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Research Article

HER2-Neu Expression In Colorectal Carcinoma: A Retrospective Study

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ABSTRACT

Colorectal carcinoma (CRC) remains one of the most prevalent malignancies worldwide and represents a significant cause of cancer-related morbidity and mortality. Understanding the prevalence and impact of HER2 neu expression and amplification in colorectal carcinoma is crucial for identifying subsets of patients who may benefit from HER2-targeted therapies, thus personalizing treatment approaches.

AIM AND OBJECTIVES: This study aims to assess the significance of HER2-neu expression in colorectal carcinoma. The objectives are to evaluate HER2-neu expression in colorectal carcinoma, analyze its association with patients' gender and age, and correlate HER2-neu expression with the histological grade and subtype of colorectal tumor.

MATERIAL AND METHODS: This retrospective cross-sectional study was conducted on 29 cases of colorectal carcinoma. Patients undergoing surgery for colorectal tumor were selected over 12 months at MGMIHS, Kamothe, Navi Mumbai. Clinical and demographic parameters were collected from the patients. Tumor specimens were subjected to HER2-neu immunohistochemical (IHC) staining.

RESULT: On HER2-neu IHC examination on 29 cases, 11 (38%) cases showed 3+ score, 4 cases (14%) showed 2+ score, 5 cases (17%) showed 1+ score, and remaining 9 cases (31%) showed a score of 0. A male predominance was observed in CRCs, with 21 cases occurring in men and 8 in women. Majority of cases were observed in 41-60 age group.

CONCLUSION: The study is expected to demonstrate a significant correlation between histopathological features and immunohistochemical expression of HER2-neu in colorectal carcinomas. Overexpression of HER2-neu is anticipated to reflect underlying gene amplification, supporting its role as a reliable biomarker. The findings will emphasise the importance of combining histopathology and immunohistochemistry for accurate evaluation of HER2 status in colorectal cancer.

Keywords: *Her 2-neu, colorectal carcinoma, adenocarcinomas.*

INTRODUCTION

Colorectal carcinoma is the third most prevalent cancer in both men and women and is the second leading cause of cancer-related deaths. It is commonly diagnosed in individuals during their sixth to seventh decades of life.[1] According to the World Health Organization (WHO), colorectal cancer is the most common type of gastrointestinal cancer and is a significant contributor to cancer mortality, with an estimated 1,849,518 new cases recorded worldwide in 2018.[2,4] The most important prognostic factor for colorectal cancer is the TNM stage, determined by tumor invasion depth, lymph node involvement, and distant metastasis. However, prognosis can vary even among patients within the same stage, highlighting the need for additional prognostic and predictive factors beyond the TNM classification. The HER-2 neu gene, located on chromosome 17q21, encodes a 185-kDa transmembrane protein with tyrosine kinase activity, closely related to the epidermal growth factor receptor (EGFR). It plays a role in normal cell proliferation and tissue growth. Overexpression of HER-2 neu in nonneoplastic breast cells leads to increased protein production and malignant transformation. [6,10] HER-

2 neu has been a focus in breast cancer treatment, with trastuzumab improving survival in patients, resulting in FDA approval for HER2-positive metastatic gastric cancers. In colorectal cancer, HER2 overexpression rates vary from 0% to 84%. [3] This study aims to assess the significance of HER2-neu expression in colorectal carcinoma by evaluating its prevalence and correlating it with patients age, gender, histological grade, and tumor subtype.

MATERIAL AND METHODS

This retrospective cross-sectional study was conducted on 29 cases of colorectal carcinoma. Patients undergoing surgery for colorectal tumors were selected over 12 months at MGMIHS, Navi Mumbai. Clinical and demographic parameters were collected from the patients. Tumor specimens were subjected to HER2-neu immunohistochemical (IHC) staining.

Inclusion criteria: The study included all cell blocks and case summaries of diagnosed colorectal carcinoma in patients aged 19 years and above, involving both male and female patients.

Exclusion criteria: The study excluded non-colorectal carcinoma cases and patients aged 18 years or younger.

Procedure

Cell blocks from these cases were retrieved from the histopathology section, and 4-5 micron-thick sections were prepared and mounted on Poly-L-lysine-coated slides. These sections were subjected to immunostaining for HER2/neu. Positive and negative controls were run simultaneously with all tissue sections.

Interpretation of HER2-neu immunostaining: Positive/ Negative

- Tissue sections were deparaffinized, rehydrated, and treated with peroxidase quencher.
- Incubated with the primary antibody (as per datasheet).
- Treated sequentially with PolyExcel Target Binder, PolyExcel PolyHRP, and StunnDAB working solution.
- Counterstained with hematoxylin, dehydrated, and mounted.
- Positive control: known HER2/neu-positive breast carcinoma.
- Negative control: omission of the primary antibody.

IHC interpretation

HER2/neu immunostaining was interpreted based on established guidelines. (TABLE 1).
Intensity and percentage of staining were scored from 0 to 3+.

Scores of 0 or 1+ were considered negative, while a score of 2+ was deemed equivocal and required confirmation via Fluorescence In Situ Hybridization (FISH) or other in situ hybridization methods. And score of 3+ is considered positive.

ETHICAL CLEARANCE

The study protocol was approved by the Institutional Ethics Committee (IEC), MGM Medical College, Navi Mumbai (Approval No: DHR-EC/2025/07/68). Patient confidentiality was maintained throughout the study.

RESULTS

Out of a total of 29 colorectal carcinoma cases, 11 cases (38.0%) showed strong HER2/neu overexpression (3+), 4 cases (13.8%) had moderate expression (2+), 5 cases (17.2%) showed weak expression (1+), and 9 cases (31.0%) were negative (0). Thus, nearly two-fifths of cases demonstrated high-level HER2-neu positivity. (Table 2)

The most commonly affected age group was 41-60 years followed by age group of 61-80 years. (Figure 1 & Table 3)
Out of 21 male patients, HER2/neu overexpression (3+) was observed in 9 cases (42.9%), moderate expression (2+) in 3 cases (14.3%), weak expression (1+) in 4 cases (19.0%), and no expression (0) in 5 cases (23.8%). Among 8 female patients, 3+ positivity was observed in 2 cases (25.0%), 2+ in 1 case (12.5%), 1+ in 1 case (12.5%), and negativity in 4 cases (50.0%). Overall, HER2/neu 3+ expression was more frequent in males compared to females, while negative expression was more common among females. (Table 4, Figure 2, Figure 5)

Among well-differentiated adenocarcinomas (n=4), no cases showed 3+ expression, 1 case (25.0%) demonstrated 2+ expression, 3 cases (75.0%) showed 1+ expression, and none were negative. In moderately differentiated adenocarcinomas (n=14), strong overexpression (3+) was observed in 11 cases (78.6%), moderate expression (2+) in 3 cases (21.4%), while none showed 1+ or negative expression. Among poorly differentiated and mucinous adenocarcinomas (n=11), no cases showed 3+ or 2+ expression, 2 cases (18.2%) demonstrated 1+ expression, and 9 cases (81.8%) were negative. (Table 5, Figure 3, Figure 4)

Overall, HER2-neu 3+ positivity was confined to the moderately differentiated group, whereas poorly differentiated and mucinous tumors were predominantly negative.

Table 1: HER2/neu immunostaining interpretation

HER2neu score	HER2 pattern of staining in surgical specimen	Assessment of HER2/neu expression
0	No reactivity or membranous reactivity in <10% of cancer cells	NEGATIVE BY IHC
1+	Faint or barely perceptible membranous reactivity in ≥10% of cancer cells; cells are focally membrane positive/reactive	NEGATIVE BY IHC
2+	Weak to moderate and complete, basolateral, or lateral membranous reactivity in ≥10% of tumour cells	EQUIVOCAL BY IHC
3+	Strong and complete, basolateral, or lateral membranous reactivity in ≥10% of cancer cells	POSITIVE BY IHC

Table 2: Her-2 neu scoring

SCORE	CASES	PERCENTAGE
3+	11	38%
2+	4	14%
1+	5	17%
0	9	31%

Figure 1: Her2-neu expression in different age groups

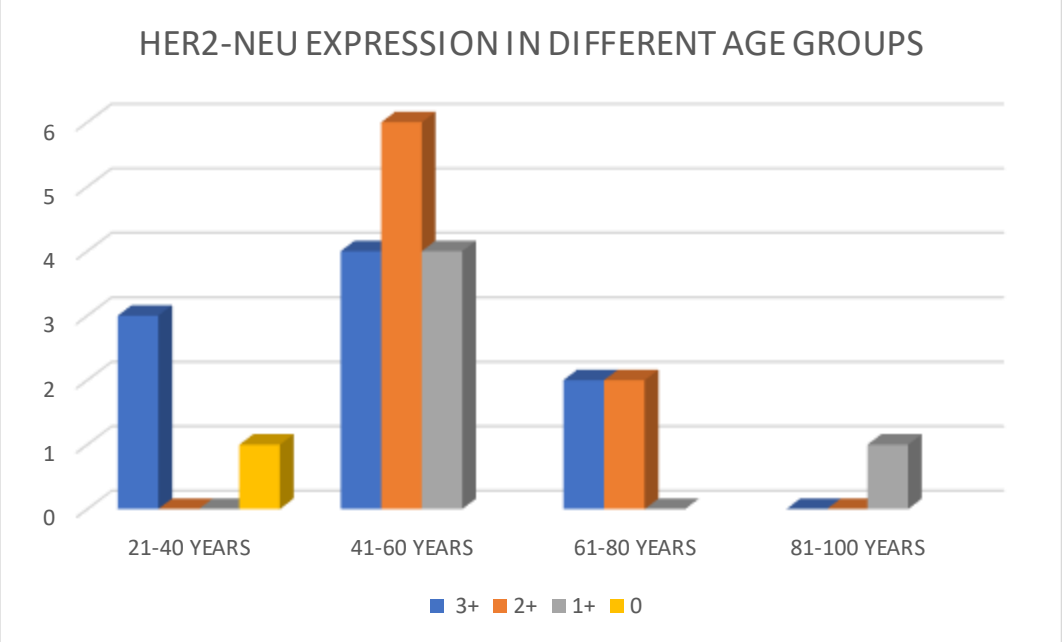

Table 3: Her2-neu expression in different age groups

AGE GROUP/ HER2NEU	3+	2+	1+	0
21-40 YEARS	1	0	0	3
41-60 YEARS	2	6	4	4
61-80 YEARS	3	2	0	2
81-100 YEARS	1	0	1	0

Figure 2: Her2-neu expression according to gender

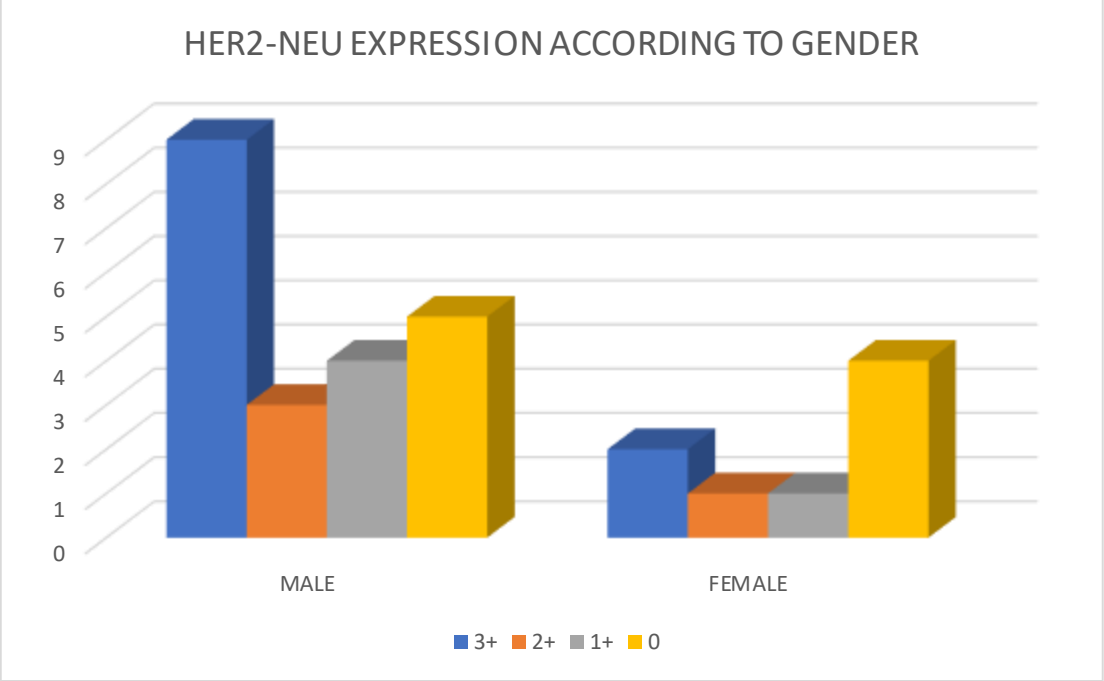

Table 4: Her2-neu expression according to gender

GENDER	3+	2+	1+	0
MALE	9	3	4	5
FEMALE	2	1	1	4

Figure 3: Her2-neu expression according to their histological grading

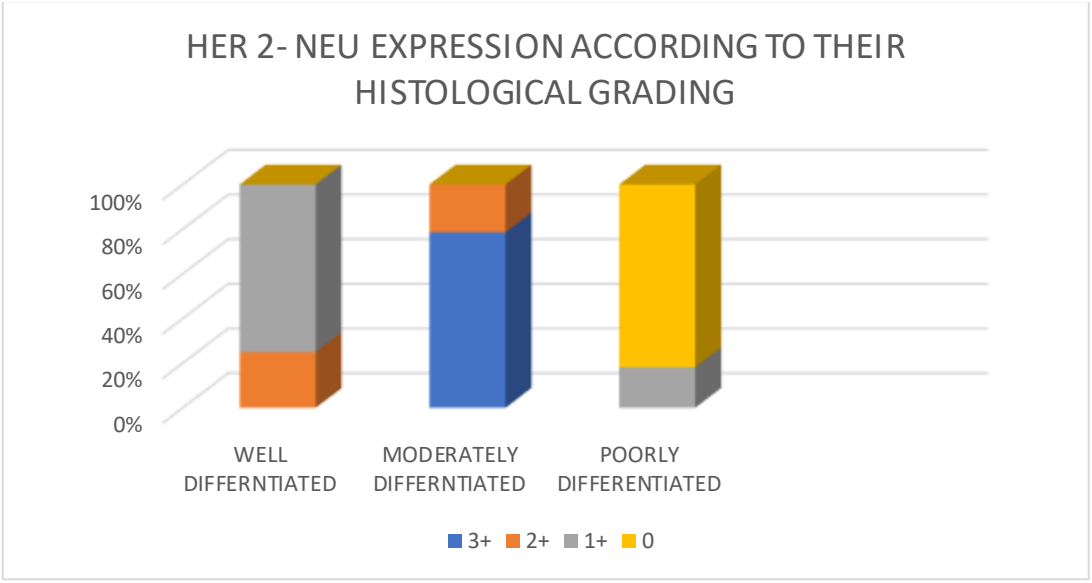

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Table 5: Her2-neu expression according to their histological grading

HISTOLOGIC GRADE	3+	2+	1+	0
WELL DIFFERENTIATED	0	1	3	0
MODERATELY DIFFERNTIATED	11	3	0	0
POORLY DIFFERENTIATED and MUCINOUS ADENOCARCINOMA	0	0	2	9

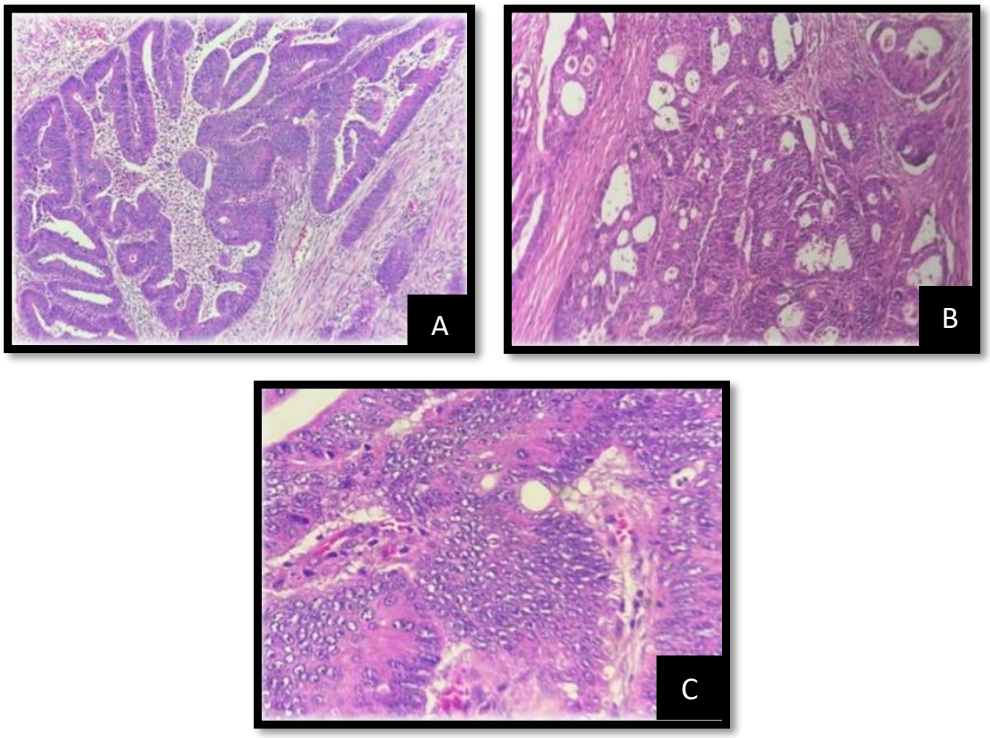

Figure 4: Representative photomicrographs of colorectal carcinoma (H&E stain).

A. Well-differentiated adenocarcinoma showing glandular architecture with preserved polarity (H&E, 10×).

B. Moderately differentiated adenocarcinoma with irregular glands, desmoplastic stroma, and loss of polarity (H&E, 10×).

C. Poorly differentiated adenocarcinoma showing solid sheets of pleomorphic tumor cells with high nuclear atypia (H&E, 40×).

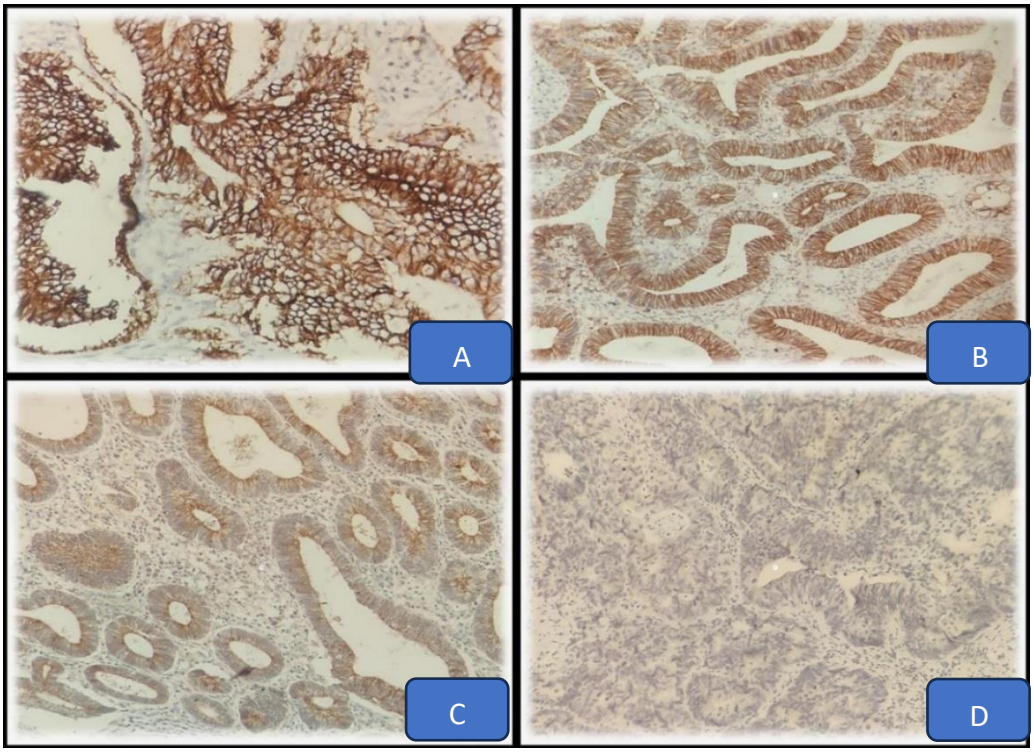

Figure 5: HER2/neu immunohistochemistry in colorectal carcinoma.

A. Strong membranous (3+) HER2/neu positivity with intense complete membranous staining in >10% of tumor cells (IHC, 40×).

B. Moderate membranous (2+) HER2/neu staining, incomplete to weakly complete membranous positivity (IHC, 40×).

C. Weak membranous (1+) HER2/neu staining with faint, incomplete membranous reactivity (IHC, 40×).

D. Negative (0) HER2/neu expression with absence of membranous staining (IHC, 40×).

DISCUSSION

The present study evaluated HER2-neu expression in 29 cases of colorectal carcinoma (CRC), including both resected specimens and biopsies. Membranous–cytoplasmic staining was the predominant pattern, followed by membranous alone and cytoplasmic alone. This variability in staining highlights the ongoing challenge of interpreting HER2 status in CRC and emphasizes the need for standardized reporting, as also suggested by Ingold Heppner et al. (9)

HER2-neu is a well-established oncogenic driver in breast and gastric cancers, and growing evidence supports its role in CRC biology. In our study, expression was most frequent in moderately differentiated adenocarcinomas, with limited positivity in poorly differentiated tumors. Similar findings were reported by Shabbir et al. (5) and Nandi et al. (1), indicating that HER2 expression is not restricted to high-grade cancers but may instead correlate with intermediate tumor differentiation.

Overexpression of HER2 has been associated with adverse prognosis and aggressive tumor behavior (Park et al. (6); Blok et al., (7)). Importantly, HER2-targeted therapies such as Trastuzumab (Herceptin) have shown clinical benefit in HER2-positive breast and gastric cancers, and exploratory trials in CRC have yielded encouraging outcomes (Achalla et al., (8)). This underlines the potential therapeutic relevance of HER2 testing in colorectal tumors, especially in advanced or refractory cases where standard chemotherapy offers limited survival.

Interestingly, cytoplasmic HER2 expression was observed in a subset of cases in our series. Although its biological significance remains debated, Blok et al. (7) demonstrated that cytoplasmic HER2 overexpression may carry prognostic implications, suggesting that non-membranous staining patterns should not be dismissed outright. This reinforces the complexity of HER2 biology in CRC and underscores the need for further investigation using harmonized scoring systems.

Taken together, our findings align with international data showing that HER2-neu positivity occurs in a meaningful subset of CRC patients. Incorporating HER2- neu testing into the diagnostic workup may refine prognostic stratification and expand therapeutic options. Future prospective, multicenter studies with larger cohorts are essential to establish HER2 neu as a routine biomarker and to clarify which patients derive the most benefit from HER2-directed therapy.

CONCLUSION

HER2-neu expression was identified in a significant subset of colorectal carcinoma cases, with membranous–cytoplasmic staining being the predominant pattern. Its association with tumor differentiation and the emerging role of HER2-directed therapy underscore its potential as both a prognostic and therapeutic biomarker. Incorporating HER2 testing into routine diagnostic protocols may help identify patients eligible for targeted therapy, thereby personalizing treatment strategies. Larger, multicenter studies are needed to validate these findings and to establish standardized HER2 scoring criteria in colorectal cancer.

LIMITATIONS

This study has certain limitations. Firstly, it was conducted in a single institution with a relatively small sample size (29 cases), which may limit the generalizability of the findings to the wider population. Secondly, the retrospective design restricted the ability to obtain detailed follow-up data and survival analysis, which would have helped in evaluating the true prognostic significance of HER2-neu expression. Thirdly, advanced molecular techniques such as fluorescence in situ hybridization (FISH) or polymerase chain reaction (PCR) for confirming HER2 amplification could not be performed due to financial constraints. Lastly, the inability to correlate HER2 status with therapeutic response represents another limitation, emphasizing the need for larger, multicentric prospective studies incorporating both molecular and clinical outcome data.

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