) patients, while the majority were in stage III & IV, with 46 (41.82%) patients.

Amongst the 110 patients, HER2 expression was observed in 69 (62.73%), while 41 (37.27%) patients were negative for HER2 expression as depicted in figure 02. Of the total 69 positive cases, 32 (29.09%) were scored as 1+, 24 (21.82%) cases were scored as 2+, and 13 (11.82%) were scored as 3+.

Immunohistochemistry (IHC) staining, which corresponds to different levels of staining intensity and completeness, suggests that in 41 (37.30%) cases, less than 10% of the tumor cells exhibit very weak staining, which is barely noticeable. In 30 (27.30%) samples, more than 10% of the tumor cells showed faint, barely noticeable membrane staining, indicating low expression of the target protein in a significant portion of the tumor cells. The details are given in Table 01.

Comparison of IHC staining intensity and completeness with various background characteristics is given in Table 01. Tumor grade, tumor stage, and HER2 expression and score were statistically significantly associated with IHC staining intensity and completeness ($p < 0.001$).

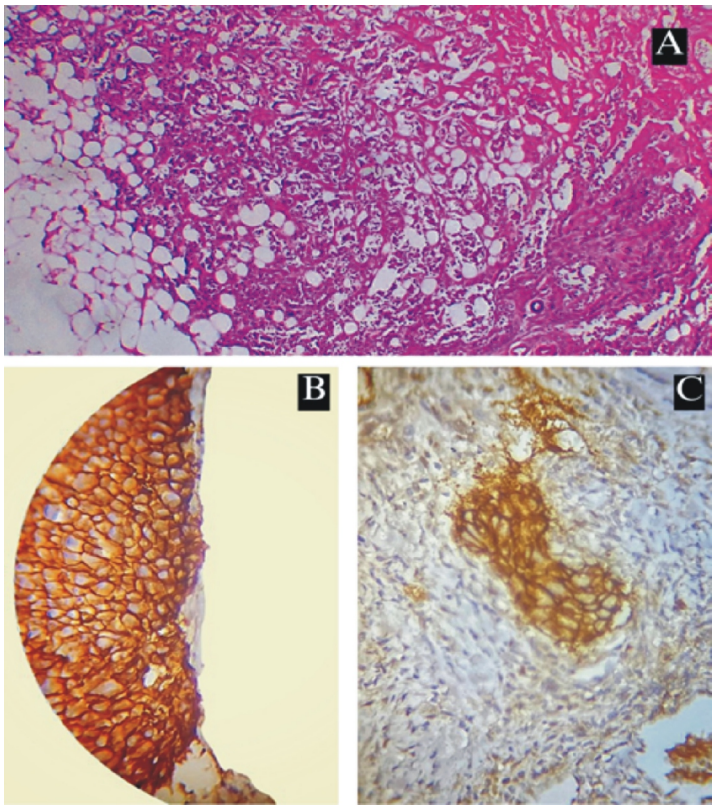


Figure 01. Positive HER2 staining; [A] HnE stain of a poorly differentiated non mucinous colorectal carcinoma 10X; [B, C]: Strong diffuse membranous HER2 IHC staining in >10% tumor cells, 40X

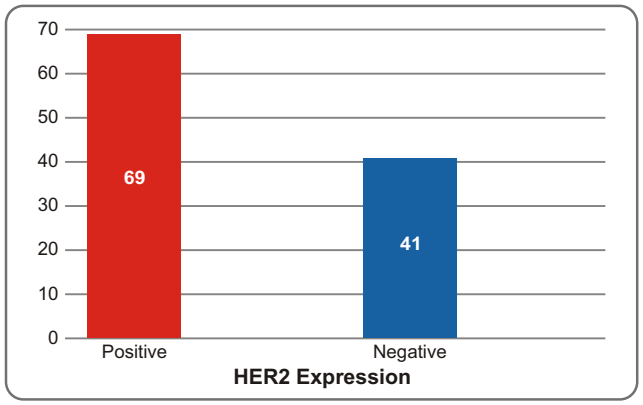


Figure 02. Frequency of HER 2 expression in colorectal adenocarcinoma

HER2 protein overexpression was found in 69 (62.73%) patients overall. The mean age was statistically significantly higher in positive cases compared to negative ones (45.70±6.40 vs. 43.13±5.04, p=0.030). Among these 69 HER2-positive patients, 54 (78.24%) lesions were present in the rectum and left colon (p=0.018). There is no significant association between tumor type, lymph node involvement, and HER2 overexpression (p > 0.05). On the other hand, tumor grade, tumor stage, and HER2 score were statistically significantly associated with overexpression (positivity) status (p < 0.001) as shown in table 02.

The intensity and completeness of membranous staining were graded from 0 to 3. Briefly, a score of 0 indicates no staining observed in tumor cells. Of the total 69 positive cases, 32 (29.09%) were scored as 1+, 24 (21.82%) were scored as 2+, and 13 (11.82%) were scored as 3+. Analysis of the data showed significant statistical relationship between the degree of differentiation (tumor grade) and the frequency/score of over expression of HER2. Similarly, a statistically significant association was observed between tumor stage, IHC staining intensity, and completeness with over expression score of HER2 in the study sample (p < 0.001) as shown in table 03.

Table 01. Comparison of background characteristics across IHC staining

Characteristics		Immunohistochemistry (IHC) Staining				Total	P-Value
		Incomplete Faint, n=24	Strong Diffuse, n=15	Faint <10%, n=41	Faint >10%, n=30		
Age (years), Mean±SD		45.90±7.09	44.94±5.86	43.13±5.04	45.93±6.25	45.0±6.03	0.173
Gender, n (%)	Male	17(70.83)	7(46.67)	18(43.90)	18(60.00)	60(54.55)	0.159
	Female	7(29.17)	8(53.33)	23(56.10)	12(40.00)	50(45.45)	
Tumor site, n (%)	Right colon	4(16.67)	4(26.67)	18(43.90)	7(23.33)	33(30.00)	0.089
	Rectum and left colon	20(83.33)	11(73.33)	23(56.10)	23(76.67)	77(70.00)	
Type of tumor, n (%)	Non-mucinous tumor	19(79.17)	11(73.33)	35(85.37)	27(90.00)	92(83.64)	0.477
	Mucinous cancer	5(20.83)	4(26.67)	6(14.63)	3(10.00)	18(16.36)	
Tumor grade, n (%)	Moderately differentiated	12(50.00)	6(40.00)	23(56.10)	8(26.67)	49(44.55)	0.000
	Poorly differentiated	9(37.50)	8(53.33)	1(2.44)	9(30.00)	27(24.55)	
	Well-differentiated	3(12.50)	1(6.67)	17(41.46)	13(43.33)	34(90.31)	
Nodal status, n (%)	Positive	13(54.17)	11(73.33)	22(53.66)	18(60.00)	64(58.18)	0.581
	Negative	11(45.83)	4(26.67)	19(46.34)	12(40.00)	46(41.82)	
Stage of tumor, n (%)	I and II stage	1(4.17)	1(6.67)	31(75.61)	6(20.00)	39(35.45)	0.000
	II and III stage	6(25.00)	1(6.67)	8(19.51)	10(33.33)	25(22.73)	
	III and IV stage	17(70.83)	13(86.67)	2(4.88)	14(46.67)	46(41.82)	
HER2 expression, n (%)	Positive	24(100.00	15(100.00)	0	30(100.00)	69(62.73)	0.000
	Negative	0	0	41(100.00)	0	41(37.27)	
HER2 score, n (%)	0	0	0	41(100.00)	0	41(37.27)	0.000
	1+	0	2(13.33)	0	30(100.00)	32(29.09)	
	2+	24(100.00)	0	0	0	24(21.82)	
	3+	0	13(86.67)	0	0	13(11.82)	

Incomplete faint membrane staining in > 10% of tumor cells; Strong diffuse complete staining in > 10% of tumor cells; Faint, barely perceptible staining in < 10% of tumor cells; Faint, barely perceptible membrane staining in > 10% of tumor cells; standard deviation (SD)

Table 02. Comparison of background characteristics between HER2 expressions

Characteristics		HER2 Expression		P-Value
		Positive	Negative	
Age (years), Mean±SD		45.70±6.40	43.13±5.04	0.030
Gender, n (%)	Male	42(60.87)	18(43.9)	0.113
	Female	27(39.13)	23(56.1)	
Tumor site, n (%)	Right colon	15(21.74)	18(43.9)	0.018
	Rectum and left colon	54(78.26)	23(56.1)	
Type of tumor, n (%)	Non-mucinous tumor	57(82.61)	35(85.37)	0.794
	Mucinous cancer	12(17.39)	6(14.63)	
Tumor grade, n (%)	Moderately differentiated	26(37.68)	23(56.1)	0.000
	Poorly differentiated	26(37.68)	1(2.44)	
	Well-differentiated	17(24.64)	17(41.46)	
Nodal status, n (%)	Positive	42(60.87)	22(53.66)	0.550
	Negative	27(39.13)	19(46.34)	
Stage of tumor, n (%)	I and II stage	8(11.59)	31(75.61)	0.000
	II and III stage	17(24.64)	8(19.51)	
	III and IV stage	44(63.77)	2(4.88)	
HER2 score, n (%)	0	0	41(100)	0.000
	1+	32(46.38)	0	
	2+	24(34.78)	0	
	3+	13(18.84)	0	
Staining, n (%)	Incomplete faint	24(34.78)	0	0.000
	Strong diffuse	15(21.74)	0	
	Faint <10%	0	41(100)	
	Faint >10%	30(43.48)	0	

DISCUSION

HER2 evaluation is an emerging prognostic factor for GI cancer. Its expression can be assessed reliably and cost-effectively using IHC, compared to other techniques like in situ hybridization and polymerase chain reaction. Positive HER2 status may warrant targeted therapy against the HER2 receptor.

Previous studies reported HER2 overexpression in CRC patients ranging from 0% to 83%,[10] but recent studies suggest prevalence closer to 10%. Thus, the potential of HER2 as a therapeutic target and prognostic marker in CRC patients remains uncertain.

In this study, 54.55% of the cases had CRC were males, and 45.45% were females. These results align with some studies but differ from the findings with other,[22,23] who reported a higher incidence among females in their study. Similarly, age consistency was noted in a study conducted in Iraq, whereas higher ages were observed in the literature.[22,23] The most common sites of tumor involvement in the present study were the rectum and left colon. Some researchers have reported that the left colon is the most common region for the occurrence of CRC. This is not in agreement with previous published study from Iran.[23] Regarding the type of tumor, the non-mucinous variant was predominant. In terms of tumor grade, well to moderately differentiate tumors were observed in 49 (44.55%) patients. Elwy et al.'s study indicated that moderately differentiated carcinoma was the most prevalent type,[24] while other study reported well differentiated carcinoma[23] suggested that discrepancies among studies could be attributed to random selection methods and small sample sizes. Nodal involvement was positive in 64(58.18%) patients. Based on stage of tumors, stage I and II tumor was observed in 39 (35.45%) patients while stage III and IV tumor was observed in 46(41.82%) patients. Literature reported inconsistent results regarding tumor characteristics.[4,23,24]

Table 03. Comparison of background characteristics with overexpression of HER2

Characteristics		HER2 Overexpression				P-Value
		0	1+	2+	3+	
Age (years), Mean±SD		43.13±5.04	45.69±6.17	45.90±7.09	45.38±6.07	0.192
Gender, n (%)	Male	18(43.9)	18(56.25)	17(70.83)	7(53.85)	0.214
	Female	23(56.1)	14(43.75)	7(29.17)	6(46.15)	
Tumor site, n (%)	Right colon	18(43.9)	7(21.88)	4(16.67)	4(30.77)	0.078
	Rectum and left colon	23(56.1)	25(78.13)	20(83.33)	9(69.23)	
Type of tumor, n (%)	Non-mucinous tumor	35(85.37)	29(90.63)	19(79.17)	9(69.23)	0.314
	Mucinous cancer	6(14.63)	3(9.38)	5(20.83)	4(30.77)	
Tumor grade, n (%)	Moderately differentiated	23(56.1)	9(28.13)	12(50)	5(38.46)	0.000
	Poorly differentiated	1(2.44)	9(28.13)	9(37.5)	8(61.54)	
	Well-differentiated	17(41.46)	14(43.75)	3(12.5)	0(0)	
Nodal status, n (%)	Positive	22(53.66)	18(56.25)	13(54.17)	11(84.62)	0.232
	Negative	19(46.34)	14(43.75)	11(45.83)	2(15.38)	
Stage of tumor, n (%)	I and II stage	31(75.61)	6(18.75)	1(4.17)	1(7.69)	0.000
	II and III stage	8(19.51)	11(34.38)	6(25)	0(0)	
	III and IV stage	2(4.88)	15(46.88)	17(70.83)	12(92.31)	
HER2 expression, n (%)	Positive	0	32(100)	24(100)	13(100)	0.000
	Negative	41(100)	0	0	0	
Staining, n (%)	Incomplete faint	0	0	24(100)	0	0.000
	Strong diffuse	0	2(6.25)	0	13(100)	
	Faint <10	41(100)	0	0	0	
	Faint >10	0	30(93.75)	0	0	

The primary focus of our study was to establish the clear positivity status of HER2 overexpression by IHC. In our study, HER2 expression was positive in 69 patients (62.73%) and negative in 41 patients (37.27%). A study from Iran and Iraq estimated the HER2 positivity rate at 24% and 53.4% respectively.[22,23] Conversely, a large cohort study on CRC reported HER2 expression in 81.8% of patients.[25] A study from Karachi showed a HER2 positivity rate of 78.9 %.[4] These variations can be attributed to multiple factors, such as technical variability in IHC performance (differences in tissue fixation, processing, epitope retrieval, primary antibody, interpretation and reporting by pathologists, and the lack of a unified and widely accepted scoring system for evaluating HER2 expression), sample size, heterogeneity of study populations, racial differences, and varied experimental designs.

The mean age was significantly higher in HER2-positive cases compared to negative ones. Nearly 80% had lesions in the rectum and left colon. No significant association was found between tumor type, lymph node involvement, and HER2 overexpression ($p > 0.05$). However, tumor grade, tumor stage, and HER2 score were significantly associated with HER2 overexpression. Membranous staining intensity was graded from 0 to 3, with 32 (29.09%) cases scored as 1+, 24 (21.82%) as 2+, and 13 (11.82%) as 3+. Significant relationships were observed between tumor grade, tumor stage, IHC staining intensity, and HER2 overexpression scores. In the present study, no significant correlation was found between the sex of the patients and HER2 expression. These findings align with some published studies but contradict others.[23, 24] For instance, Kamal et al. reported a significant association between HER2 expression and tumor grade.[22] Similarly, Farzand et al. observed a highly significant association between tumor grades and HER2 status.[11] However, some studies found no significant correlation between HER2 expression and tumor grade.[23,24] McKay et al did not find any correlation between HER2 protein overexpression and lymph node metastasis.[25] This inconsistency is partly due to the different scoring systems and antibodies used in these studies, which vary from the currently recommended standards and contribute to the variability in findings. A recent meta-analysis revealed no correlation between HER2 expression and clinic-pathological features, including tumor location, grade

of differentiation, TNM stages, and lymph node metastasis.[26] However, in our study, a significant association was found between HER2 overexpression and clinico-pathological parameters such as age, gender, tumor grade, and stage.

Although a significant association was observed between the percentage of cells stained with HER2 and tumor stage, the statistical power of this finding might be low. Our study was limited by its short duration, which prevented us from obtaining a larger sample size and including other subtypes of colorectal adenocarcinoma. Additionally, we could not include cases presented as metastatic colorectal tumors due to the unavailability of proper clinical information, lack of radiological correlation, insufficient communication with primary physicians, and limited funding.

CONCLUSION

In our study, HER2 overamplification was observed in a significant number of patients with CRC. Our findings indicate that HER2 expression correlates with specific tumor characteristics, suggesting its potential as a biomarker in disease management. To understand the precise biological function of HER2 overamplification, its role in tumor dissemination and its potential as a prognostic and predictive biomarker, as well as a therapeutic target for CRC and metastatic CRC, more extensive research is needed. This research should involve larger sample sizes, diverse geographical representation, and standardized testing techniques.

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Ethical Consideration

This study was approved by the ethical board of Rehman Medical Institute, Peshawar, Pakistan.

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Conflict of Interest

Authors declared no conflict of interest.

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AUTHORS' CONTRIBUTION

The following authors fullfill authorship criteria as per ICMJE guidelines;

Javaid F, Basharat S:	Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Sajjad A, Mehmood R:	Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Safdar A, Khattak MT:	Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Khan IM:	Analysis and interpretation of data, critical revision,final approval, agreed to be accountable for all the work.

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