Clinicopathological features and prognoses of HER-2-positive gastric cancer

HUIQUN SHEN[1], XIAJUAN XUE[2], HUIDUAN HE[3] and SHUJUN LIN[1]

[1]Department of Oncology, Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou, Fujian 363000, P.R. China;
[2]Department of Colorectal Surgery, Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou, Fujian 363000, P.R. China;
[3]Department of Pathology, Zhangzhou Affiliated Hospital of Fujian Medical University, Zhangzhou, Fujian 363000, P.R. China

Received November 12, 2025; Accepted August 19, 2026

DOI: 10.3892/mco.2026.2974

Abstract. The present study aimed to investigate the clinicopathological characteristics of human epidermal growth factor receptor-2 (HER-2)-positive gastric cancer and their association with HER-2 protein expression levels and prognosis. In total, 99 patients diagnosed with HER-2-positive gastric cancer who underwent radical gastrectomy were included in the study. χ^2 testing explored the association between HER-2 protein expression and clinical features. Disease-free survival (DFS) and overall survival (OS) were evaluated through Kaplan-Meier survival curves. Univariate and multivariate Cox regression analyses were performed to evaluate the impact of clinical variables on DFS and OS. HER-2 protein expression, tumor size, tumor invasion, lymph node metastasis, Tumor-Node-Metastasis stage, perineural invasion (PNI) and lymphovascular invasion (LVI) were associated with inferior DFS. HER-2 protein expression emerged as an independent prognostic factor of DFS in HER-2-positive gastric cancer, but showed no association with OS. Compared with HER-2 immunhistochemistry (IHC) 2+ groups, patients with HER-2 IHC 3+ exhibited a higher prevalence of PNI and LVI, a shorter median DFS time, and a lower tumor-free survival rate at 1, 3 and 5 years post-surgery. In conclusion, HER-2 is a significant negative prognostic factor, associated with a poorer DFS time, although data on OS remain limited. HER-2 IHC 3+ gastric cancer is characterized by a higher prevalence of PNI and LVI.

Introduction

Gastric cancer is a notable contributor to cancer-related morbidity and mortality worldwide, ranking fifth in terms of incidence and fourth in terms of mortality among all malignancies (1) Patients with gastric cancer in China represent over one-half of the worldwide total. Recent national data from 2022 reveal that gastric cancer has the third highest incidence and mortality rates among all cancer types in the country (2). Despite advancements in diagnosis and treatment, the overall survival (OS) rate remains low, with a 5-year survival rate <50%, dropping to <30% for advanced stages of the disease. Although trastuzumab has improved survival in human epidermal growth factor receptor-2 (HER-2)-positive disease and established anti-HER-2 therapy as a standard of care (3,4), overall outcomes remain poor. HER-2-positive tumors comprise 12-20% of gastric cancer cases (5) and represent a distinct therapeutic entity defined by the efficacy of anti-HER-2 agents. Although HER-2 upregulation portends inferior survival and heightened metastatic potential relative to HER-2-negative disease, existing evidence largely derives from dichotomous comparisons between these subgroups (6-9). Although research on the specific subtype of disease with low HER-2 expression in gastric cancer has increased (10,11), few studies have further differentiated this subgroup of HER-2-positive gastric cancer, leading to a limited understanding of whether variations in clinical characteristics and prognosis exist among patients with HER-2-positive gastric cancer with differing levels of HER-2 protein expression. Clinical data comparing immunohistochemistry (IHC) 2+ and 3+ HER-2-positive tumors, scored according to the Rüschoff/Hofmann grading system (12,13), remain limited. The present study stratified HER-2-positive gastric cancer by protein expression to evaluate its impact on clinicopathological features and survival.

Patients and methods

Patient enrollment and data collection. The present retrospective study examines clinical data from patients with HER-2-positive gastric cancer who underwent a radical gastrectomy at the Zhangzhou Affiliated Hospital of Fujian Medical University (Zhangzhou, China) between March 2017 and March 2023. All patients were of Asian ethnicity and originated from Zhangzhou, Fujian, China. Inclusion criteria necessitated patients to meet the following conditions: Preoperative clinical and imaging assessments indicating stage I-III gastric cancer

Correspondence to: Dr Shujun Lin, Department of Oncology, Zhangzhou Affiliated Hospital of Fujian Medical University, 59 Sheng Li Road West, Xiangcheng, Zhangzhou, Fujian 363000, P.R. China
E-mail: linsj932@163.com

Key words: gastric cancer, clinicopathological features, prognoses, HER-2 protein, disease-free survival

according to the 8th edition of the American Joint Committee on Cancer Tumor-Node-Metastasis (TNM) system (14); successful radical resection (D2 lymphadenectomy and negative resection margins); postoperative pathological confirmation of gastric adenocarcinoma (International Classification of Diseases for Oncology no. C16 M8140/3); HER-2 status determined as IHC 3+ or 2+, with positive fluorescence *in situ* hybridization (FISH) in postoperative pathological specimens; and availability of comprehensive medical records. Exclusion criteria encompassed distant organ metastasis, concurrent malignancies, residual gastric cancer, incomplete medical documentation, or perioperative mortality attributed to surgical complications such as bleeding, septic shock or multiple organ failure. The study was approved by the Institutional Ethics Review Board of Zhangzhou Affiliated Hospital of Fujian Medical University (approval no. 2025LWB426).

Treatment strategy. All patients were treated according to clinical TNM staging. cT1-3N0-1M0 cases proceeded directly to radical gastrectomy, whereas cT3-4N1-3M0 cases received 2-4 cycles of neoadjuvant chemotherapy (fluoropyrimidine- or taxane-based plus platinum: FLOT, FOLFOX, XELOX/SOX or taxane-cisplatin) before surgery. Doses were as follows: Docetaxel, 50 mg/m^2; oxaliplatin, 85-130 mg/m^2; 5-FU, 2,400-2,600 mg/m^2; capecitabine, 1,000 mg/m^2 BID; S-1, 40 mg/m^2 BID; cisplatin, 70-75 mg/m^2; all on day 1, every 2-3 weeks. Adjuvant fluoropyrimidine-based chemotherapy was given to patients with pII (pT1-2N3M0) or pIII (pT3-4aN1-3M0) disease. Perioperative trastuzumab was not routinely used, in line with National Comprehensive Cancer Network, European Society for Medical Oncology, Chinese Society of Clinical Oncology and Japanese Gastric Cancer Association guidelines (15-18).

Detection of HER-2 expression. The expression of HER-2 protein in gastric cancer tissues was assessed using the Elivision two-step immunohistochemical method. The HER-2/neu rabbit monoclonal antibody (4B5; catalog number 790-2991; prediluted) from Roche Diagnostics (Shanghai) Co., Ltd., was applied on a Roche BenchmarkXT automated IHC platform. HER-2 IHC scoring was independently performed by two experienced gastrointestinal pathologists who were blinded to clinical outcomes. Discrepant or equivocal cases were resolved by consensus review using a multi-headed microscope. Immunostaining of HER-2 was categorized as 0, 1+, 2+ or 3+ utilizing the Rüschoff/Hofmann grading system (12,13). Tumor tissues with a score of 2+ underwent fluorescence *in situ* hybridization (FISH) analysis to confirm that they were indeed HER-2$^+$. Scores of 0 were designated as HER-2-negative; 1+ and FISH-non-amplified 2+ cases were classified as low expression; and 3+ and FISH-amplified 2+ cases were considered HER-2-positive. FISH was performed on 4-μm FFPE sections using the Abbott PathVysion HER-2 DNA Probe Kit. Specimens were fixed in 10% neutral buffered formalin at room temperature for 24-48 h before processing and embedding. Deparaffinized sections were post-fixed in 10% neutral buffered formalin for 10 min at room temperature, then processed per the manufacturer's protocol (pretreatment at 80˚C for 30 min, protease digestion at 37˚C for 10 min, overnight hybridization at 37˚C with HER-2/neu and CEP17 probes). Tumor cells were identified on the corresponding H&E sections. At least 20 consecutive nuclei were scored, and the HER-2/CEP17 ratio was calculated. A HER-2/CEP17 ratio ≥2 indicated a HER-2-positive result, while a ratio <1.8 indicated a HER-2-negative result. Samples with ratios between 1.8 and

Table I. Clinical characteristics of patients with gastric cancer.

Characteristics	n (%)
Total	99 (100.0)
Sex	
Male	75 (75.8)
Female	24 (24.2)
Age, years	
<65	41 (41.4)
≥65	58 (58.6)
Differentiation	
Poor	42 (42.4)
Well	57 (57.6)
Lymphovascular invasion	
No	23 (23.2)
Yes	76 (76.8)
TNM stage	
I-II	40 (40.4)
III	59 (59.6)
Tumor invasion	
T1-2	26 (26.3)
T3-4	73 (73.7)
HER-2 expression	
IHC 2+	38 (38.4)
IHC 3+	61 (61.6)
Lauren type	
Intestinal	79 (79.8)
Non-intestinal	20 (20.2)
Tumor size, cm	
<5	60 (60.6)
≥5	39 (39.4)
Perineural invasion	
No	24 (24.2)
Yes	75 (75.8)
Lymph node metastasis	
Negative	39 (39.4)
Positive	60 (60.6)
Neoadjuvant therapy	
No	79 (79.8)
Yes	20 (20.2)
Follow-up outcome	
Recurrence	47 (47.5)
Death	33 (33.3)

TNM stage, Tumor-Node-Metastasis stage; IHC, immunohistochemistry; HER-2, human epidermal growth factor receptor-2.

Table II. Univariate and multivariate Cox regression analysis of disease-free survival.

	Univariate analysis			Multivariate analysis		
Variables	HR (95% CI)		P-value	HR (95% CI)		P-value
Sex (male/female)	1.081	0.516-2.006	0.960			
Age (<65/≥65 years)	1.030	0.577-1.838	0.921			
Differentiation (well/poor)	0.778	0.437-1.384	0.393			
TNM stage (I-II/III)	4.392	2.048-9.421	<0.001	0.759	0.219-2.629	0.664
Lauren type (intestinal/non-intestinal)	1.281	0.637-2.578	0.487			
Tumor size (<5/≥5 cm)	2.372	1.332-4.228	0.003	1.718	0.934-3.159	0.082
Tumor invasion (T1-2/T3-4)	5.277	1.889-14.74	0.002	1.510	0.416-5.477	0.531
Lymph node metastasis (no/yes)	4.842	2.166-10.82	<0.001	3.796	1.140-12.63	0.030
Perineural invasion (no/yes)	9.978	2.417-41.18	0.001	7.592	1.101-52.36	0.040
Lymphovascular invasion (no/yes)	4.113	1.474-11.47	0.007	0.337	0.081-1.397	0.134
HER-2 expression (IHC 2+/IHC 3+)	3.045	1.504-6.167	0.002	2.167	1.038-4.520	0.039

TNM, Tumor-Node-Metastasis; IHC, immunohistochemistry; HR, hazard ratio; CI, confidence interval; HER-2, human epidermal growth factor receptor-2.

2 necessitated the evaluation of an additional 20-40 tumor cells, with a final ratio <1.8 classified as HER-2-negative and ≥2 as HER-2-positive. For cases between 1.8 and 2, a further 80-160 nuclei were counted, and the assessment was independently repeated by at least two observers to reach a consensus.

Statistical analysis. The associations between HER-2 protein expression and clinical characteristics were assessed through χ^2 testing. DFS and OS were analyzed using Kaplan-Meier curves with log-rank testing for between-group comparisons, and univariate and multivariate Cox regression analyses were performed to identify the associations between clinicopathological features and survival outcomes. All statistical analyses were conducted using SPSS 18.0 software (SPSS, Inc.), with P<0.05 used to indicate a statistically significant difference.

Results

Characteristics of the overall population. A total of 99 patients with HER-2-positive gastric cancer were included in the present study (Table I). The age of participants ranged from 32 to 86 years, with a median age of 68 years. The majority of individuals (58.6%) were aged ≥65 years, and the cohort was predominantly male (75.8%). The cohort primarily consisted of patients with intestinal-type gastric cancer (79.8%), well-differentiated tumors (57.6%), T3-4 infiltration depth (73.7%), stage III disease (59.6%), tumor size <5 cm (60.6%), lymph node metastasis (60.6%), LVI (76.8%), and PNI (75.8%). All patients exhibited proficient mismatch repair (pMMR), and 20 patients (20.2%) underwent neoadjuvant therapy. As of the last follow-up in February 2025, recurrence was observed in 47 patients (47.5%), and 33 patients (33.3%) passed away.

Univariate and multivariate analysis of the overall population. Univariate and multivariate analyses were conducted to determine the prognostic risk factors for HER-2-positive gastric cancer. The univariate Cox regression analysis showed that HER-2 expression (P=0.002), tumor size (P=0.003), depth of tumor invasion (P=0.002), presence of lymph node metastasis (P<0.001), TNM stage (P<0.001), PNI (P=0.001) and LVI (P=0.007) were associated with poor DFS. Furthermore, the multivariable Cox regression analysis revealed that HER-2 expression (P=0.039), lymph node metastasis (P=0.030) and PNI (P=0.040) were independent prognostic factors impacting DFS among patients with gastric cancer (Table II). Notably, the univariate Cox regression analysis showed that tumor size (P=0.014), tumor invasion (P=0.010), TNM stage (P=0.002), lymph node metastasis (P=0.009), and PNI (P=0.018) were associated with decreased OS. HER-2 expression (P=0.074) did not exhibit a significant association with OS in patients with gastric cancer. The multivariable Cox regression analysis revealed no independent prognostic factors for OS in these patients (Table III).

Different characteristics of gastric cancer with different HER-2 protein expression levels. HER-2 positivity was identified in 99 patients: 61 (61.6%) were IHC 3+ and 38 (38.4%) were IHC 2+ with FISH confirmation. These 38 FISH-positive cases represent 22.6% (38/168) of the initial IHC 2+ screening cohort (Fig. 1). Based on an analysis of clinicopathological characteristics according to HER-2 expression, it was found that PNI and LVI were more frequent in HER-2 IHC 3+ patients (51/61 and 51/61, respectively) than in IHC 2+ patients (24/38 and 25/38, respectively), with P=0.021 and P=0.041 for the respective comparisons. However, there were no statistically significant differences in terms of sex, age, TNM stage, Lauren classification, tumor size, tumor invasion or lymph node metastasis between the two groups (Table IV).

Survival outcome. The study involved 99 patients, with a median DFS time of 29 months [95% CI, 21-37) and a median OS time of 39 months (95% CI, 36-50). Kaplan-Meier survival

Table III. Univariate and multivariate analysis of overall survival.

	Univariate analysis			Multivariate analysis		
Variables	HR (95% CI)		P-value	HR (95% CI)		P-value
Sex (male/female)	0.948	0.623-1.441	0.801			
Age (<65/≥65 years)	0.829	0.581-1.184	0.303			
Differentiation (well/poor)	1.645	0.911-1.180	0.154			
TNM stage (I-II/III)	4.354	1.680-11.28	0.002	1.699	0.329-8.767	0.526
Lauren type (intestinal/non-intestinal)	1.827	0.848-3.937	0.124			
Tumor size (<5/≥5 cm)	2.364	1.188-4.703	0.014	1.657	0.810-3.390	0.167
Tumor invasion (T1-2/T3-4)	6.611	1.581-27.64	0.010	2.443	0.393-15.19	0.338
Lymph node metastasis (no/yes)	3.239	1.337-7.849	0.009	1.340	0.337-5.332	0.678
Perineural invasion (no/yes)	5.630	1.347-23.53	0.018	1.525	0.241-9.646	0.654
Lymphovascular invasion (no/yes)	2.422	0.850-6.896	0.098			
HER-2expression (IHC 2+/IHC 3+)	2.015	0.934-4.349	0.074			

TNM, Tumor-Node-Metastasis; IHC, immunohistochemistry; HR, hazard ratio; CI, confidence interval; HER-2, human epidermal growth factor receptor-2.

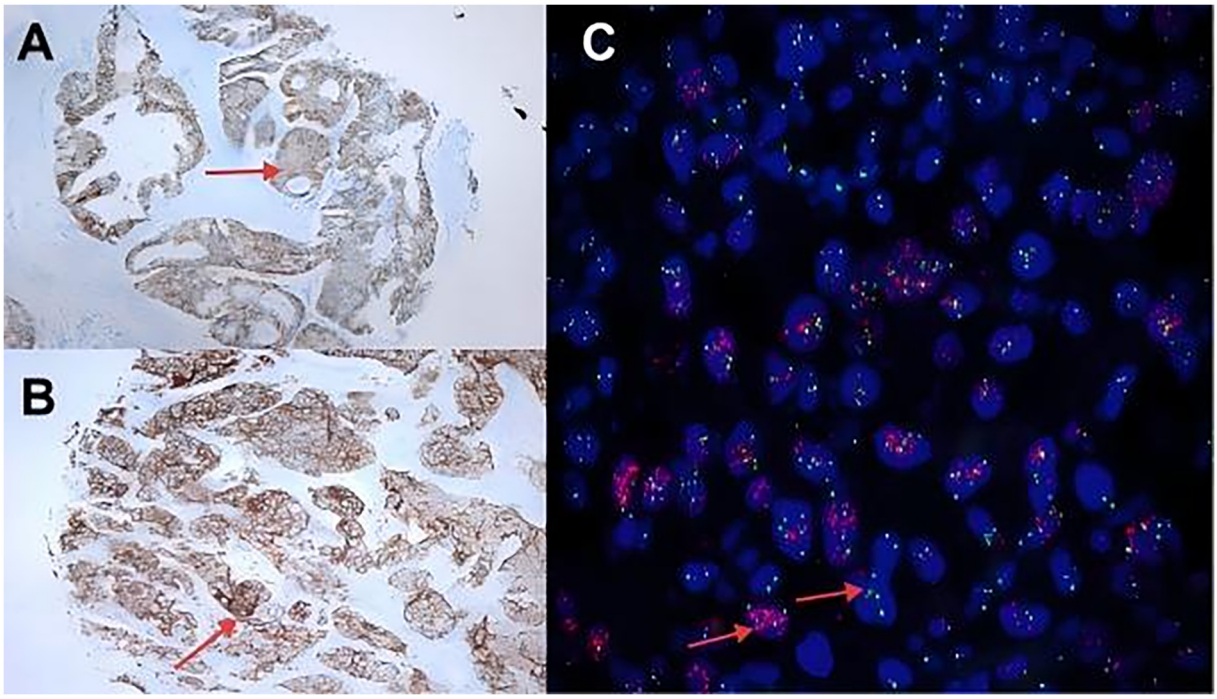

Figure 1. Immunohistochemical staining and fluorescence *in situ* hybridization of HER-2. (A) HER-2 2+ (x200 magnification); (B) HER-2 3+ (x200 magnification); (C) positive HER-2 gene amplification (x1,000 magnification). Arrows indicate HER2 (red) and CEP17 (green) signals. HER-2, human epidermal growth factor receptor-2; CEP17, chromosome enumeration probe 17.

analysis revealed a significantly shorter median DFS time in patients with HER-2 IHC 3+ compared with those in patients with HER-2 IHC 2+ (24 months vs. not reached, P=0.002). The disease-free survival rates at 1, 3 and 5 years post-operation were notably lower in patients with HER-2 IHC 3+ gastric cancer compared with those in patients with HER-2 IHC 2+ gastric cancer (81.96, 43.38 and 28.34% vs. 89.47, 76.02 and 72.02%; P=0.0009). However, the OS rates at 1, 3, and 5 years post-surgery exhibited no differences between patients with HER-2 IHC 3+ gastric cancer and those with HER-2 IHC 2+ gastric cancer (93.84, 63.47 and 52.01% vs. 94.74, 83.59 and 76.43%; P=0.0629) (Fig. 2).

Discussion

The HER-2 gene, located on the long arm of chromosome 17, encodes the ERBB-2 receptor protein situated on the cell membrane (19). This protein belongs to the epidermal growth factor receptor family and regulates various cellular functions, such as differentiation, apoptosis, adhesion, migration and

Table IV. Characteristics of gastric cancer with different HER-2 protein expression.

Characteristics	HER-2 IHC 2+	HER-2 IHC 3+	P-value
Sex, n (%)			0.919
Male	29	46	
Female	9	15	
Age, n (%)			0.912
<65 years	16	25	
≥65 years	22	36	
Differentiation, n (%)			0.713
Poor	17	25	
Well	21	36	
TNM stage, n (%)			
I-II	19	21	0.125
III	19	40	
Lauren type, n (%)			0.232
Intestinal	28	51	
Non-intestinal	10	10	
Tumor size, n (%)			0.093
<5 cm	27	33	
≥5 cm	11	28	
Tumor invasion, n (%)			0.059
T1-2	14	10	
T3-4	24	51	
Lymph node metastasis, n (%)			0.088
No	19	20	
Yes	19	41	
Perineural invasion, n (%)			0.021
No	14	10	
Yes	24	51	
Lymphovascular invasion, n (%)			0.041
No	13	10	
Yes	25	51	
Neoadjuvant therapy, n (%)			
No	33	46	0.168
Yes	5	15	

TNM, Tumor-Node-Metastasis; HER-2, human epidermal growth factor receptor-2; IHC, immunohistochemistry.

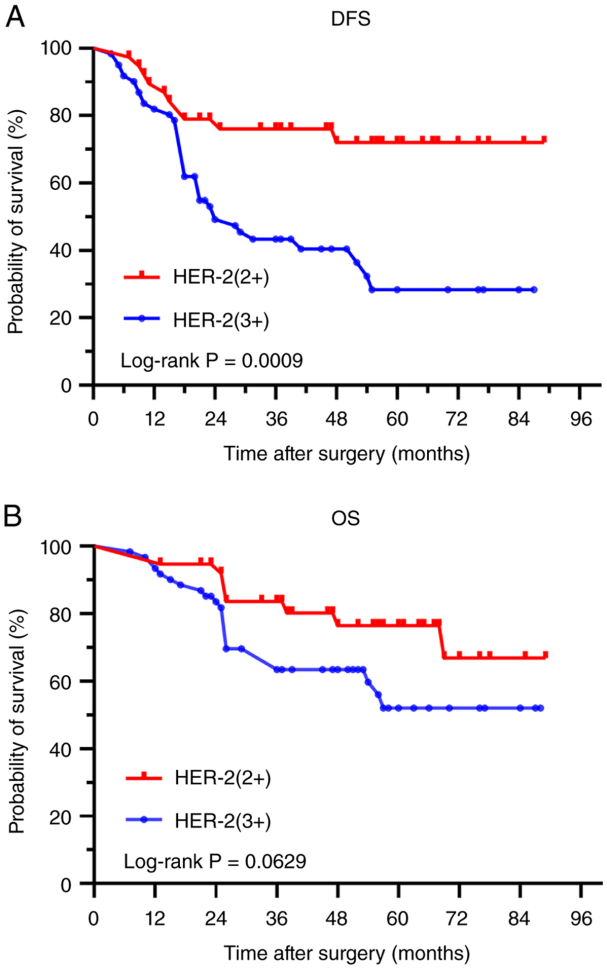

Figure 2. DFS and OS of patients in the HER-2 IHC 2+ and HER-2 IHC 3+ groups. (A) DFS and (B) OS. DFS, disease-free survival; OS, overall survival.

growth, through the tyrosine kinase pathway upon activation (20). Overexpression or amplification of HER-2/ERBB-2 has been observed in breast cancer (21), colorectal cancer (22), lung cancer (23), tumors of the reproductive system (24), and gastric cancer (25).

Upregulation/amplification of HER-2 in breast cancer is associated with an unfavorable prognosis. Similarly, the HER-2 gene is an important prognostic factor for gastric cancer. Aznab *et al* (6) observed a marked difference in survival and mortality rates between patients with HER-2-positive and HER-2-negative gastric cancer. The analysis of HER-2 status and prognostic indicators in 97 patients with gastric cancer revealed a strong association between HER-2 status and the stage of the disease. Zhang *et al* (7) reported that patients with HER-2 upregulation had higher recurrence rates and shorter survival times. Moreover, HER-2 upregulation was identified as an independent prognostic factor following surgery for T3 gastric adenocarcinoma. Kurokawa *et al* (8) conducted a large-scale multicenter study to evaluate the prognostic implications of HER-2 expression in gastric cancer. The research demonstrated that patients with HER-2 positivity had markedly poorer survival outcomes compared with HER-2-negative individuals. Cheng *et al* (26) pooled 30 studies (n=9,945) and showed HER-2 upregulation was associated with worse OS in both resectable (HR, 1.56; 95% CI, 1.32-1.85) and advanced (HR, 1.70; 95% CI, 1.23-2.35) gastric cancer, supporting HER-2 positivity as an unfavorable prognostic biomarker. However, Kung *et al* (9) reported no marked differences in OS or DFS between patients with HER-2-negative and HER-2-positive gastric cancer after surgical resection (n=334), suggesting that HER-2 is not an independent prognostic factor. Notably, HER-2-positive tumors were associated with a higher risk of distant lymphatic recurrence. The present study identified HER-2 expression, tumor size, tumor invasion, lymph node metastasis, TNM stage, PNI and LVI as factors associated

with reduced DFS in patients with HER-2-positive gastric cancer. Importantly, HER-2 expression, lymph node metastasis and PNI were identified as independent prognostic factors influencing DFS in patients with gastric cancer, which is consistent with the findings of Zhang *et al* (27). Additionally, the present study indicated that tumor size, tumor invasion, lymph node metastasis, PNI and LVI were associated with reduced OS time; however, no factors, including HER-2 protein expression, were independent prognostic factors in HER-2-positive gastric cancer. This result is in line with previous research by Fisher *et al* (28). Although individual studies report inconsistent prognostic implications of HER-2 in gastric cancer, most investigations and meta-analyses support HER-2 positivity as a marker of poor survival (7-9,26,27). Endogenous HER-2 upregulation drives an aggressive phenotype, largely through preferential formation of HER2/HER3 heterodimers that constitutively activate the PI3K/Akt and MAPK pathways, thereby promoting proliferation, angiogenesis, epithelial-mesenchymal transition and chemoresistance (29).

HER-2 status in clinical practice is primarily assessed by IHC and FISH. Although FISH is considered the gold standard owing to its high sensitivity, specificity and reproducibility, its widespread use is limited by technical complexity, specialized equipment requirements and high cost. IHC is a commonly used method to evaluate HER-2 protein expression due to its cost-effectiveness, rapid detection, and broad applicability in gastric and breast cancer (30,31). In the present study, the IHC method was employed for the initial screening of HER-2-positive gastric cancer. For cases with ambiguous IHC interpretation results, the FISH method was subsequently utilized for confirmation, which not only reduced testing costs but also enhanced the accuracy of the results. For the first time, HER-2-positive gastric cancer was stratified by protein expression level to evaluate its association with clinicopathological features and survival. These findings provide evidence to guide prognostic assessment and targeted therapy in this patient population.

In the present study, HER-2 protein expression was not significantly associated with sex, age, tumor differentiation, TNM stage, Lauren classification, tumor size, depth of invasion or lymph node status. However, HER-2-positive tumors, particularly IHC 3+ cases, were more frequently characterized by perineural and lymphovascular invasion. Although the current TNM classification does not include LVI and PNI, these factors are widely recognized by researchers as being linked to the aggressive biological behavior of tumors (32-34). LVI refers to the invasion, destruction or presence of tumor cells within the lumen of small blood vessels and lymphatic vessels in and around the tumor area under microscopic examination (35). A previous study found that LVI is a prognostic factor for gastric cancer. Positive LVI in patients with gastric cancer was linked to malignancy, deeper invasion, lymph node metastasis and a worse prognosis (36). Wu *et al* (37) showed that LVI correlates with deeper invasion, greater nodal burden and lower overall survival rate. PNI, an independent dissemination pathway, is a well-established predictor of early recurrence and poor prognosis in gastric cancer. Patients with gastric cancer positive for PNI have higher rates of postoperative local recurrence and lower OS rates (38). Sun *et al* (39) reported that, in patients with locally advanced gastric cancer receiving neoadjuvant therapy followed by surgery, PNI and lymph node metastasis were independent prognostic factors. These findings underscore that both LVI and PNI are key determinants of survival in gastric cancer. Patients with both perineural and lymphovascular invasion in gastric cancer face an increased risk of lymph node metastasis and a poorer prognosis (34). Studies show that nerves, together with blood vessels and lymphatic vessels, collectively constitute the external microenvironment for tumor growth; their interaction with tumor cells promotes tumorigenesis and progression (40,41). A study also showed that VEGF expression is upregulated in gastric cancer tissues. By promoting angiogenesis and generating structurally immature vessels with defective basement membranes, VEGF facilitates tumor cell intravasation and hematogenous dissemination (42). PNI is currently considered a special mode of tumor metastasis; it involves complex interactions between tumor cells, stromal cells, surrounding immune cells and nerve fibers (40,43). Current understanding of the biological mechanisms underlying LET/PNI in gastric cancer is limited, and the interaction with the HER-2 gene is even more poorly understood. This gap highlights the imperative for future, in-depth research to elucidate these clinically important mechanisms.

Patients with HER-2 IHC 3+ gastric cancer may exhibit unfavorable biological characteristics associated with increased recurrence and risk of metastasis. The present study found that HER-2 IHC 3+ patients had significantly shorter median DFS times compared with HER-2 2+ patients. Additionally, the DFS rates at 1, 3 and 5 years post-surgery were notably lower for patients with HER-2 3+ gastric cancer compared with patients with HER-2 2+ gastric cancer, indicating a heightened vulnerability to postoperative recurrence and metastasis. Although 1-, 3- and 5-year OS rates did not differ significantly between patients with HER-2 IHC 3+ and 2+ gastric cancer, survival trends suggested a potential disadvantage for HER-2 IHC 3+ cases, a pattern that may become more pronounced with extended follow-up.

In conclusion, patients with HER-2 IHC 3+ gastric cancer demonstrate elevated rates of post-surgical recurrence and metastasis, resulting in a reduced OS time. It is advisable to maintain vigilant monitoring and implement intensified postoperative surveillance protocols for this patient group to detect signs of tumor recurrence and metastasis promptly. Furthermore, the potential efficacy of anti-HER-2 therapy in enhancing survival outcomes among these individuals warrants additional investigation.

Limitations include the single-center, retrospective design and selection of only surgically resectable cases, limiting generalizability. Potential bias from HER-2 heterogeneity across Lauren subtypes and the absence of dynamic HER-2 monitoring may further affect interpretation. Larger, multi-center prospective studies with serial HER-2 assessments are needed.

In conclusion, HER-2 is a significant negative prognostic factor associated with poorer DFS, although data on OS remain limited. HER-2 IHC 3+ gastric cancer exhibits a higher prevalence of PNI and LVI, as well as an elevated risk of postoperative recurrence and metastasis.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Startup Fund for Scientific Research, Fujian Medical University (grant no. 2022QH1276).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HS contributed substantially to study conception, design, data acquisition, analysis, and interpretation, and wrote the main manuscript. SL conceived the research idea and critically revised the manuscript. HS and HH confirm the authenticity of all the raw data. XX contributed to data acquisition through active participation in both data analysis and interpretation, and co-wrote the first draft. HH prepared the figures and tables, involving data selection and organization for visual presentation, and contributed to manuscript revision. HH was also actively engaged in the interpretation of pathological data, playing a crucial role in elucidating the pathological findings and their correlation with the clinical data. All authors commented on previous versions of the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

All procedures involving human participants were performed according to the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Institutional Research Ethics Committee of Zhangzhou Hospital Affiliated with Fujian Medical University (approval no. 2025LWB426). As a retrospective study, the requirement for informed consent was waived by the ethics committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
2. Xia C, Dong X, Li H, Cao M, Sun D, He S, Yang F, Yan X, Zhang S, Li N and Chen W: Cancer statistics in China and United States, 2022: Profiles, trends, and determinants. Chin Med J (Engl) 135: 584-590, 2022.
3. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, Lordick F, Ohtsu A, Omuro Y, Satoh T, *et al*: Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. Lancet 376: 687-697, 2010.
4. Boku N: HER2-positive gastric cancer. Gastric Cancer 17: 1-12, 2014.
5. Meric-Bernstam F, Johnson AM, Dumbrava E, Raghav K, Balaji K, Bhatt M, Murthy RK, Rodon J and Piha-Paul SA: Advances in HER2-targeted therapy: Novel agents and opportunities beyond breast and gastric cancer. Clin Cancer Res 25: 2033-2041, 2019.
6. Aznab M, Maleksabet D, Khazaei S, Khazaei M and Rezaei M: The role of human epidermal growth factor receptor (HER2/neu) in the prognosis of patients with gastric cancer. Asian Pac J Cancer Prev 20: 1989-1994, 2019.
7. Zhang Z, Wang B, Huang G, Wang R, Song J, Lin S, Wang W, Jiang Y, Huang Q and Wang L: Overexpression of HER-2 protein is a high-risk factor for patients with surgically-resected stage T3 gastric adenocarcinoma. Clin Lab 63: 115-125, 2017.
8. Kurokawa Y, Matsuura N, Kimura Y, Adachi S, Fujita J, Imamura H, Kobayashi K, Yokoyama Y, Shaker MN, Takiguchi S, *et al*: Multicenter large-scale study of prognostic impact of HER2 expression in patients with resectable gastric cancer. Gastric Cancer 18: 691-697, 2015.
9. Kung CY, Huang KH, Lin SC, Hung YP, Chen MH, Chao Y, Lo SS, Wu CW, Li AFY, Fang WL and Lan YT: Clinicopathologic features and prognosis of HER2-positive gastric cancer. Int Surg 108: 68-77, 2024.
10. Narita Y, Mizuno T, Ishizuka Y, Sakakida T, Masuishi T, Taniguchi H, Kadowaki S, Honda K, Ando M, Tajika M, *et al*: Clinicopathological and prognostic significance of HER2-low expression in advanced gastric cancer: A retrospective observational study. Oncologist 30: oyae328, 2025.
11. Gokon Y, Nakashima Y, Ohki Y, Ogino T, Hatoyama K, Shimizu K, Kashiwadate T, Katsura K, Abe T and Sato K: Prognostic significance of low HER2 expression in gastric cancer: A retrospective, single-center analysis. BMC Cancer 24: 1081, 2024.
12. Hofmann M, Stoss O, Shi D, Büttner R, van de Vijver M, Kim W, Ochiai A, Rüschoff J and Henkel T: Assessment of a HER2 scoring system for gastric cancer: Results from a validation study. Histopathology 52: 797-805, 2008.
13. Rüschoff J, Dietel M, Baretton G, Arbogast S, Walch A, Monges G, Chenard MP, Penault-Llorca F, Nagelmeier I, Schlake W, *et al*: HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. Virchows Arch 457: 299-307, 2010.
14. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, *et al*: AJCC cancer staging manual. 8th ed. New York: Springer; 2017. 1032 p. ISBN 978-3-319-40617-6.
15. Ajani JA, D'Amico TA, Almhanna K, Bentrem DJ, Chao J, Das P, Denlinger CS, Fanta P, Farjah F, Fuchs CS, *et al*: Gastric cancer, version 3.2016, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 14: 1286-1312, 2017.
16. Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D; ESMO Guidelines Committee: Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 27(suppl 5): v38-v49, 2016.
17. Chinese Society of Clinical Oncology (CSCO) Guidelines Working Committee. Guidelines of Chinese Society of Clinical Oncology (CSCO): Primary Gastric Cancer. 2017.V1. Beijing: People's Medical Publishing House; 2017. ISBN 978-7-117-24380-3. https://www.pmphmall.com/gdsdetail/609686-284313.
18. Japanese Gastric Cancer Association: Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer 20: 1-19, 2017.
19. Wang T, Amemiya Y, Henry P, Seth A, Hanna W and Hsieh ET: Multiplex ligation-dependent probe amplification can clarify HER2 status in gastric cancers with 'Polysomy 17'. J Cancer 6: 403-408, 2015.
20. Sekaran A, Kandagaddala RS, Darisetty S, Lakhtakia S, Ayyagari S, Rao GV, Rebala P, Reddy DB and Reddy DN: HER2 expression in gastric cancer in Indian population-an immunohistochemistry and fluorescence in situ hybridization study. Indian J Gastroenterol 31: 106-110, 2012.
21. Dempsey N, Sandoval A and Mahtani R: Metastatic HER2-positive breast cancer: Is there an optimal sequence of therapy?. Curr Treat Options Oncol 24: 1120-1137, 2023.

22. Benli Y, Arikan H and Akbulut-Caliskan O: HER2-targeted therapy in colorectal cancer: A comprehensive review. Clin Transl Oncol 27: 3607-3624, 2025.
23. Odintsov I, Makarem M, Nishino M, Bachert SE, Zhang T, LoPiccolo J, Paweletz CP, Gokhale PC, Ivanova E, Saldanha A, *et al*: Prevalence and therapeutic targeting of high-level ERBB2 amplification in NSCLC. J Thorac Oncol 19: 732-748, 2024.
24. Edjtemaei R, Nili F, Jahanzad I, Ameli F and Ghasemi D: HER-2 overexpression in female genital tract clear cell carcinomas: Evaluation of different scoring guidelines, clinicopathological features and prognostic impact. Ann Diagn Pathol 66: 152184, 2023.
25. Matsusaka S, Nashimoto A, Nishikawa K, Miki A, Miwa H, Yamaguchi K, Yoshikawa T, Ochiai A, Morita S, Sano T, *et al*: Clinicopathological factors associated with HER2 status in gastric cancer: Results from a prospective multicenter observational cohort study in a Japanese population (JFMC44-1101). Gastric Cancer 19: 839-851, 2016.
26. Cheng J, Cai M, Wang G and Tao K: HER2 becomes a novel survival biomarker for gastric cancer patients: A pooled analysis. Ther Adv Med Oncol 16: 12716649, 2024.
27. Zhang X, Fu M, Li Z, Shen F, Chen H, Wang Z and Zheng J: The expression and prognostic predictive value of PD-L2 in patients undergoing radical gastric cancer surgery. Future Sci OA 11: 2526993, 2025.
28. Fisher SB, Fisher KE, Squires MR III, Patel SH, Kooby DA, El-Rayes BF, Cardona K, Russell MC, Staley CA III, Farris AB III and Maithel SK: HER2 in resected gastric cancer: Is there prognostic value?. J Surg Oncol 109: 61-66, 2014.
29. Gravalos C and Jimeno A: HER2 in gastric cancer: A new prognostic factor and a novel therapeutic target. Ann Oncol 19: 1523-1529, 2008.
30. Sakaguchi M, Maebayashi T, Aizawa T and Ishibashi N: Whole-brain radiation therapy for breast cancer patients with dural metastasis without concomitant brain metastasis and leptomeningeal metastasis. Anticancer Res 38: 6405-6411, 2018.
31. The Society of Breast Cancer China Anti-Cancer Association; Breast Oncology Group of the Oncology Branch of the Chinese Medical Association: Guidelines and Specifications for the Diagnosis and Treatment of Breast Cancer in China (2024 Edition). Chinese J Cancer 33: 1092-1187, 2023.
32. Kang JH, Son IT, Kim BC, Park JH, Kim JY and Kim JW: Recurrence-free survival outcomes based on novel classification combining lymphovascular invasion, perineural invasion, and T4 status in stage II-III colon cancer. Cancer Manag Res 14: 2031-2040, 2022.
33. Sun Q, Liu T, Liu P, Luo J, Zhang N, Lu K, Ju H, Zhu Y, Wu W, Zhang L, *et al*: Perineural and lymphovascular invasion predicts for poor prognosis in locally advanced rectal cancer after neoadjuvant chemoradiotherapy and surgery. J Cancer 10: 2243-2249, 2019.
34. Zhang F, Chen H, Luo D, Xiong Z, Li X, Yin S, Jin L, Chen S, Peng J and Lian L: Lymphovascular or perineural invasion is associated with lymph node metastasis and survival outcomes in patients with gastric cancer. Cancer Med 12: 9401-9408, 2023.
35. Li P, He H, Zhu C, Ling YH, Hu WM, Zhang XK, Luo RZ, Yun JP, Xie D, Li YF and Cai MY: The prognostic significance of lymphovascular invasion in patients with resectable gastric cancer: A large retrospective study from Southern China. BMC Cancer 15: 370, 2015.
36. Fujikawa H, Koumori K, Watanabe H, Kano K, Shimoda Y, Aoyama T, Yamada T, Hiroshi T, Yamamoto N, Cho H, *et al*: The clinical significance of lymphovascular invasion in gastric cancer. In Vivo 34: 1533-1539, 2020.
37. Wu L, Liang Y, Zhang C, Wang X, Ding X, Huang C and Liang H: Prognostic significance of lymphovascular infiltration in overall survival of gastric cancer patients after surgery with curative intent. Chin J Cancer Res 31: 785-796, 2019.
38. Zhao B, Lv W, Mei D, Luo R, Bao S, Huang B and Lin J: Perineural invasion as a predictive factor for survival outcome in gastric cancer patients: A systematic review and meta-analysis. J Clin Pathol 73: 544-551, 2020.
39. Sun Y, Yang L, Wang C, Zhao D, Cai J, Li W, Zhang W, Huang J and Zhou A: Prognostic factors associated with locally advanced gastric cancer patients treated with neoadjuvant chemotherapy followed by surgical resection. Oncotarget 8: 75186-75194, 2017.
40. Lv C, Zhou T, Chen W, Yin XD, Yao JH and Zhang YF: Preliminary study correlating CX3CL1/CX3CR1 expression with gastric carcinoma and gastric carcinoma perineural invasion. World J Gastroenterol 20: 4428-4432, 2014.
41. Gao P, Zhou G, Zhang Q, Su ZX, Zhang TG, Xiang L, Wang Y, Zhang SL and Mu K: Lymphangiogenesis in gastric carcinoma correlates with prognosis. J Pathol 218: 192-200, 2009.
42. Tao H, Qin L, Lin Y and Wang R: Expression of vascular endothelial growth factor and its prognostic significance in gastric carcinoma. World J Gastroenterol 2: 128-130, 1996.
43. Amit M, Na'ara S and Gil Z: Mechanisms of cancer dissemination along nerves. Nat Rev Cancer 16: 399-408, 2016.