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Human epidermal growth factor receptor 2 expression and socio-demographic, clinical, and histopathological characteristics in gastric carcinoma at St Francis Hospital Nsambya, Uganda

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Abstract

Introduction Gastric carcinoma is a significant global health burden with diverse clinicopathological features and molecular alterations influencing prognosis and treatment. Human epidermal growth factor receptor 2 (HER2) overexpression is a critical biomarker in gastric carcinoma, guiding targeted therapeutic interventions. This study aimed to assess HER2 expression and its association with clinicopathological characteristics of gastric carcinoma.

Methods A retrospective cross-sectional study was conducted using consecutive sampling to retrieve gastric carcinoma tissue blocks that met the inclusion criteria. A total of 136 formalin-fixed, paraffin-embedded tissue blocks from patients aged 18 years and above (2013–2023) at St. Francis Hospital Nsambya were analyzed. HER2 expression was evaluated using immunohistochemistry (IHC) with a standardized test kit. Associations between HER2 expression and demographic and histopathological characteristics were analyzed.

Results Among 136 patients, the mean age was 59.63 years, with 48.53% aged 48–67 years. Most were male (63.24%) and from the Central region (60.70%). The intestinal subtype was the most common (78.68%), with 52.21% of tumors poorly differentiated, and tumors predominantly located in the antrum (32.35%), cardia (30.15%), and body (24.26%). Regarding HER2 expression, 11.76% were positive (3+), 2.21% equivocal (2+), and 86.03% negative (0 or 1+). HER2 positivity was significantly associated with residence in the Western region (aPR = 3.67; 95% CI: 1.33–10.11; $p = 0.02$) and with mixed-type tumors (aPR = 3.00; 95% CI: 1.70–5.30; $p < 0.001$).

Conclusion HER2 overexpression in gastric carcinoma was low. Nevertheless, the findings underscore the importance of routine HER2 testing and access to targeted therapy. Observed associations point to potential high-risk groups warranting further investigation in larger, multicenter studies.

Keywords HER2 expression, Gastric carcinoma, Uganda, Immunohistochemistry, Targeted therapy

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Background

Gastric carcinoma remains a major global health concern, contributing significantly to cancer-related morbidity and mortality [1]. Approximately one million individuals are diagnosed annually, with around 770,000 deaths attributed to this disease [2]. In Africa, the incidence is approximately 5.3 per 100,000 population, resulting in an estimated 31,000 deaths annually [3]. In East Africa, the incidence ranges from 6 to 8 per 100,000, and in Uganda, it is reported at 4.8 per 100,000, with a mortality rate of 4.5 per 100,000 [4, 5].

Despite this burden, Uganda faces significant challenges in diagnosing and treating gastric carcinoma. Most patients present with advanced-stage disease due to limited awareness, lack of screening programs, and inadequate access to diagnostic tools like endoscopy, particularly in rural areas [6, 7]. Misdiagnosis is common, and resource constraints severely limit the availability of curative surgery, chemotherapy, and radiotherapy, leading to poor prognosis [6, 7].

Gastric carcinoma develops through a complex interplay of genetic and environmental factors that drive tumor initiation, growth, and spread [8, 9]. At the molecular level, it involves mutations and alterations in critical genes such as TP53 and KRAS, as well as amplification of proto-oncogenes like *c-met* and Human epidermal growth factor receptor 2 (HER2) [8, 9]. These genetic changes disrupt normal cell regulation, promoting uncontrolled proliferation, invasion, and metastasis [8, 9].

HER2 is a cell surface protein that partners with related receptors to activate signaling pathways controlling cell growth, survival, and movement [8]. Overexpression of HER2 is a common genetic alteration in gastric carcinoma, though its prevalence varies widely by population and region, ranging from 4.4 to 53.4% in immunohistochemistry studies [9–13]. Africa reports HER2-positivity, ranging from 11 to 42% [11, 12]. In the East African region, HER2-positivity in gastric carcinoma ranges from 10.1 to 42% [12, 13]. HER2 overexpression in gastric carcinoma has been linked to tumor characteristics such as tumor location (with higher rates in proximal stomach and gastroesophageal junction tumors), histological subtype (more common in intestinal-type tumors), and tumor differentiation [14, 15]. Retrospective studies have further shown associations between HER2 overexpression and clinicopathological features such as age, tumor size, sex, tumor site, TNM stage, lymph node metastasis, lymph vascular invasion, and histopathological type [14, 15].

HER2 is also linked to more aggressive tumor behavior and poorer clinical outcomes, making it a key target for molecular therapies in advanced gastric carcinoma [16–18]. This has led to the use of trastuzumab, a monoclonal

antibody that targets HER2, in combination with chemotherapy as the standard first-line treatment, which has been shown to improve survival rates in the landmark TOGA trial [19]. However, resistance to trastuzumab frequently develops, creating a need for newer second-line therapies [20, 21].

Recently, trastuzumab deruxtecan, an antibody-drug conjugate, has shown significant survival benefits over standard chemotherapy in advanced HER2-positive gastric carcinoma, as reported in the DESTINY-Gastric04 trial [22, 23]. Additionally, emerging therapies that combine HER2-targeted agents with immunotherapy and novel antibody constructs show promise in overcoming resistance and expanding treatment options, even for patients with low or moderate HER2 expression [20–23].

These advances highlight the importance of identifying HER2 status accurately to guide therapy. However, a few studies have explored HER2 expression in gastric carcinoma patients in Uganda, and the data remain limited and inconclusive regarding prevalence, sociodemographic and clinicopathological correlations [24]. Therefore, this study aims to provide a comprehensive assessment of HER2 receptor prevalence and its relationship with sociodemographic, clinical, and histopathological characteristics among gastric carcinoma patients at St. Francis Hospital Nsambya (SFHN), offering context-specific data to better inform targeted therapy adaptation and improve patient outcomes in Uganda.

Study methods

Study design

This was a retrospective cross-sectional study utilizing stored data from the gastrointestinal endoscopy unit and histopathology samples in determining HER2 expression among gastric carcinoma patients at St Francis Hospital Nsambya admitted between the periods of 2013 to 2023.

Study setting

The study was conducted at St. Francis Hospital Nsambya, located in Kampala, the capital city of Uganda, within the Central Region. St. Francis Hospital Nsambya is a private, not-for-profit hospital with multidisciplinary services, including an Oncology department, a well-established Gastroenterology unit with radiological services, and a diagnostic pathology laboratory. The hospital has a 375-bed capacity and annually manages approximately 183,405 outpatient visits and 19,000 admissions, including both new and returning patients. Each year, around 300 patients are diagnosed and treated for various malignancies in the Oncology department, of whom about 20 are newly diagnosed with gastric carcinoma, as recorded in the hospital's Cancer Registry. Its central location and urban referral status make the hospital accessible to patients from neighboring regions, which

may influence the regional distribution of gastric carcinoma cases included in this study.

Study population

Target population

Gastric carcinoma patients aged 18 and above.

Accessible population

Patients aged 18 and above diagnosed with gastric carcinoma at St Francis Hospital Nsambya.

Study population

Patients aged 18 and above diagnosed with gastric carcinoma at St Francis Hospital Nsambya, whose tissue blocks were present at the Pathology department during the period of study.

Eligibility criteria

Inclusion criteria

Existing gastric carcinoma tissue blocks of patients diagnosed with gastric carcinoma at St Francis Hospital Nsambya in the last 10 years (2013 to 2023), aged 18 years and above, present at the pathology laboratory during the period of study, and were well preserved (embedded in paraffin).

Exclusion criteria

Tissues were excluded if they were poorly processed and lacked the specimen, or if they exhibited poor uptake of Hematoxylin and Eosin (H&E) stain, preventing accurate microscopic evaluation.

Sample size estimation

Epi Info version 7.2.4.0 was used to estimate the sample size for comparing HER2 expression between tumor types using the Fleiss [25] formula. Assuming a HER2-positivity rate of 25% in differentiated tumors and 5% in undifferentiated tumors [26], with a 2:1 ratio, 95% confidence level, and 80% power, the estimated sample size was 123. After adjusting for a 10% non-response rate, the final sample size was 136.

Study variables

Dependent variables

The primary outcome was the prevalence of HER2-positivity in gastric carcinomas.

Independent variables

Independent variables were grouped as social demographics and histopathological characteristics. The social demographic characteristics included age, sex and region and the histopathological characteristics included tumor grade, tumor location and histological classification. This study focused on adenocarcinomas and applied

the Lauren classification system (intestinal, diffuse, and mixed types). Other gastric carcinoma subtypes, such as adenosquamous and neuroendocrine tumors, were excluded due to their rarity in our setting and differing biological behavior.

Quality control

The data collection tool was subjected to pre-testing using the initial three tissue samples. The analysis explicitly excluded the results obtained from the pilot study. Adjustments to the data collection tool were made when necessary. Research assistants received training in the use of the data collection tool and the associated procedures. Instances of incorrect data, missing data, and other data collection inconsistencies were identified and rectified. The identities of patients associated with the pathological specimens remained anonymous throughout the study.

The Principal Investigator conducted thorough checks of the completed questionnaires to ensure both completeness and accuracy, and developed standard operating procedures for data collection. Additionally, internal positive and negative controls were integrated into each immunohistochemistry (IHC) run, and the reproducibility of staining was validated through an independent review by two pathologists, with any discrepancies resolved by a third pathologist. Reflex testing, such as in situ hybridization (ISH), was not conducted on equivocal cases defined as IHC 2+ due to resource constraints. While this exclusion may have resulted in an underestimation of true HER2-positivity, the methodology employed was aligned with available resources and yielded valuable insights into HER2 expression within this population.

Data collection

Data collection tool

A data collection tool was designed by the study team and validated. The tool consisted of three sections that is the social demographics section, HER2 status and the clinical histopathological section.

Data collection procedure

Demographic and clinical pathological data, encompassing age, gender, geographic region, tumor grade, tumor location, and histological classification, were extracted from the medical records corresponding to the labeling of the tissue specimens. The geographic region was defined by the patients' district of residence, which was systematically categorized into four distinct geographical regions of Uganda. This study employed archived surgically excised gastric carcinoma tissues to conduct an assessment of HER2 status utilizing Immunohistochemistry. The evaluation of receptor expression was

performed in alignment with the recommended reagents for optimal accuracy and reliability.

Preparation of IHC reagents

To prepare a 250 mL epitope retrieval solution, we measured 25 mL of the stock retrieval solution and transferred it into a measuring cylinder, subsequently bringing the total volume to the 250 mL mark with distilled water. For the 3,3'-diaminobenzidine (DAB) substrate mixture, we pipetted 1 mL of the substrate and added one drop of DAB chromogen. The TBS wash buffer was prepared as a 25-fold concentrate by diluting it with distilled water.

Immunohistochemical staining

HER2 immunohistochemistry (IHC) analysis was conducted on 4 μ m thick sections of formalin-fixed, paraffin-embedded tissue specimens. Following deparaffinization and rehydration, thin slices of tissue were prepared using a microtome and subsequently placed in water. Epitope retrieval was performed by immersing the sections in a retrieval solution contained within a plastic jar, which was then Heated for 30 min in a vegetable steamer with the lid closed. After cooling, the slides underwent three washes with Tris-buffered saline (TBS), and the back and edges of each slide were dried using gauze. The tissue sections were outlined with a marker pen, followed by the application of the primary HER2 antibody, which was incubated for one hour at room temperature. The slides were then washed with TBS three times before applying the secondary antibody and incubating for an additional 30 min. Following another TBS wash, the endogenous enzymes were blocked by the application of a peroxidase block for 15 min at room temperature, followed by a TBS wash. A polymer solution intended to enhance amplification was then applied and incubated for 30 min, after which it was washed off with TBS. The subsequent step involved adding a chromogen substrate mixture (DAB chromogen and substrate), which was left for 3 min at room temperature, followed by washes with TBS. The sections were then counterstained with Mayer's Hematoxylin for 30 s, rinsed in running tap water for 5 min, and rapidly dehydrated in alcohol before being cleared using two changes of xylene. Finally, the slides were mounted with D.P.X and examined under a light microscope at magnifications of $\times 4$, $\times 10$, and $\times 40$.

HER2 expression was evaluated in accordance with the guidelines established by CAP/ASCO. Cases demonstrating strong complete, basolateral, or lateral membranous reactivity in $\geq 10\%$ of tumor cells (IHC 3+) were categorized as HER2 positive. Cases exhibiting weak to moderate complete, basolateral, or lateral membranous reactivity in $\geq 10\%$ of tumor cells (IHC 2+) were classified as equivocal. Furthermore, cases demonstrating faint, barely perceptible, or incomplete membranous reactivity

in $\geq 10\%$ of tumor cells (IHC 1+) and those with no reactivity or $< 10\%$ membranous staining (IHC 0) were classified as HER2 negative. Each IHC slide was independently reviewed by two seasoned pathologists adhering to the CAP/ASCO scoring criteria. In instances of scoring discrepancies, a consensus was achieved through joint review to ensure accuracy and enhance inter-observer reliability.

This study was retrospective and based on archived specimens derived from a national referral center; thus, there exists a potential for selection bias, particularly in favor of more advanced or referred cases. To mitigate this potential bias, all available and eligible gastric carcinoma specimens within the study period that met the inclusion criteria were included, irrespective of disease stage, treatment status, or source of referral. However, it is acknowledged that limiting inclusion to cases with comprehensive clinical data and prior research consent may have resulted in inherent selection bias, potentially limiting the generalizability of the findings to the broader gastric carcinoma population in Uganda.

Sampling procedure

The gastric carcinoma tissue specimens were consecutively selected until the required sample size was reached.

Selection of tissue samples

Archived gastric carcinoma tissue blocks were obtained from the Pathology Laboratory at St. Francis Hospital Nsambya. Inclusion criteria were restricted to specimens sourced from patients who had previously provided written informed consent for the utilization of their samples in research. Only tissue blocks accompanied by complete and corresponding clinical records were included to maintain the integrity of clinicopathological correlations. The study encompassed both endoscopic biopsies and surgical resections. The selection process was conducted in collaboration with a pathologist, who reviewed the study protocol and granted permission for access to the tissue blocks. All available and eligible gastric carcinoma samples within the designated study period were included. No specimens were excluded, and the final dataset contained no missing clinical or histological data.

Although both biopsy and resection specimens were utilized, there was no analysis of multiple samples from the same patient. Each specimen was marked and tracked to ensure accurate identification; as only one specimen per patient was examined, there was no risk of duplication or bias affecting the sample size.

Human ethics and consent to participate

All methods were carried out following relevant guidelines and regulations. The study adhered to the Declaration of Helsinki. Ethical approval was granted by St

Francis Hospital Nsambya REC Research Ethics Committee (Ref no: SFHN-2023-111). Tissue blocks from gastric carcinoma patients were collected at the Pathology laboratory with prior written informed consent for research use.

Statistical analysis

Data analysis was done using STATA version 15. Continuous variables were shown as mean $\pm$ standard deviation if they were normally distributed, or as median and range if they were skewed. Categorical variables were reported as counts and percentages. HER2 positivity was calculated as the percentage of positive tissue samples, with 95% confidence intervals. Equivocal (2+) and positive (3+) results were grouped as HER2-positive (coded 1), while 0 and 1+ results were grouped as HER2-negative (coded 0). Associations between HER2 positivity and histopathological features were tested using binary Poisson regression. In bivariate analysis, prevalence ratios with 95% confidence intervals were reported. Variables with p -values ≤ 0.2 were included in the multivariate Poisson regression to find independent predictors of HER2 positivity. To reduce false positives from multiple testing, p -values were adjusted using the Benjamini-Hochberg method. Results with adjusted p -values (q -values) ≤ 0.05

were considered statistically significant (q -values) of ≤ 0.05 .

Results

HER2 status among the gastric carcinomas

Human epidermal growth factor receptor 2 (HER2) protein expression in gastric carcinoma was classified as follows: (A) Negative (score 0), (B) Negative (score 1+), (C) Equivocal (score 2+), and (D) Positive (score 3+) (Fig. 1). Of the 136 gastric tissue blocks studied, 16 (11.76%) were HER2 positive (3+), 3 (2.21%) were equivocal (2+), and 117 (86.03%) were HER2 negative (0 or 1+).

Descriptive statistics

Among the 136 participants, most were male (63.24%). The average patient age was 59.63 years, with almost half (48.53%) aged 48–67 years, followed by 30.15% aged 68–88 years. Regional data ($n=107$) showed that the majority were from the Central region (60.75%), with smaller proportions from the Western (28.04%), Eastern (7.48%), and Northern (3.74%) regions. Histologically, the intestinal subtype was most common ($n=107$, 78.68%), followed by the diffuse subtype ($n=25$, 18.38%), with the remainder classified as mixed. More than half of the tumors were poorly differentiated ($n=71$, 52.21%). Gastric carcinoma was predominantly located in the antrum

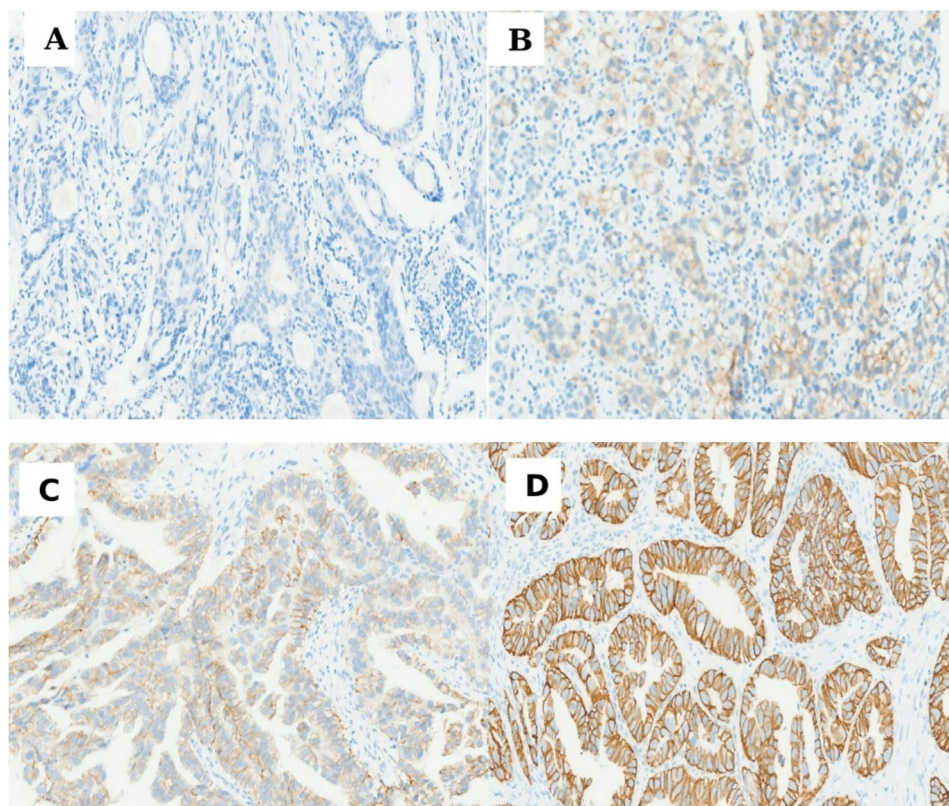


Fig. 1 HER2 staining

Table 1 Socio-demographic characteristics by HER2 expression

Variable	HER2 Negative n (%) n = 117	HER2 Positive n (%) n = 19	cPR (95% CI)	p-value	q-value (FDR- adjusted p-value)
Age					
27–47	22(75.86)	7(24.14)	1		
48–67	59(89.39)	7(10.61)	0.44(0.17– 1.14)	0.09*	0.26
68–88	36(87.80)	5(12.20)	0.51(0.18– 1.44)	0.2	0.48
Sex					
Male	44(88.00)	6(12.00)	1		
Female	73(84.88)	13(15.12)	1.26(0.51– 3.12)	0.62	0.86
Region* n = 107					
Central	60(92.31)	5(7.69)	1		
Eastern	7(87.50)	1(12.50)	1.62(0.21– 12.34)	0.64	0.81
Western	21(70.00)	9(30.00)	3.9(1.42– 10.70)	0.01*	0.04*
Northern	4(100.00)	0(0.00)	0(0.00– 0.00)	0	0

cPR Crude prevalence ratio

*p-value; significant variable

Table 2 Tumor characteristics by HER2 expression

Variable	HER2 Negative n (%) (n = 117)	HER2 Positive n (%) (n = 19)	cPR (95% CI)	p-value	q-value (FDR- adjusted p-value)
Histological subtype					
Intestinal	90(84.1)	17(15.9)	1		
Diffuse	25(100)	0(0.00)	0 (0.00–0.00)	0.00	0.00
Mixed	2(50)	2(50.00)	3.15(1.07– 9.24)	0.04*	0.13
Tumor differentiation					
Poorly differentiated	63(88.73)	8(11.27)	1		
Moderately differentiated	25(86.21)	4(13.79)	1.22(0.40– 3.77)	0.72	0.78
Well differentiated	29(80.56)	7(19.44)	1.73(0.68– 4.40)	0.25	0.51
Tumor location					
Antrum	37(84.09)	7(15.91)	1		
Body	28(84.85)	5(15.15)	0.95(0.33– 2.75)	0.93	0.93
Cardia	37(90.24)	4(9.76)	0.61(0.19– 1.95)	0.41	0.41
Fundus	9(90.00)	1(10.00)	0.63(0.09– 4.58)	0.65	0.65
Pylorus	6(75.00)	2(25.00)	1.57(0.39– 6.27)	0.52	0.52

cPR Crude prevalence ratio

*p-value; significant variable

($n = 44$, 32.35%), followed by the cardia ($n = 41$, 30.15%) and body ($n = 33$, 24.26%), with fewer cases in the fundus ($n = 10$, 7.35%) and pylorus ($n = 8$, 5.88%).

Association of HER2 expression with socio-demographic characteristics and tumor characteristics

Variables with p-values less than 0.2 in the bivariate analysis, specifically region and histological subtype (Tables 1 and 2), were included in the multivariable model. A stepwise approach was used to control for potential confounding. After adjusting for multiple comparisons using the Benjamini-Hochberg procedure (FDR = 0.05), both region and histological subtype remained statistically significant. Patients from the Western region were nearly four times more likely to have HER2-positive gastric carcinoma compared to those from the Central region (aPR = 3.67; 95% CI: 1.33–10.11; $p = 0.02$). Similarly, patients with mixed-type tumors were three times more likely to be HER2 positive compared to those with intestinal-type tumors (aPR = 3.00; 95% CI: 1.70–5.30; $p < 0.001$) (Table 3).

Discussion

HER2 expression among gastric carcinomas

Among the 136 gastric carcinoma cases analyzed in this study, 11.76% demonstrated HER2-positivity (3+), while 2.21% were classified as equivocal (2+). Although these findings are lower than those reported in many international studies, they exceed rates previously documented in Ugandan cohorts. The relatively low HER2-positivity observed may reflect several contributing factors, including the histological distribution of tumors within the study population, the application of strict scoring criteria during immunohistochemical evaluation, and the limited quantity of available tissue in some specimens, which may have affected detection sensitivity [27, 28]. A previous Ugandan study, for instance, reported an even lower HER2-positivity rate of 8.1%, possibly influenced by a smaller sample size of 86 cases, suggesting that these lower rates may be more common in certain African settings [28]. In comparison, studies from Saudi Arabia found 13.5% of cases to be HER2 positive, and research from East Asia showed higher rates ranging from 9 to 20% [29, 30].

Other studies have reported significantly higher prevalence rates than those observed in our study. A large international study (the ToGA trial) reported 22.1% HER2-positivity [11], and a study from Vietnam found 24.5% of cases had strong HER2 expression [31]. Global reviews estimate that about 19% of gastric carcinomas are HER2 positive [32]. These differences likely come from a mix of factors, including patient genetics, the type and location of the cancer, and differences in how the testing is done in different parts of the world [28, 33].

Table 3 Multivariate poisson analysis showing factors associated with HER2 expression

Variable	cPR (95% CI)	p-value	aPR (95% CI)	p-value	q-value (FDR-adjusted p-value)
Region					
Central	1		1		
Eastern	1.62(0.21–12.34)	0.64	1.38(0.18–10.41)	0.758	1
Western	3.9(1.42–10.70)	0.01	3.67(1.33–10.11)	0.012*	0.02*
Northern	0(0.00–0.00)	0.00	0(0.00–0.00)	0.00	0.00
Histological subtype					
Intestinal	1		1		
Diffuse	0 (0.00–0.00)	0.00	0(0.00–0.00)	0.00	0.00
Mixed	3.15(1.07–9.24)	0.04	3(1.70–5.30)	<0.001*	<0.001*

cPR Crude prevalence ratio, aPR Adjusted prevalence ratio

*p-value; significant variable

Importantly, our study did not perform FISH testing on the three equivocal (2+) cases, representing a significant clinical Limitation. According to published data, between 13.9% and 46.7% of IHC 2+ gastric carcinomas harbor HER2 gene amplification [27, 34, 35]. This means that one to two patients in our study may have been truly HER2-positive and therefore eligible for trastuzumab therapy, which has been shown to improve median survival by approximately 4.2 months [36, 37]. The absence of reflex FISH testing contradicts ASCO/CAP recommendations, which emphasize its necessity in all equivocal cases to guide treatment decisions [38]. Without confirming HER2 status, these patients face missed therapeutic opportunities, are ineligible for trials requiring proof of amplification, and are left with prognostic uncertainty [33, 39]. This is particularly important because HER2-amplified 2+ tumors tend to behave like strongly positive (3+) cancers, while non-amplified 2+ tumors follow the course of HER2-negative disease [33, 39].

Factors associated with HER2-positivity among patients aged 18 and above

Our study found that residents of Western Uganda were approximately 3.7 times more likely to be HER2-positive compared to those from the Central region. This strong regional association is notable, especially given that stomach cancer incidence is already known to be relatively high in Western Uganda [40]. Several local factors may help explain this pattern. Prior ecological studies have pointed to environmental exposures such as the frequent use of unrefined rock salt, known to contain carcinogenic metals, and a high prevalence of *Helicobacter pylori* infection as potential contributors to increased gastric carcinoma risk in the region [40]. While a direct link between these exposures and HER2 overexpression remains unproven, they may influence tumor biology [40]. Genetic differences among Uganda's ethnically diverse populations could also play a role in HER2-driven carcinogenesis [40]. Moreover, disparities in healthcare access, such as limited screening, referral, or diagnostic

capacity in some regions, might result in regional sampling bias [28, 40]. For instance, patients from more remote areas may only reach tertiary centers when the disease is advanced, potentially skewing the sample toward more aggressive, HER2-positive tumors [28, 40]. Although these are hypotheses, the observed regional differences highlight the need for targeted epidemiologic and molecular studies to better understand the drivers of HER2 expression [28, 40].

Similar regional variations in HER2-positivity have been reported in other settings. In Tanzania, a study found a HER2-positivity rate of 6.0% in gastric carcinoma, with marked differences across referral centers [11]. Likewise, research from Korea has shown significant geographic variation, with urban centers having higher HER2 expression rates than rural areas [41]. These patterns suggest that a combination of environmental, genetic, and healthcare system factors may underlie regional disparities in HER2 expression [28, 40]. Further research is needed to clarify whether these factors influence HER2 biology directly or simply affect which patients are captured in clinical samples [28, 40].

This study also found that participants with a mixed histology subtype were approximately 3 times more likely to be HER2-positive compared to those with other subtypes, a finding that warrants further investigation, as most existing literature has reliably linked HER2 overexpression primarily to intestinal-type gastric carcinoma [42, 43]. This observation contrasts with studies such as the HER-EAGLE study, which reported significantly higher HER2-positivity among intestinal-type tumors compared to diffuse-type tumors [43]. Similarly, Bokhary [42] noted that HER2-positivity was more common in well-differentiated histologies than in poorly differentiated ones, suggesting a link between HER2 expression and more structured tumor architecture. Our finding may reflect true biological variation in HER2 expression among mixed-type tumors, which contain both intestinal and diffuse features and may behave differently from either subtype alone [42]. Alternatively, this association

could be influenced by challenges in histologic classification or sample size limitations that might have led to overlapping diagnostic categories [44]. It is also possible that mixed-type tumors in our setting represent a more aggressive or advanced phenotype with higher HER2 expression, especially if they were overrepresented among referred cases [45]. These possibilities highlight the need for further research with larger, well-classified samples to determine whether mixed histology is independently associated with HER2 overexpression and to better understand its clinical and therapeutic relevance.

This study has some limitations. First, it was a single-center, retrospective analysis based on available archived specimens, which may have introduced selection bias. Second, the number of HER2-positive cases was small ($n = 16$), limiting statistical power for subgroup analysis. Third, our study relied solely on IHC without confirmatory molecular testing; notably, none of the equivocal (IHC 2+) cases underwent FISH, which may have led to misclassification of HER2 status and an underestimation of HER2-positivity. Published data on gastric carcinoma indicate that 13.9–46.7% of IHC 2+ tumors demonstrate HER2 gene amplification by FISH testing, suggesting that approximately 1 to 2 patients in our series could have been truly HER2-positive and potentially eligible for trastuzumab therapy [46, 47]. The clinical implications of this limitation include missed opportunities for HER2-targeted treatment, as trastuzumab has shown proven efficacy and survival benefits in HER2-positive gastric carcinoma [47]. Failure to detect these cases may negatively impact patient prognosis and skew study conclusions regarding HER2 prevalence and treatment response [47]. To address this limitation, future studies should adopt standardized diagnostic pathways aligned with evolving guideline criteria to improve diagnostic accuracy and reproducibility.

Fourth, we lacked treatment and outcome data, preventing analysis of the prognostic or therapeutic implications of HER2 expression. Another limitation of this study was the exclusion of rare gastric carcinoma subtypes, including neuroendocrine neoplasms, mixed adenoneuroendocrine carcinomas (MANEC), adenosquamous, Hepatoid, and enteroblastic variants. Although these subtypes collectively account for less than 1% of gastric carcinomas, they may exhibit distinct clinical behavior and higher rates of HER2 overexpression, particularly hepatoid adenocarcinomas associated with AFP production [48–50]. Their exclusion was due to their low prevalence in our cohort and the study's focus on conventional gastric adenocarcinomas classified according to Lauren's system (intestinal, diffuse, and mixed types). As a result, our findings may not be generalizable to these histologically diverse but clinically significant subtypes. Future studies with larger sample

sizes or multicenter collaboration should aim to include and report on these rare variants to improve understanding of HER2 expression across the full histopathological spectrum of gastric carcinoma. Finally, despite efforts to standardize scoring, using independent review by two pathologists and a third for adjudication, some interobserver variability in IHC interpretation was unavoidable.

Nonetheless, our findings have important clinical implications. They support the need for routine HER2 testing in gastric carcinoma, even in resource-limited settings like Uganda, where trastuzumab, now listed as an essential medicine, is becoming more accessible. Prioritizing testing for subgroups more likely to be HER2-positive (e.g., intestinal-type tumors) and establishing clear protocols for handling equivocal cases could improve treatment access. Our data also highlights potential regional differences that warrant further investigation, including possible environmental risk factors in Western Uganda. Strengths of this study include standardized IHC assessment and adjustment for confounding in analysis. Ultimately, this work provides locally relevant evidence to guide HER2 testing and policy in Uganda.

Conclusion

The prevalence of HER2 overexpression in gastric carcinoma was low. We identified an association between HER2-positivity and patients from the Western region of Uganda and patients with mixed-type tumors, findings that both merit further studies. Although our single-center sample limits broad generalizability, this study establishes a basis for national surveillance of HER2 in gastric carcinoma. We recommend that Uganda consider routine HER2 testing for gastric carcinoma patients, coupled with access to targeted therapy (e.g. trastuzumab) for eligible cases. Such measures have the potential to improve outcomes by enabling more effective, personalized treatment.

Abbreviations

HER2	Human epidermal growth factor receptor 2
IHC	Immunohistochemistry
SFHN	St. Francis Hospital Nsambya, DAB = 3,3'-diaminobenzidine

Authors' contributions

SW was the principal investigator, conceived and designed the study, collected data, analysed data and wrote the draft of the manuscript. GN, BB and EO supervised the work and revised the manuscript. FB, JA, DN, PN, MDO and JM contributed to data collection, discussion of results and revised the manuscript. All authors approved the final manuscript.

Funding

This study did not receive any specific grant from funding agencies in public, commercial, or not for profit sectors.

Data availability

Data is available upon request. Requests should be sent to steveswanda@gmail.com (SW).

Declarations

Ethical approval and consent to participate

All methods were carried out in accordance with relevant guidelines and regulations. The study adhered to the Declaration of Helsinki. Ethical approval was granted by St Francis Hospital Nsambya REC Research Ethics Committee (Ref no: SFHN-2023-111). Existing gastric carcinoma tissue blocks at the Pathology laboratory were collected from gastric carcinoma patients who had previously provided written informed consent for using of their tissue blocks for research.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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Received: 21 April 2025 / Accepted: 26 August 2025

Published online: 26 September 2025

References

1. Thrift AP, El-Serag HB. Burden of gastric cancer. *Clin Gastroenterol Hepatol*. 2020;18(3):534–42.
2. Gecer M, Büyükpınarbaşı N, Turna S, Beşiroğlu M, Guzin Z. Comparison of human epidermal growth factor receptor 2 and cancer stem cell markers like CD44 and CD133 expressions with clinicopathological parameters in gastric cancer. *Eur Res J*. 2023;9(5):1015–26.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209–49.
4. Asombang AW, Rahman R, Ibdah JA. Gastric cancer in Africa: current management and outcomes. *World J Gastroenterol*. 2014;20(14):3875–9.
5. Shokouhi F, Amiripour A, Raeisi Shahraki H. The main patterns in the trend change of stomach cancer incidence amongst selected African countries. *Glob Health Epidemiol Genom*. 2021;2021:5065707.
6. Obayo S, Lukwago L, Orem J, Faulx AL, Probert CS. Gastrointestinal malignancies at five regional referral hospitals in Uganda. *Afr Health Sci*. 2017;17(4):1051–8.
7. Galukande M, Luwaga A, Jombwe J, Fualal J, Kigula-Mugamba J, Kanyike A, et al. Gastric cancer diagnosis and treatment guidelines 2008: Uganda cancer working group. *East Cent Afr J Surg*. 2008;13(2):142–9.
8. Fanotto V, Ongaro E, Rihawi K, Avallone A, Silvestris N, Fornaro L, et al. HER-2 inhibition in gastric and colorectal cancers: tangible achievements, novel acquisitions and future perspectives. *Oncotarget*. 2016;7(42):69060.
9. Iqbal N, Iqbal N. Human epidermal growth factor receptor 2 (HER2) in cancers: overexpression and therapeutic implications. *Mol Biology Int*. 2014;2014:852748.
10. Abrahao-Machado LF, Scapulatempo-Neto C. HER2 testing in gastric cancer: an update. *World J Gastroenterol*. 2016;22(19):4619.
11. Ngaiza A, Vuhahula E, Yahaya J, Ndayisaba MC, Kawishe GJ, Grenert JP, et al. Evaluation of human epidermal growth factor receptor 2 expression in gastric and gastroesophageal cancers in Tanzania. *Arch Pathol Lab Med*. 2022;146(12):1523–9.
12. Omulo TM RE. HER2/Neu Protein Over-Expression in Patients with Gastric and Gastro- Esophageal Junction Carcinoma Seen at Kenyatta National Hospital, Kenya. *J Carcinog Mutagen*. 2014;05(05):1–10.
13. Hategekimana E, Ruhangaza D, Hansen C, Musoni E, Rugwizangoga B, Hammel K, et al. Immunohistochemical profile of human epidermal growth factor receptor 2 in gastric cancer in Rwanda. *Open Journal of Gastroenterology*. 2022;12(11):336–46.
14. Chu Y, Li H, Wu D, Guo Q. HER2 protein expression correlates with Lauren classification and P53 in gastric cancer patients. *Medicine*. 2022;101(37):e30647.
15. Li H, Li L, Zhang N, Wang Z, Xu N, Linghu E, Chai N. Relationship between HER2 overexpression and long-term outcomes of early gastric cancer: a prospective observational study with a 6-year follow-up. *BMC Gastroenterol*. 2022;22(1):238.
16. Duduyemi B, Asante EAE, Afihene M. The analysis of human epidermal growth Receptor-2 (HER-2) in gastric cancer in A tertiary hospital in Sub-Saharan africa.: human epidermal growth receptor-2 (HER-2) in gastric cancer. *Nigerian Med J*. 2021;62(4):178–82.
17. Rajadurai P, Fatt HK, Ching FY. Prevalence of HER2 positivity and its clinicopathological correlation in locally advanced/metastatic gastric cancer patients in Malaysia. *J Gastrointest Cancer*. 2018;49:150–7.
18. Joshi SS, Badgwell BD. Current treatment and recent progress in gastric cancer. *CA Cancer J Clin*. 2021;71(3):264–79.
19. Gutierrez C, Schiff R. HER2: biology, detection, and clinical implications. *Arch Pathol Lab Med*. 2011;135(1):55–62.
20. O'Donnell CDJ, Majeed U, Rutenberg MS, Croome KP, Poruk KE, Toskich B, et al. Advancements in Locoregional Therapies for Unresectable Intrahepatic Cholangiocarcinoma. Vol. 32, *Current Oncology*. 2025. p. 1–22.
21. Cai J, Wang W, Cong D, Bai Y, Zhang W. Development of treatment strategies for advanced HER2-positive gastric cancer: insights from clinical trials. *Crit Rev Oncol Hematol*. 2025;207:104617.
22. He L, Liu B, Wang Z, Han Q, Chen H. Evolving landscape of HER2-targeted therapies for gastric cancer patients. *Curr Treat Options Oncol*. 2025;26(4):260–77.
23. Ratti M, Citterio C, Orlandi E, Vecchia S, Anselmi E, Toscani I, et al. Fighting HER2 in Gastric Cancer: Current Approaches and Future Landscapes. *Int J Mol Sci*. 2025;26(15):7285.
24. Kahiye M, Yahaya J, Kalungi S, Nalwoga H. HER2 immunohistochemical expression and its association with clinicopathological features of gastric adenocarcinoma in Uganda. *Turk J Surg*. 2024;40(4):328.
25. Fleiss JL, Levin B, Paik, MC. Statistical Methods for Rates and Proportions. 3rd Edition, Wiley, Hoboken. 2003. <https://doi.org/10.1002/0471445428>.
26. Li H, Li L, Zhang N, Wang Z, Xu N, Linghu E, Chai N. Relationship between HER2 overexpression and long-term outcomes of early gastric cancer: a prospective observational study with a 6-year follow-up. *BMC Gastroenterol*. 2022;22(1):1–7.
27. Xu B, Chen H, Zhang J, Cong Y, Ning L, Chen L, et al. A comparative study of gastric adenocarcinoma HER2 IHC phenotype and mass spectrometry-based quantification. *Front Oncol*. 2023;13:1152895.
28. Kahiye M, Yahaya J, Kalungi S, Nalwoga H. HER2 immunohistochemical expression and its association with clinicopathological features of gastric adenocarcinoma in Uganda. *Turk J Surg*. 2024;40(4):328–35.
29. Shen L, Li Y, Huang H, Lu Z, Chen B. HER2 in gastric cancer: a comprehensive analysis combining meta-analysis and DCE-MRI radiomics. *Cancer Control*. 2024;31:10732748241293700.
30. Hu HH, Wang SQ, Zhao H, Chen ZS, Shi X, Chen XB. HER2(+) advanced gastric cancer: current state and opportunities (review). *Int J Oncol*. 2024. <https://doi.org/10.3892/ijo.2024.5624>.
31. Phan DAT, Nguyen VT, Hua TNH, Ngo QD, Doan TPT, Nguyen ST, et al. HER2 status and its heterogeneity in gastric carcinoma of Vietnamese patient. *J Pathol Transl Med*. 2017;51(4):396–402.
32. Lei Y-y, Huang J-y, Zhao Q-r, Jiang N, Xu H-m, Wang Z-n, et al. The clinicopathological parameters and prognostic significance of HER2 expression in gastric cancer patients: a meta-analysis of literature. *World J Surg Oncol*. 2017;15(1):68.
33. Abrahao-Machado LF, Scapulatempo-Neto C. HER2 testing in gastric cancer: an update. *World J Gastroenterol*. 2016;22(19):4619–25.
34. Liu X, Wang X, Wang B, Ren G, Ding W. HER2 gene amplification by fluorescence in situ hybridization (FISH) compared with immunohistochemistry (IHC) in 122 equivocal gastric cancer cases. *Appl Immunohistochem Mol Morphol*. 2016;24(7):459–64.
35. Raj N, Verma D, Kumar A, Rai P, Rao RN. HER2 oncogene amplification and immunohistochemical profiling in gastric adenocarcinoma. *Discoveries (Craiova)*. 2018;6(4):e83.
36. Davidson M, Starling N. Trastuzumab in the management of gastroesophageal cancer: patient selection and perspectives. *Oncotargets Therapy*. 2016;9(null):7235–45.

37. Yoon DokHyun YD, Kang YoonKoo KY. Results and implications of the trastuzumab for gastric cancer (ToGA) trial. *Clin Invest*. 2011;1(1):87–95.
38. Wolff AC, Somerfield MR, Dowsett M, Hammond MEH, Hayes DF, McShane LM, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: ASCO-College of American Pathologists Guideline Update. *J Clin Oncol*. 2023;41(22):3867–72.
39. Rüschoff J, Nagelmeier I, Baretton G, Dietel M, Höfler H, Schildhaus HU, et al. [Her2 testing in gastric cancer. What is different in comparison to breast cancer?]. *Pathologe*. 2010;31(3):208–17.
40. Obayo S, Lukwago L, Orem J, Faulx AL, Probert CS. Gastrointestinal malignancies at five regional referral hospitals in Uganda. *Afr Health Sci*. 2017;17(4):1051–8.
41. Kim WY, Yang EJ, Jang EB, Lee AJ, So KA, Shim S-H, et al. The expression and amplification of HER2 has a significant impact on the prognosis of endometrial carcinoma in Korean patients. *J Clin Med*. 2024;13(8):2158.
42. Bokhary RY. Prevalence of HER2 expression and its association with clinicopathological parameters in gastric and gastroesophageal junction adenocarcinoma: A 10-year experience of an academic center. *Mol Clin Oncol*. 2025;22(6):49.
43. Kim WH, Gomez-Izquierdo L, Vilardell F, Chu KM, Soucy G, Dos Santos LV, et al. HER2 status in gastric and gastroesophageal junction cancer: results of the large, multinational HER-EAGLE study. *Appl Immunohistochem Mol Morphol*. 2018;26(4):239–45.
44. Chen H, Strickland AL, Castrillon DH. Histopathologic diagnosis of endometrial precancers: updates and future directions. *Semin Diagn Pathol*. 2022;39(3):137–47.
45. Hohmann L, Sigurjonsdottir K, Campos AB, Nacer DF, Veerla S, Rosengren F, et al. Genomic characterization of the HER2-enriched intrinsic molecular subtype in primary ER-positive HER2-negative breast cancer. *Nat Commun*. 2025;16(1):2208.
46. Liu X, Li H, Zeng L, Lu Z, Chen S, Bibikova M, et al. P-129 evaluation of HER2 status in equivocal gastric cancer tissue samples using surrogate DNA methylation markers. *Ann Oncol*. 2022;33:S296.
47. Wali RMH, Kama MS. HER2/neu estimation by ISH (FISH and CISH) technique in equivocal cases (+2) by IHC in breast cancer. *Int J Clin Diagnostic Pathol*. 2023;6(3):43–7.
48. Fujimoto M, Matsuzaki I, Nishino M, Iwahashi Y, Warigaya K, Kojima F, et al. HER2 is frequently overexpressed in hepatoid adenocarcinoma and gastric carcinoma with enteroblastic differentiation: a comparison of 35 cases to 334 gastric carcinomas of other histological types. *J Clin Pathol*. 2018;71(7):600–7.
49. Lin J, Zhao Y, Zhou Y, Tian Y, He Q, Lin J, et al. Comparison of survival and patterns of recurrence in gastric neuroendocrine carcinoma, mixed adenoneuroendocrine carcinoma, and adenocarcinoma. *JAMA Netw Open*. 2021;4(7):e2114180–e.
50. Campos SAM, Vilhena Pereira B, Carroll CB, Gonçalves R, Rondinelli R, Bulzico D. Gastric neuroendocrine neoplasms: analysis of a cohort of patients followed at the Brazilian National Cancer Institute. *Endocr Oncol*. 2025;5(1).

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