Section: Pathology

Original Research Article

CLINICOPATHOLOGICAL STUDY OF HER2/NEU EXPRESSION IN PROXIMAL AND DISTAL COLORECTAL CARCINOMA AND ITS PROGNOSTIC CORRELATION WITH CLINICOPATHOLOGICAL PARAMETERS

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Received *: 07/01/2026*
Received in revised form *: 04/02/2026*
Accepted *: 22/02/2026*

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DOI: 10.70034/ijmedph.2026.1.355

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (1); 2041-2046

ABSTRACT

Background: Colorectal carcinoma (CRC) is one of the most common malignancies worldwide and remains a major cause of cancer-related morbidity and mortality. Identification of reliable prognostic biomarkers is essential for improved risk stratification and therapeutic decision-making. HER2/neu overexpression has been studied extensively in various malignancies; however, its role in colorectal carcinoma remains under evaluation. The aim is to study the clinicopathological features of proximal and distal colorectal carcinoma and to assess the expression of HER2/neu and its prognostic utility in relation to established clinicopathological parameters.

Materials and Methods: This prospective study included 55 cases of colorectal carcinoma diagnosed on resected colectomy and biopsy specimens in the Department of Pathology, S.V.S. Medical College. Detailed clinical and colonoscopic findings were recorded. Histopathological examination was performed to determine tumor type, grade, and invasion. TNM staging was applied for pathological staging. HER2/neu expression was evaluated using immunohistochemistry and scored as 0, 1+, 2+, and 3+ based on membranous staining intensity. Statistical analysis was performed to determine the association between HER2/neu expression and clinicopathological variables.

Results: The age of patients ranged from 35 to 75 years (mean 55.8 years), with female predominance. The most common presenting complaint was altered bowel habits (70%). Ulceroproliferative growth was the predominant gross pattern (74%). Conventional adenocarcinoma constituted 92.7% of cases. Most tumors were Grade I and II (45.5% each), and 76.4% presented at Stage I. HER2/neu overexpression was observed in 58.2% of cases, including 45.5% with moderate (2+) and 12.7% with strong (3+) membranous staining. A statistically significant association was found between HER2/neu expression and tumor site and configuration.

Conclusion: HER2/neu overexpression was observed in a substantial proportion of colorectal carcinomas and showed significant correlation with certain clinicopathological parameters. HER2/neu may serve as a potential prognostic biomarker and could help identify patients who may benefit from targeted therapy.

Keywords: Colorectal Neoplasms, Adenocarcinoma, Receptor, ErbB-2 (HER2/neu), Immunohistochemistry, Tumor Staging, Prognosis.

INTRODUCTION

Colorectal carcinoma (CRC) is one of the most common malignancies worldwide. It is the third most common cancer in women and the fourth most common in men, accounting for approximately 9.4% of all cancer cases according to the 2008 global cancer report[1]. Colorectal cancer is also the

second most common cause of cancer-related mortality, with nearly one million new cases diagnosed annually.[1,2]

The highest annual incidence rates are reported in Australia, New Zealand, North America, and Japan,[2] whereas developing countries including those in Africa, India, and several parts of Southeast Asia show relatively lower incidence rates.[1] In India, the reported incidence is approximately 7 per 100,000 population.[3,4]

The risk of colorectal carcinoma is influenced by both endogenous (constitutional) and exogenous (environmental) factors. It predominantly affects elderly and late middle-aged individuals. Common presenting symptoms include hematochezia, abdominal pain, and alterations in bowel habits[2].[1,2]

Surgical resection remains the primary modality of treatment for colorectal carcinoma. The need for adjuvant therapy is determined by pathological staging of the resected specimen.[1] Tumor staging and grading remain essential determinants of prognosis and therapeutic decision-making.

The proto-oncogene HER2/neu (ERBB2) is located on chromosome 17q. It encodes a transmembrane tyrosine kinase receptor that plays a crucial role in regulating normal cell growth, differentiation, and motility. Dysregulation of HER2/neu signaling pathways in malignant cells results in overexpression of the receptor, leading to increased cellular proliferation, survival, and tumor progression.[5] HER2/neu overexpression has been extensively studied in breast and gastric carcinomas; however, its significance in colorectal carcinoma remains under investigation.

Patients with colorectal carcinoma demonstrating HER2/neu overexpression may potentially benefit from monoclonal antibody therapy such as trastuzumab[5]. However, the relatively low prevalence of HER2/neu amplification in CRC has led to inconsistent findings regarding its prognostic significance. Some studies suggest that HER2/neu may have a comparatively modest prognostic impact when compared with other molecular alterations such as BRAF mutations.[6]

The pathogenesis of colorectal carcinoma is a multistep process driven by cumulative genetic and epigenetic alterations. These changes lead to activation of oncogenes and inactivation of tumor suppressor genes, resulting in malignant transformation. Three major molecular pathways have been implicated in colorectal carcinogenesis: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP). Chromosomal instability is typically initiated by mutations in the APC tumor suppressor gene, followed by mutations in KRAS, BRAF, SMAD4, and TP53. The MSI pathway and CIMP pathway are also important contributors to colorectal tumorigenesis.[7]

Notably, right-sided (proximal) and left-sided (distal) colorectal carcinomas differ in their epidemiology, molecular profile, pathophysiology, and morphology. These differences are partly attributed to their distinct embryological origins. Proximal tumors are more frequently associated with microsatellite instability and DNA hypermethylation compared to distal tumors[8].

In view of these molecular and clinicopathological variations, the present study was undertaken to evaluate HER2/neu expression in proximal and distal colorectal carcinoma and to assess its prognostic utility in relation to established clinicopathological parameters.

AIM

To study the clinicopathological profile of HER2/neu expression in proximal and distal colorectal carcinoma and to assess its prognostic utility with respect to established clinicopathological criteria.

MATERIALS AND METHODS

Study Design & Setting: This is a prospective and observational study conducted in the Department of Pathology, S.V.S. Medical College and Hospital, Yenugonda, Mahabubnagar, Telangana over a period of two years.

Study duration: January 2023 to December 2024.

Colonic and rectal biopsies as well as colectomy specimens received from the Department of Surgery were included in the study.

Study Population: A total of 55 colorectal specimens were analyzed during the study period, comprising:

- 30 colonic specimens
- 25 rectal specimens

These included both biopsy and colectomy specimens.

Inclusion Criteria

- All colorectal specimens histologically diagnosed as premalignant or malignant lesions
- Cases irrespective of age, sex, tumor grade, and stage

Exclusion Criteria

- Non-neoplastic lesions
- Inadequate or autolyzed tissue samples

Method of Data Collection: Detailed clinical data were obtained for all cases during the study period, including:

- Age
- Sex
- Personal history
- Presenting symptoms
- Tumor site
- Type of surgical procedure performed

All colorectal specimens were processed according to standard histopathological protocols. Representative sections were taken, processed, and examined microscopically.

The following clinicopathological parameters were evaluated:

- Age
- Tumor grade

- Tumor stage
- Depth of invasion / invasiveness

Histopathological Evaluation

Colorectal carcinoma was graded as:

- Low grade
- High grade

Grading was based on:

- Architectural distortion
- Cytological atypia
- Nuclear atypia

Based on invasion status, tumors were categorized as:

- Invasive
- Non-invasive

Equal proportions of high-grade and low-grade colorectal carcinoma cases were selected randomly for immunohistochemical analysis of HER2/neu expression.

Tissue Processing for Immunohistochemistry: All biopsy specimens were fixed in 10% neutral buffered formalin and embedded in paraffin.

Formalin-fixed paraffin-embedded (FFPE) tissue blocks were sectioned at 4-micron thickness and mounted on positively charged slides.

Heat-induced antigen retrieval was performed prior to immunostaining.

Immunohistochemical Evaluation of HER2/neu: Immunohistochemical staining for HER2/neu was performed using a super-sensitive polymer HRP detection system based on non-biotin polymeric technology.

Antibody Details:

Antigen	Vendor	Species	Dilution	Positive Control
HER2/neu	PATHINSITU	Rabbit monoclonal	Ready-to-use	Known colorectal carcinoma

After incubation with primary rabbit monoclonal antibodies against HER2/neu:

- Secondary antibodies conjugated with horseradish peroxidase (HRP) polymer were applied
- Diaminobenzidine (DAB) was used as chromogen
- Slides were counterstained and mounted

Interpretation and Scoring System

Slides were evaluated for:

- Presence or absence of staining
- Localization of staining pattern
- Percentage of tumor cells stained
- Intensity of staining

Evaluation Criteria: HER2/neu expression was assessed using the ASCO scoring system.

Only membranous staining was considered positive. Cytoplasmic staining was considered nonspecific.

Scoring was done semi-quantitatively as follows:

- 0 – No staining
- 1+ – Faint/incomplete membranous staining
- 2+ – Weak to moderate complete membranous staining (equivocal)
- 3+ – Strong complete membranous staining (positive)

For analysis:

- Score 0 and 1+ were considered negative
- Score 2+ was considered equivocal
- Score 3+ was considered strong positive

Data analysis: All data were entered into Microsoft Excel and analyzed using Statistical Package for Social Sciences (SPSS) software, version 26.0 (IBM Corp., Armonk, NY, USA).

Descriptive statistics were used to summarize the data:

- Continuous variables (e.g., age) were expressed as mean ± standard deviation (SD).
- Categorical variables (e.g., HER2/neu expression, tumor grade, stage, site, invasiveness) were expressed as frequencies and percentages.

Inferential Statistics

- The Chi-square test was used to assess the association between HER2/neu expression and categorical clinicopathological variables such as tumor grade, tumor stage, tumor site (proximal vs distal), and invasiveness.
- When the expected cell frequency was less than 5, Fisher's exact test was applied.
- For comparison of continuous variables between two groups (e.g., age between HER2-positive and HER2-negative cases), the Independent sample t-test was used.
- A p-value of < 0.05 was considered statistically significant.

RESULTS

Table 1: Demographic and Gross Characteristics of Colorectal Carcinoma Cases (n = 55)

Parameter	Category	Frequency (n)	Percentage (%)
Age Group (Years)	30–50	22	40.0
	51–70	26	47.3
	71–90	7	12.7
Gender	Female	29	52.7
	Male	26	47.3
Tumor Size	Up to 5 cm	44	80.0
	6–10 cm	11	20.0
Tumor Configuration	Ulceroproliferative	44	80.0
	Polypoidal	7	12.7

	Narrowing of lumen	4	7.3
	Total Cases	55	100.0

Table 2: Combined Pathological Characteristics of Colorectal Carcinoma (n = 55)

Parameter	Category	Frequency (n)	Percentage (%)
Histological Type	Adenocarcinoma	51	92.7
	Mucinous adenocarcinoma	4	7.3
Differentiation	Well differentiated	21	38.2
	Moderately differentiated	24	43.6
	Poorly differentiated	6	10.9
	Mucinous adenocarcinoma	4	7.3
Tumor Grade	Grade 1 (G1)	25	45.5
	Grade 2 (G2)	25	45.5
	Grade 3 (G3)	5	9.1
	Total	55	100.0

Table 3: Staging and Site Distribution of Colorectal Carcinoma Cases (n = 55)

Parameter	Category	Frequency (n)	Percentage (%)
Stage	Stage I	42	76.4
	Stage II	13	23.6
	Stage III	0	0.0
	Stage IV	0	0.0
Tumor Site	Colon (Ascending)	21	38.2
	Descending colon	1	1.8
	Rectum	31	56.4
	Sigmoid colon	2	3.6
	Total Cases	55	100.0

Among 55cases, ascending colon lesions were 21 (38.2%), descending colon lesions were 1 (1.8%), rectum lesions were 31 (56.4%), & sigmoid colon lesions were 2 (3.6%).

Immunohistochemical expression of Her2/neu: The immunohistochemical expression of Her2/neu was evaluated by ASCO scoring and it was scaled from 0 to 3+ score. For assessment of Her2/neu, score 0 and score 1+ are taken as negative, score 2+ taken as equivocal, score 3+ is taken as strong positive.

Table 4: Distribution of HER2/neu Immunohistochemical Expression According to Clinicopathological Parameters (n = 55)

Parameter	Category	1+ n (%)	2+ n (%)	3+ n (%)	Total
Age (years)	30–50	10 (45.5)	5 (22.7)	7 (31.8)	22
	51–70	13 (50.0)	13 (50.0)	0 (0.0)	26
	71–90	0 (0.0)	7 (100.0)	0 (0.0)	7
Gender	Female	13 (44.8)	11 (37.9)	5 (17.2)	29
	Male	10 (38.5)	14 (53.8)	2 (7.7)	26
Tumor Site	Colon	7 (33.3)	13 (61.9)	1 (4.8)	21
	Descending colon	0 (0.0)	0 (0.0)	1 (100.0)	1
	Rectum	14 (45.2)	12 (38.7)	5 (16.1)	31
	Sigmoid colon	2 (100.0)	0 (0.0)	0 (0.0)	2
Stage	Stage I	17 (40.5)	22 (52.4)	3 (7.1)	42
	Stage II	6 (46.2)	3 (23.1)	4 (30.8)	13
Grade	Grade 1	9 (36.0)	13 (52.0)	3 (12.0)	25
	Grade 2	12 (48.0)	11 (44.0)	2 (8.0)	25
	Grade 3	2 (40.0)	1 (20.0)	2 (40.0)	5
Tumor Size	Up to 5 cm	17 (38.6)	24 (54.5)	3 (6.8)	44
	6–10 cm	6 (54.5)	1 (9.1)	4 (36.4)	11
Overall	—	23 (41.8)	25 (45.5)	7 (12.7)	55

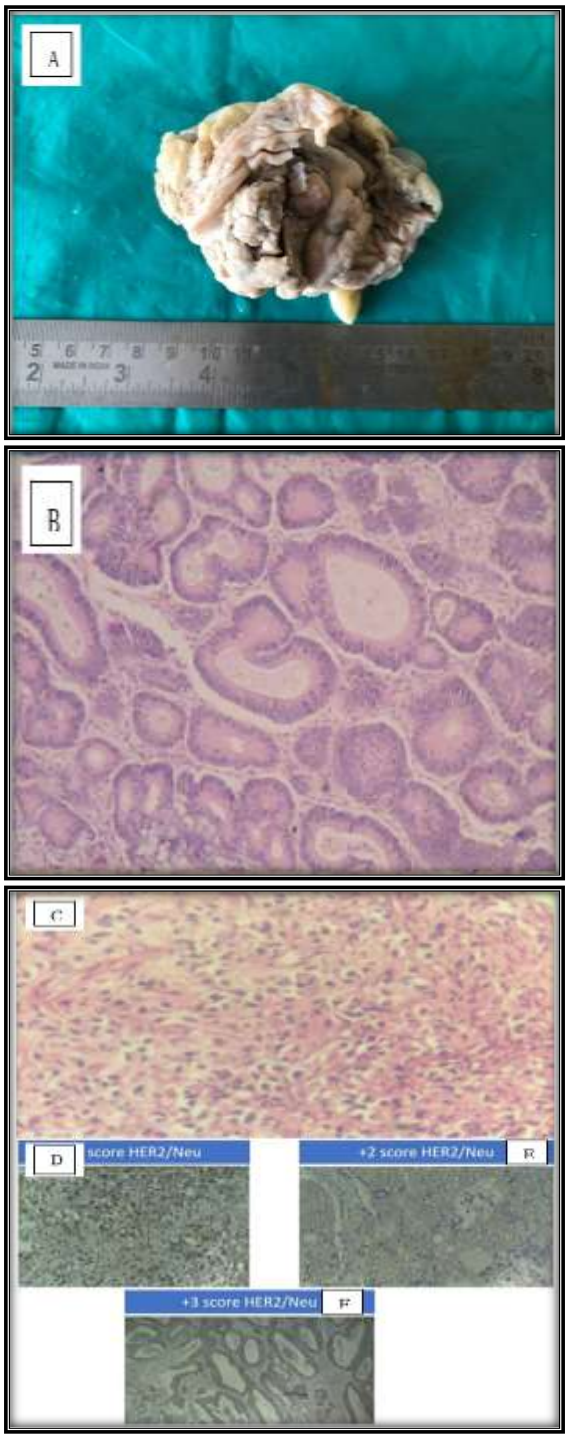

Figure 1: (A) Gross specimen showing ulceroproliferative growth pattern in descending colon with irregular mucosal surface and luminal narrowing.(B) Well differentiated adenocarcinoma (Grade 1) showing well-formed glandular structures (Hematoxylin & Eosin stain, 40X).(C) Moderately differentiated adenocarcinoma (Grade 2) demonstrating irregular gland formation with nuclear atypia (H&E, 40X).(D) Poorly differentiated adenocarcinoma (Grade 3) exhibiting marked pleomorphism and minimal gland formation (H&E, 40X).(E) HER2/neu immunohistochemistry score 1+ showing faint/incomplete membranous staining in tumor cells.(F) HER2/neu immunohistochemistry score 2+ showing moderate complete membranous staining.(G) HER2/neu immunohistochemistry score 3+ showing strong, circumferential membranous staining in tumor cells.

DISCUSSION

Colorectal carcinoma (CRC) is one of the most common malignancies worldwide and remains a leading cause of cancer-related mortality despite advances in diagnostic and therapeutic modalities. The development of CRC involves complex interactions between genetic susceptibility and environmental factors[1]. Identification of reliable prognostic biomarkers is essential for improving risk stratification and therapeutic targeting.

The present study evaluated the immunohistochemical expression of HER2/neu in colorectal carcinoma and correlated it with various clinicopathological parameters including age, gender, tumor size, site, grade, and stage.

Clinicopathological Profile

In the present study of 55 cases, the majority of patients belonged to the 51–70 years age group (47.3%), followed by 30–50 years (40%) and 71–90 years (12.7%). These findings are consistent with Kumar et al.[2], who reported that the incidence of colorectal carcinoma increases after 50 years of age, with peak incidence between 60–70 years.

Gender distribution showed a slight female predominance (52.7%) compared to males (47.3%). However, previous studies have reported variable gender distribution. Won Suk Lee et al observed male predominance, whereas Pappas et al reported a relatively balanced distribution.[3,4]

Regarding tumor location, rectal tumors were most common (56.4%), followed by colon (38.2%), sigmoid colon (3.6%), and descending colon (1.8%). Most tumors were moderately differentiated adenocarcinomas (43.6%), followed by well-differentiated (38.2%) and poorly differentiated carcinomas (10.9%). Mucinous adenocarcinoma accounted for 7.3% of cases.

Stage distribution showed predominance of Stage I tumors (76.4%) compared to Stage II (23.6%). Histological grading revealed equal distribution of Grade 1 and Grade 2 tumors (45.5% each), with Grade 3 comprising 9.1%.

Tumor size analysis demonstrated that 80% of tumors measured ≤5 cm, while 20% measured 6–10 cm. Ulceroproliferative configuration was the most common gross pattern (80%).

HER2/neu Immunohistochemical Expression

HER2/neu expression was evaluated using ASCO scoring criteria.[5] Scores 0 and 1+ were considered negative, 2+ equivocal, and 3+ strong positive.

Age and HER2 Expression

A statistically significant association was observed between age and HER2/neu expression ($p < 0.001$). In the 30–50 year group, 31.8% showed strong positivity (3+), whereas no 3+ expression was observed in patients above 50 years. The 71–90 year group demonstrated exclusively 2+ expression. This suggests a possible age-related variation in HER2 expression.

Gender and HER2 Expression

HER2 expression did not show a strong gender-based predilection. Females showed 17.2% strong positivity compared to 7.7% in males. These findings are comparable to Pappas et al,[6] who found no significant association between HER2 expression and gender.

Site and HER2 Expression

Rectal tumors demonstrated relatively higher 3+ expression (16.1%) compared to colon tumors (4.8%). Descending colon showed 100% 3+ expression, although this was based on a single case. Previous studies, including Anwar et al, reported no significant association between tumor location and HER2 expression.[7]

Stage and HER2 Expression

Stage II tumors showed higher strong positivity (30.8%) compared to Stage I (7.1%), suggesting increasing HER2 expression with advancing stage. Tavangar et al also reported significant correlation between HER2 overexpression and advanced disease stage ($p < 0.05$).[8]

Grade and HER2 Expression

A statistically significant positive correlation was observed between tumor grade and HER2 expression. Grade 3 tumors showed a higher proportion of strong positivity compared to Grade 1 and Grade 2 tumors. Similar findings were reported by Tavangar et al, who observed significant correlation between tumor grade and HER2 overexpression ($p < 0.001$). However, Park et al reported that tumor grade was not significantly correlated with HER2 status.[8,9]

Tumor Size and HER2 Expression

Tumors measuring 6–10 cm demonstrated higher strong positivity (36.4%) compared to tumors ≤5 cm (6.8%), showing a statistically significant association ($p < 0.001$). Li et al also reported significant association between tumor size and HER2 expression ($p < 0.05$).[10]

Comparison with Literature

The reported frequency of HER2 overexpression in colorectal carcinoma varies widely in literature (3%–47%). Pappas et al reported 3.9% positivity, while Park et al reported 47.4%. Such variability may be attributed to differences in scoring criteria, sample size, antibody clones, and interpretation methods.[6,9]

Some studies, including Kruszewski et al and McKay et al, reported no prognostic significance of HER2 expression, whereas others such as Park et al and Tavangar et al suggested HER2 as an independent prognostic factor associated with recurrence and advanced disease.[8,9,11,12]

CONCLUSION

The present clinicopathological study assessed the expression of HER2/neu in proximal and distal colorectal carcinoma and analyzed its correlation with established prognostic parameters. HER2/neu overexpression was identified in a subset of cases and demonstrated statistically significant association with tumor size, histological grade, tumor stage, age group, and tumor location. Increased HER2 expression was more frequently observed in higher-grade tumors, larger tumor size, and advanced stage disease, suggesting its possible role in tumor progression and aggressive biological behavior.

Although no significant independent association was found with gender, the overall findings indicate that HER2/neu expression may have prognostic relevance in colorectal carcinoma. Assessment of HER2 status may help in identifying a subgroup of patients with potentially aggressive disease and could provide a basis for considering targeted therapeutic strategies.

However, the relatively small sample size and limited follow-up restrict definitive conclusions regarding survival outcomes. Larger multicentric studies with long-term follow-up and molecular correlation are recommended to further validate the prognostic and therapeutic utility of HER2/neu in colorectal carcinoma.

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