Original Article

DOI: 10.7860/NJLM/2025/77413.2946

Pathology Section

Immunoexpression of HER2/Neu and Ki-67 in Gastrointestinal Carcinomas and their Association with Histomorphological Parameters: A Cross-sectional Study

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ABSTRACT

Introduction: Gastrointestinal (GI) malignancies have been considered as one of the leading causes of deaths worldwide lately. Personalised cancer therapy is an emerging approach for tumour treatment currently as treatment is chosen based on tumour genomics. Over expression of HER2/Neu has been identified in these tumours particularly in gastric and colonic carcinomas and availability of anti-HER2 monoclonal antibody can serve as an effective tool to improve the survival outcomes in these patients.

Aim: To analyse the expression of HER2/Neu and Ki-67 in GI carcinomas.

Materials and Methods: The present descriptive cross-sectional study was conducted for a period of one year from July 2023 to June 2024 in the Department of Pathology, Hind Institute of Medical Sciences, Barabanki, Uttar Pradesh, India. Out of 67 GI specimens received during the study period, a total of 50 cases of GI carcinomas were included. All relevant clinicopathological data were obtained from patient's medical record file. Histopathological examination and Immunohistochemistry (IHC) using HER2/Neu and Ki-67 biomarkers was performed and their association with various histomorphological parameters including tumour type, grade, lymphovascular and perineural invasion and lymph node status was assessed. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) Statistics version 28.0. Pearson Chi-square or Fisher-exact test was used to detect the association between histopathological features and HER2/Neu and Ki-67 expression status.

Results: Positive HER2/Neu expression was seen in 14 (28%) of the cases while high Ki-67 index was observed in 29 (58%) of the cases. Positive Her2 expression was more common in Gastric adenocarcinoma (n=40; 6%) as compared to other sites. Most well differentiated (n=10/28; 35.71%) tumours showed strong HER2/Neu positivity. Although most HER2/Neu positive cases (n=13/14; 92.85%) showed high Ki-67 index, Ki-67 independently did not show any significant association with other morphological parameters.

Conclusion: The study recommends use of both HER2/Neu and Ki-67 index in GI carcinomas as their expression and association can provide a comprehensive data of a specific tumour type stemming in different sites of GI tract.

Keywords: Gastric carcinoma, Histopathological parameters, Prognosis, Perineural invasion

INTRODUCTION

The rising trends in GI tumours in India underscores the importance of continued surveillance, early detection strategies, and advancements in treatment modalities to effectively manage and reduce the burden of these malignancies in the country. The landscape of cancer diagnostics is continually advancing, with markers such as HER2/Neu and Ki-67 playing crucial roles in understanding GI carcinomas [1]. These carcinomas, encompassing both gastric and colorectal cancers, are notorious for their alterations in these markers, affecting prognosis and treatment outcomes [1,2].

HER2/Neu, a gene coding for a tyrosine kinase receptor, and Ki-67, a cell proliferation protein, are significant in predicting the aggressive behaviour of these malignancies, with varied expression levels correlating to different survival rates [1]. Gastric carcinomas with HER2/Neu over-expression generally show a worse outcome and more aggressive disease course [3]. Oesophageal cancers show a range of HER2/Neu expression from 0-83%, with adenocarcinoma having higher positivity rates compared to squamous cell carcinomas [4-7].

The present study has been undertaken to extensively evaluate the immunohistochemical expression of HER2/Neu and Ki-67 in GI carcinomas, with the aim of elucidating their prognostic and potential therapeutic significance. In addition, the study seeks to analyse the association between these biomarkers and established histomorphological parameters including tumour type, grade, lymphovascular invasion, perineural invasion and nodal status, thereby contributing to a better understanding of tumour biology and aiding in personalised management strategies for these patients.

MATERIALS AND METHODS

The present descriptive cross-sectional study was conducted for a period of one year from July 2023 to June 2024 in the Department of Pathology, Hind Institute of Medical Sciences, Barabanki, Uttar Pradesh, India. The study was approved by the ethics committee of our institute (HIMS/ IHEC/MD/MS/ 0035/2023). Out of 67 GI specimens received during the study period from oncology as well as GI Department, a total of 50 cases of GI carcinomas were included. All cases were evaluated for histopathological confirmation by two expert Pathologists before selecting the case for the study.

Inclusion and Exclusion criteria: Inclusion criteria was all formalin fixed paraffin-embedded tissues diagnosed as GI carcinomas with available complete clinicopathological data. Inadequate biopsies, inflammatory diseases and/or malignancies other than epithelial tumours of GI tract were excluded from the study. Thus, 17 cases were excluded and only 50 cases were enrolled for the study.

Study Procedure

All relevant clinicopathological data were obtained from patient's medical record file. The parameters carefully studied were age,

gender, tumour site, tumour type, tumour differentiation (grade), lymphovascular and perineural invasion, lymph node involvement and expression of HER2/Neu and Ki-67.

Immunohistochemistry (IHC): The IHC was done according to the manufacturer's instructions. Formalin-fixed paraffin-embedded (FFPE) blocks were cut into 3 µm thin tissues. Sections were placed on poly-L lysine coated glass slides followed by de-paraffinisation and rehydration. The standard streptavidin-biotin peroxidase method for IHC was then employed and expression of HER2/Neu (ErbB2-EP3, Rabbit Monoclonal Antibody by PathnSitu, USA) and Ki-67 (MIB-1, Mouse Monoclonal Antibody, PathnSitu, USA) was noted. Tissue from appendix and breast cancer was used as positive controls for Ki-67 and HER2/Neu, respectively.

Ki-67 IHC scoring method [8,9]: The samples were scored based on the intensity and extent of nuclei staining (the percentage of positive nuclei), as follows:

Score 1+: Less than 5% of tumour cells were stained.

Score 2+: Between 5% and 19% of tumour cells were stained.

Score 3+: more than 20% of tumour cells were stained.

Immunoreactivity intensity scores: negative (0), mild (1), moderate (2), and strong or intense (3) [2].

HER2/Neu IHC scoring method [10]: The immunoreactivity of Her2 protein was assessed as: 0= no staining or cytoplasmic or membrane staining in <10% of tumour cells; 1+= incomplete cytoplasmic or membrane staining in >10% of tumour cells; 2+ = weak to moderate complete membrane or cytoplasmic staining in > 10% of tumour cells; 3+ = moderate to strong complete membrane staining in >10% of tumour cells. Cases with 0 and 1+ score were considered as negative (normal expression) while a score of 2+ and 3+ were contemplated as positive (overexpression) [2]. All equivocal (2+) cases were subjected to Fluorescent In Situ Hybridisation technique for the confirmation of Her 2 neu status and cases with an average Her2 copy number of ≥6.0 signals/cell were considered positive [1].

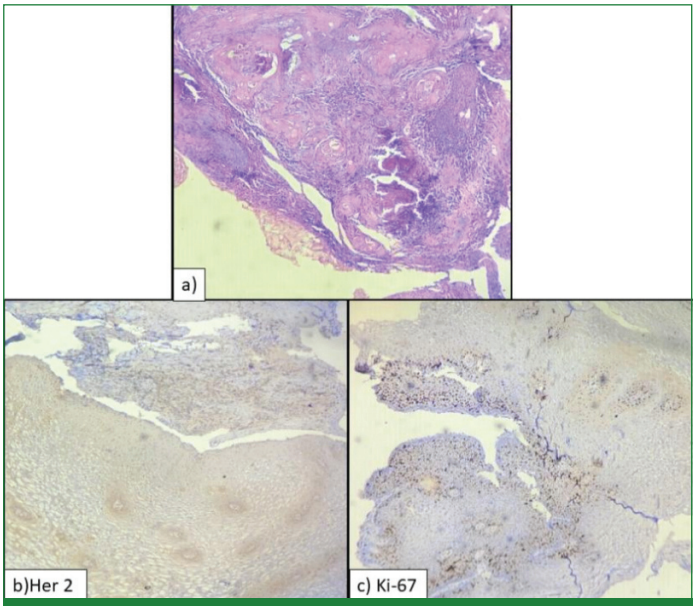
STATISTICAL ANALYSIS

Data were represented as mean±Standard Error of Mean (SEM) and for analysis of statistical differences between groups, Pearson Chi-square or Fisher-exact test was used to detect the association between histopathological features and Ki-67 and HER2/Neu expression status. SPSS 16 software was used to analyse the data. The p-values less than 0.05 were considered significant.

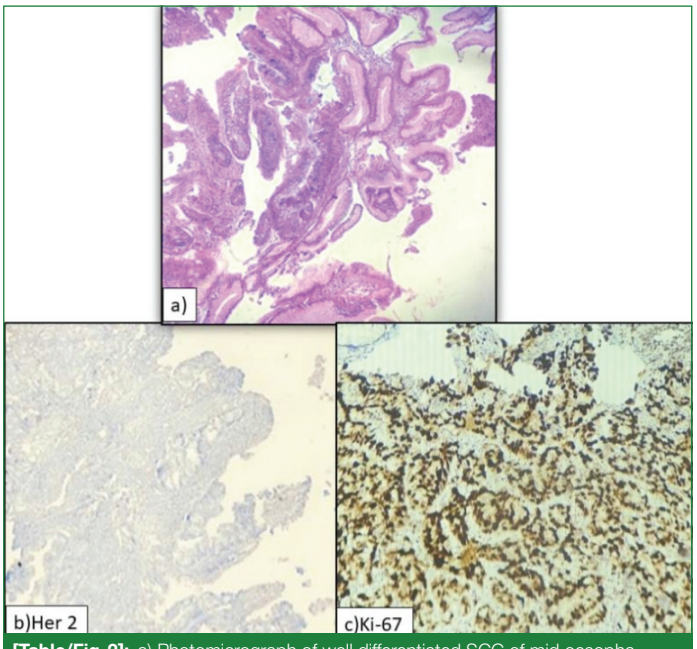
RESULTS

Amongst 50 histopathologically confirmed cases of GI carcinomas, the commonest site of involvement observed in our study was stomach 16 (32%), followed by colon and rectum 14 (28%), oesophagus 12 (24 %), periampullary region 5 (10%) and anal canal 3 (6%). The age range of these patients was between 35 to 75 years and mean age of presentation was 53.76±12.54. Most cases 16 (32%) were in the age range of 46 to 55 years followed by 35 to 45 years of age 15 (30%). Males 28 (56%) cases outnumbered females 22 (44 %) with male to female ratio of 1.27:1. Most common symptom among these patients was weight loss 25 (50%), followed by difficulty in swallowing 14 (28%), malena 11 (22%), vomiting 9 (18%), constipation 5 (10 %), yellowish discolouration 5 (10%), dyspepsia 4 (8%) and lastly pain abdomen 1 (2%). Of all the cases, 26 (52%) had vegetarian diet while the rest of them 24 (48%) were on non-vegetarian diet. History of NSAID usage was frequent in 18 (36%) of the cases.

Out of 50 cases of GI carcinomas, 38 (76%) were adenocarcinoma and 12 (24%) were squamous cell carcinoma. Amongst the adenocarcinomas, 33 (86.84%) cases were adenocarcinoma-NOS, 3 (7.89%) cases were of mucinous adenocarcinoma and 2 (5.26%) cases were of signet cell carcinoma. Most adenocarcinoma-NOS were well differentiated type 26 (68.42%) [Table/Fig-1] and rest were moderately differentiated type 7 (18.42%). All mucinous carcinomas 3 (7.89%) and signet cell carcinomas 2 (5.26%) were categorised as poorly differentiated tumours [Table/Fig-2]. Of all the squamous cell carcinomas, 10 (83.33%) cases were of moderately differentiated type and 2 (16.66%) cases were of well differentiated type [Table/Fig-3]. Thus, a total of 28 (56%) cases of well differentiated carcinomas [Table/Fig-4], 17 (34%) cases of moderately differentiated and 5 (10%) cases of poorly differentiated carcinomas (mucinous carcinoma; n=3, signet cell carcinomas; n=2) were observed in the present study [Table/Fig-4].

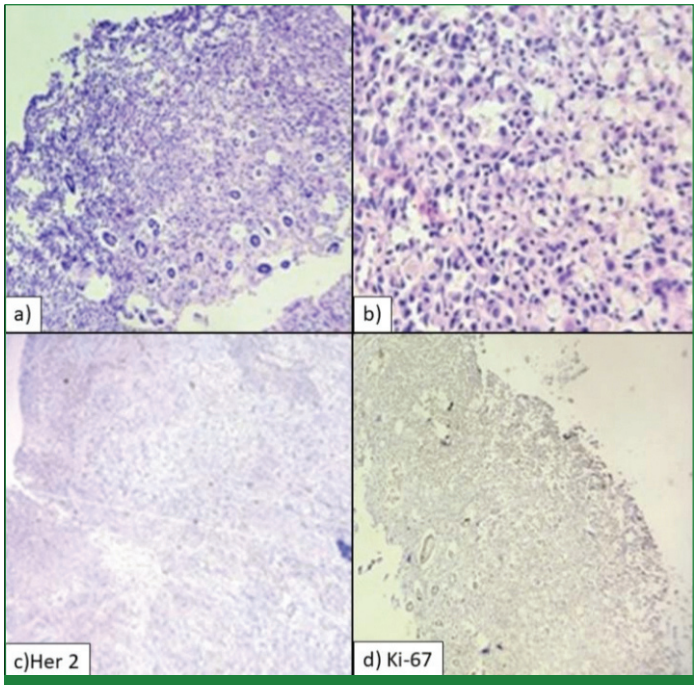


[Table/Fig-1]: a) Photomicrograph of colonic growth with well differentiated adenocarcinoma (H&E, 100x); b) Photomicrograph of tumour cells showing negative expression for Her 2; c) Photo micrograph showing high Ki-67 (3+) expression.



[Table/Fig-2]: a) Photomicrograph of well differentiated SCC of mid oesophagus (H&E, 100x) showing round to polygonal cells with keratin pearl formation; b) Photomicrograph of well differentiated SCC showing Her2 positivity; c) Photomicrograph of well differentiated SCC showing high Ki-67 PI.

Out of all 50 cases, nodal status was available in 19 cases only wherein 6 (31.57%) cases showed nodal metastasis while lymphovascular and perineural invasion was present in 9 (18%) cases and 3 (6%) cases, respectively. Nodal metastasis was observed in two cases of Adenocarcinoma- NOS, two cases of squamous cell carcinoma, one case of mucinous carcinoma and one case of signet cell carcinoma. Perineural invasion was noted in two cases of SCC and one case of Adenocarcinoma- NOS while lymphovascular invasion was seen in five cases of Adenocarcinoma- NOS, 2 cases of SCC and two cases of Mucinous carcinomas.



[Table/Fig-3]: a) Photomicrograph of distal antrum with signet cell carcinoma (H&E, 100x view); b) Photomicrograph of signet cell carcinoma showing fair number of signet cells with eccentric nuclei and abundant cytoplasm; c) Photomicrograph of signet cell carcinoma showing negative Her 2 expression (1+); d) Photomicrograph of signet cell carcinoma showing low ki-67 PI.

S. no.	Histopathological parameters	Number of cases N=50	Percentage
1.	**Morphological types**		
a)	Adenocarcinoma	N=38	76.00%
I.	Adenocarcinoma, NOS	33	86.84%
II.	Mucinous adenocarcinoma	3	7.89%
III.	Signet ring cell carcinoma	2	5.26%
b)	Squamous cell carcinoma	N=12	24.00%
2.	**Grade**		
I.	Well differentiated	28	56.00%
II.	Moderately differentiated	17	34.00%
III.	Poorly differentiated	05	10.00%
3.	**Lymphovascular invasion**	9/50	18.00%
4.	**Perineural invasion**	3/50	6.00%
5.	**Lymph node status**	6/19	31.58%
6.	**HER2/Neu Expression (IHC)**		
I.	Negative	36	72.00%
II.	Positive	14	28.00%
7.	**Ki-67 expression**		
I.	High	29	58.00%
II.	Intermediate	17	34.00%
III.	Low	4	8.00%

[Table/Fig-4]: Distribution of cases based on different histomorphological parameters and Immunohistochemistry expression.

Association between HER2/Neu and other histopathological parameters: HER2/Neu positivity was highest in gastric carcinomas 6 (40%) followed by oesophagus 4 (27%), colon and rectum 2 (13% each). Positive HER2/Neu expression was typically noticed in elderly patients 14 (93%) in the present study. Additionally, biopsies from female patients 6 (67%) showed stronger HER2/Neu positivity then males. However, no statistical significance was noted with age, gender and tumour site (p-value=0.100).

Out of 50 cases of GI Carcinomas, nine cases (18%) showed strong (3+) HER2/Neu positivity on IHC while a score of 2+ (moderate intensity) was noted in six cases (12%). These six cases were subjected to in situ hybridisation technique for the confirmation of HER2/Neu status. Five out of six cases turned out positive while one case was reported as negative. Therefore, a total of 14 cases showed HER2/Neu positivity in the present study [Table/Fig-4]. Amongst these 14 positive cases, 11 cases were adenocarcinomas and three cases were squamous cell carcinomas. The association between HER2/Neu and histologic type was statistically significant (p-value=0.02) [Table/Fig-5].

Histologic type	Her2 expression (N=50)			Ki-67 expression (N=50)			
	Her2 positive	Her2 negative	p-value	High	Intermediate	Low	p-value
Adenocarcinoma	11/38	27/38	0.02	24/38	12/38	2/38	0.06
Squamous cell carcinoma	3/12	9/12		5/12	5/12	2/12	

[Table/Fig-5]: Association between histologic type, Her2 and Ki-67 expression.

Depending upon tumour differentiation, 10 cases of well differentiated, three cases of moderately differentiated and one case of poorly differentiated carcinoma were found to be HER2/Neu positive. The association between HER2/Neu and histologic grade was statistically significant (p-value=0.04). Thus, immunoexpression of HER2/Neu was remarkable in well differentiated carcinomas [Table/Fig-6].

However, no association between HER2/Neu expression and lymphovascular invasion, perineural invasion and nodal status was noted in the present study (p-value=0.10; p-value=0.87; p-value=0.90).

Association between Ki-67 and other histopathological parameters: Of all the 50 cases, Ki-67 index was high in 29 (66%) cases, intermediate in 17 (32%) cases and low in 4 (02%) cases [Table/Fig-4]. Higher Ki-67 index was noted in stomach 13 (45%) followed by oesophagus 9 (31%). Most middle-aged (72%) patients under the age of 55 years showed increased Ki-67 proliferative index. However, no statistical significance was seen with age, gender, tumour site, lymphovascular and perineural invasion, and nodal status (p-value was >0.05).

Ki-67 was high in 24 (58%) cases of adenocarcinomas and five cases of squamous cell carcinomas. The association between Ki-67 and histologic type was statistically insignificant (p-value=0.06) [Table/Fig-5].

Amongst 28 cases of well differentiated carcinomas, 12 (43%) cases showed high Ki-67 index. In 17, moderately differentiated carcinomas, 13 (76%) cases showed high Ki-67 index while in poorly differentiated group, 4 (80%) cases showed high Ki-67. Although association between tumour differentiation and Ki-67 was statistically insignificant (p-value=0.50), higher Ki-67 was repeatedly a finding that was observed in most cases of poorly differentiated and moderately differentiated tumours [Table/Fig-6].

Histologic grade	Her2 Expression (N= 50)			Ki-67 Expression (N= 50)			
	Her2 Positive	Her2 Negative	p-value	High	Intermediate	Low	p-value
Well differentiated	10/28	18/28	0.04	12/28	12/28	4/28	0.50
Moderately differentiated	3/17	14/17		13/17	4/17	0/17	
Poorly differentiated	1/5	4/5		4/5	1/5	0/5	

[Table/Fig-6]: Association between histologic grade Her2 and Ki-67 expression.

When expression of both HER2/Neu and Ki-67 index were analysed together in each case, it was observed that out of 14 HER2/Neu positive cases, 13 (93%) cases showed high Ki-67 index. Thus, a positive association was seen between HER2/Neu expression and Ki-67 index (p-value=0.005).

DISCUSSION

In the present study, age range of the enrolled patients was between 35 to 75 years, with mean age of presentation being 53.76±12.54

years which is similar to the study by Amrani HJ et al., and Pramanik P et al., [11,12]. Male to female ratio was 1.27:1 with preponderance of males (56%) who suffered more from GI carcinomas. This finding that GI carcinomas were more common in males in the present study correlates well with the study of Rajagopal I et al., and Lazar D et al., [13,14].

In the present study, commonest site was stomach followed by colon and rectum. Gastric carcinoma is the third most common cause of cancer-related deaths globally, with East Asia, South America, and Eastern Europe reporting the greatest rates of occurrence. It usually starts in the secretory cells lining the gut [15]. Oesophagus and anal canal carcinomas was the least common in the study. Asia has a higher incidence of oesophageal cancer than any other region in the globe. This cancer is becoming more frequent, ranking sixth globally in terms of incidence [16]. The incidence of gastric carcinomas was in concordance with other studies [15,17].

Association between HER2/Neu andhistopathological parametersin Gastrointestinal (GI) carcinomas: HER2/Neu is a transmembrane receptor protein which is a part of Epidermal Growth Factor Receptor (EGFR) family being positioned on the 17th chromosome. Its overexpression is associated with increased cell growth and angiogenesis that makes it a marker of poorer prognosis in different cancers. Most studies have been undertaken in breast carcinomas with regard to HER2/Neu expression and its overexpression has been considered as a valuable therapeutic target [18]. However, role of HER2/Neu in gastrointestinal malignancies has not been established as studies have demonstrated its heterogenous expression in various tumours of GI tract. In the present study, patients in their sixth decade and above showed a stronger HER2/Neu positivity. This can be attributed to the fact that increasing age contributes to higher tumour stage. In addition, biopsies obtained from females showed a 2+ to 3+ HER2/Neu expression on IHC. This was a very peculiar finding which did not correlate with the findings of other authors [19-21]. This is because most Indian women till today tend to ignore their health needs putting the needs of their families above their own which worsens their illness.

In the present study, statistically significant association was observed between HER2/Neu and histologic type and HER2/Neu and differentiation. Most adenocarcinomas were HER2/Neu positive as compared to Squamous malignancies and most well differentiated tumours showed stronger HER2/Neu expression but HER2/Neu positivity was not significantly associated with tumour location, lymphovascular or neural invasion and nodal status. This finding was similar to the observations made by Jagani R et al., and Ghosh P et al., [22,23]. However, in a study by Wei Z et al., stronger HER2/Neu expression was associated with better tumour differentiation but with neurovascular invasion [1]. The above findings in the present study appeared contradictory to the well-known knowledge that overexpressions of HER2/Neu is associated with poorly differentiated tumours with higher nodal stage and perineural invasion. This discrepancy might have arisen due to greater number of endoscopic biopsies and smaller sample size in the present study.

Association between Ki-67 and histopathological parametersin Gastrointestinal (GI) carcinomas: Numerous researchers have studied the association of Ki-67 and its prognostic significance in GI carcinomas. Higher Ki-67 expression has been shown to be substantially related to both Disease-free Survival (DFS) and poor Overall Survival (OS) [18]. High Ki-67 expression was also demonstrated to be predictive of locoregional recurrence and distant metastases in patients with GI cancer [24]. In the present study, Ki-67 proliferative activity was markedly increased in 29 cases of GI carcinomas, of which 24 were adenocarcinomas and rest five were squamous cell carcinomas. In the present study, aggressive behaviour with poor prognosis was linked to increased Ki-67 expression in the setting of adenocarcinoma. Although higher Ki-67 was observed in most adenocarcinomas, statistical significance was not noted between the histologic type and Ki-67. This finding was similar to the observations made by Lakshmi AB et al., [17].

Of all the 50 cases, 12 cases of well-differentiated, 13 cases of moderately differentiated and four cases of poorly differentiated GI carcinomas showed high Ki-67 index. It is evident that moderately differentiated and poorly differentiated carcinomas showed high Ki-67 index in the present study suggesting that these tumours are more aggressive. However, no statistically significant association was seen between tumour differentiation and Ki-67 index. In a study by Nisar S et al., high Ki-67 PI was a feature of poorly differentiated tumours [25]. Also, no association was seen between Ki-67 expression and other histopathological parameters in the present study. Previous studies also revealed that high Ki-67 expression was not significantly associated with higher stage, differentiation, lymphovascular invasion and nodal status but that it could be considered as a predictive biomarker for bad prognosis in GI carcinomas [26].

In the present study, higher Ki-67 was an observation in patients below 55 years of age which was not in concordance with the findings of Ghosh P et al., wherein higher Ki-67 index positively correlated with older age of the patients [23]. This discordance in the present study could be due to smaller sample size and heterogenous Ki-67 staining pattern within the tumour.

In the present study, a significant association was seen between HER2/Neu positivity and high Ki-67 index but together their association with other clinicopathological parameters is puzzling. Most studies in the past could not reflect the precise association between Her2, Ki-67 and various clinicopathological variables [1,23,27]. Despite discrepancies in the expression of HER2/Neu in these tumours, its over-expression has been frequently observed by various authors in colonic, gastric and oesophageal carcinomas ranging from 4.4 to 56% describing it a potential target for therapy in these tumours [28]. Moreover, well differentiated tumours in our study were found to show strong HER2/Neu positivity as against many other studies which invite future studies to justify its prognostic relevance.

Limitation(s)

The study has its limitations as nodal status was not available in all cases, and sample size was relatively small. Such factors may interfere with the analysis producing a fallacious outcome. Moreover, subjective immunohistochemical interpretation errors cannot be excluded. Inspite of all these confounders, an in-depth assessment was performed in each case which can be helpful to the Oncologist when planning their patient-oriented management. However, it is highly recommended that more of such future studies should be undertaken for the validation of these markers in GI tumours.

CONCLUSION(S)

Expression of HER2/Neu in GI malignancies has been found to show a very striking association with tumour type and differentiation while Ki-67 expression had a very limited role to play as an independent marker and can best serve as a valuable prognostic biomarker in GI carcinomas.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 07, 2025
- Manual Googling: Aug 19, 2025
- iThenticate Software: Aug 27, 2025 (9%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Mar 06, 2025**
Date of Peer Review: **Jun 08, 2025**
Date of Acceptance: **Aug 28, 2025**
Date of Publishing: **Oct 01, 2025**