Prognostic value of HER2 expression in cervical adenocarcinoma: A retrospective cohort study

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Abstract. Human epidermal growth factor receptor 2 (HER2) is an important therapeutic target in various types of cancer, although the prognostic value and therapeutic potential of HER2 in cervical adenocarcinoma are still underexplored. The present study aimed to examine the association between HER2 expression levels and prognosis in cervical adenocarcinoma, offering new insights into targeted therapies for HER2-expressing cervical adenocarcinoma. A total of 179 patients with cervical cancer who received surgery were included, and HER2 status in surgical specimens of the included patients were assessed using two classification methods: Immunohistochemistry (IHC) alone and traditional combined IHC/fluorescence *in situ* hybridization (FISH). IHC alone was used to categorize patients into the HER2 zero expression (IHC 0) and HER2 expression (IHC 1+, 2+ and 3+) groups, while traditional combined IHC/FISH classified the HER2 expression as negative (IHC 0 and 1+ or IHC 2+/FISH-) or positive (IHC 3+ or IHC 2+/FISH+). Kaplan-Meier survival analysis and log-rank tests were used to assess the patients' survival prognosis. A Cox proportional hazards regression model was used to identify independent prognostic factors. The HER2 expression rate was 44.1% (79/179) according to IHC alone, while 5.0% (9/179) were classified as HER2-positive according to the traditional method. HER2 expression was significantly associated with advanced International Federation of Gynecology and Obstetrics stages, higher rates of lymph node metastasis, vascular or perineural invasion, elevated cancer antigen 125 levels and increased recurrence rate (P<0.05). Moreover, HER2 expression was significantly associated with shorter progression-free survival (PFS) time [51.02±2.75 vs. 56.01±2.22 months; hazard ratio (HR), 0.559; 95% confidence interval (CI), 0.313-0.998; P=0.049]. Additionally, programmed death-ligand 1 expression levels were significantly higher in HER2-expressing patients who died (P=0.039). When HER2 status was assessed using the traditional combined IHC/FISH method, HER2 positivity was significantly associated with poorer PFS time (36.44±7.85 vs. 55.17±1.78 months; HR, 0.125; 95% CI, 0.03033-0.5156; P=0.004). In conclusion, classification of HER2 status in patients with cervical adenocarcinoma using IHC alone may provide a promising method for predicting patient outcomes and optimizing therapeutic strategies to improve treatment efficacy.

Introduction

Cervical cancer is the fourth most prevalent malignancy among women globally (1). Adenocarcinoma, which accounts for 10-25% of cervical cancer cases, typically exhibits distinct cytological features on cytology smears. These include uniform polygonal cells arranged in flat sheets and glandular structures, granular cytoplasm, indistinct cell boundaries and round to oval nuclei with prominent nucleoli (2). Moreover, due to its higher propensity for metastasis and poorer prognosis, adenocarcinoma also presents significant challenges in patient management (3,4). The current treatment strategy for cervical adenocarcinoma primarily involves surgery for early stage disease and chemoradiotherapy for advanced-stage disease. The overall 5-year survival rate for early stage cases is 70-90%, while the survival rate for advanced-stage cases is typically <20% (5). Despite advancements in immunotherapy that have provided therapeutic breakthroughs for patients with cervical cancer, the prognosis of cervical adenocarcinoma remains poor (6). There is an urgent need to explore new targeted therapies to improve patient survival. Therefore, it is necessary to study new biomarkers to improve prognostic accuracy and promote the further development of targeted therapies.

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Abbreviations: HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization; PD-L1, programmed death-ligand 1; ADC, antibody-drug conjugate; PFS, progression-free survival; OS, overall survival

Key words: HER2, cervical adenocarcinoma, IHC, prognosis

Human epidermal growth factor receptor 2 (HER2), a member of the EGFR family, serves a pivotal role in tumor growth and progression by inhibiting apoptosis and promoting angiogenesis and metastasis (7). HER2 upregulation occurs in various types of cancer (8), and numerous studies (9-12) have indicated that HER2 protein expression levels are a poor prognostic factor in malignant tumors and are associated with tumor sensitivity to chemotherapy and biological therapy. Particularly in breast and gastric cancer, HER2 has been extensively studied and successfully applied as a therapeutic target in clinical practice (13-15). However, in cervical cancer, especially in the subtypes of cervical adenocarcinoma and squamous cell carcinoma, the role and clinical significance of HER2 remains controversial. Studies (16,17) have shown that HER2 expression levels are higher in cervical adenocarcinoma compared with those in squamous cell carcinoma, particularly in advanced and high-risk patients, suggesting that HER2 may be involved in the pathological progression of adenocarcinoma. Other studies (17-19) have suggested that HER2 could be a valuable therapeutic target in cervical adenocarcinoma, especially for patients with advanced disease or disease progression. Although some studies (20-22) have found that HER2 expression levels are associated with a poor prognosis, significant variations in HER2 expression levels and prognostic significance across studies could be attributed to factors such as sample size, and detection methods such as immunohistochemistry (IHC)/fluorescence *in situ* hybridization (FISH). Moreover, in previous studies (17,23), the expression of HER2 in cervical adenocarcinoma was low according to the traditional assessment method of combined IHC/FISH, and its association with prognosis in cervical adenocarcinoma remains unclear.

In recent years, anti-HER2-drug conjugates (ADCs) have garnered attention for their ability to target HER2-expressing cancer cells and improve therapeutic outcomes (24). The prevalence of IHC 1+ and 2+/FISH-HER2 expression in gynecological tumors has become an important focus for clinicians. Research has demonstrated that in the C018 cervical cancer cohort study, the range of patients benefiting from RC48 anti-HER2 therapy expanded to include IHC 1+, 2+ and 3+ groups. Notably, an objective response rate (ORR) of up to 50% was observed in IHC 1+ patients (25). This underscores the importance of more precise classification of HER2 expression levels, which is essential for guiding personalized treatment strategies for cervical cancer.

At present, traditional HER2 detection methods have the disadvantage of low detection rates, which limits treatment options for HER2 patients with low expression and thus affects prognosis (26). Standalone IHC could provide the sensitivity of HER2 status detection, with the advantages of being fast, simple, cost-effective and highly specific, making it more effective in assessing clinical prognosis, and will help more accurately evaluate the therapeutic effects of HER2-targeted drugs (27). However, there is a lack of research investigating the association between standalone IHC and clinical prognosis. The present study aimed to investigate HER2 expression levels in patients with cervical adenocarcinoma, with a particular focus on IHC 1+ and 2+/FISH-cases, and to evaluate its prognostic significance, as well as its association with programmed death-ligand 1 (PD-L1) expression levels.

Patients and methods

Patients. The present study retrospectively analyzed HER2 status via IHC in 179 female patients with cervical adenocarcinoma undergoing radical surgery (including 10 patients who received neoadjuvant chemotherapy before surgery) between January 2018 and November 2020 at Zhejiang Cancer Hospital (Hangzhou, China). The present study was conducted in accordance with the Declaration of Helsinki with the approval of the Medical Ethics Committee of Zhejiang Cancer Hospital (approval no. IRB-2023-656), and all patients provided written informed consent for publication of their data.

Patients included in the present study were required to meet the following criteria: Aged between 18 and 70 years, with pathologically confirmed cervical adenocarcinoma, who received radical surgery, with complete clinical and pathological data, and who signed an informed consent form at admission (which included consent for their samples to be used for research). Exclusion criteria included patients lost to follow-up or those with insufficient tissue samples for HER2 testing.

Data collection and follow up. Patients' age, clinical stage, pathological diagnosis, tumor size, lymph vascular space invasion (LVSI), extent of invasion, lymph node metastasis status, whether neoadjuvant therapy was administered before surgery, HER2 expression status, pre-treatment carbohydrate antigen 19-9 (CA19-9), pre-treatment cancer antigen 125 (CA-125), recurrence status, recurrence time, survival status, last follow-up time and time of death were recorded. Progression-free survival (PFS) and overall survival (OS) were followed up through outpatient visits and telephone interviews. The data cut-off date was June 2024.

Clinical characteristics [including age, International Federation of Gynecology and Obstetrics (FIGO) stage, tumor size, depth of invasion, vascular invasion or perineural invasion, pre-treatment CA19-9 values and pre-treatment CA-125 values] and prognostic factors (metastasis, recurrence and survival data) were analyzed in the IHC alone group. Additionally, the expression ratio between PD-L1 and HER2 in patients with cervical adenocarcinoma who died was analyzed. OS and PFS were measured from pathological diagnosis to death from any cause and to the first disease progression, respectively. The clinical data were obtained from the medical records of Zhejiang Cancer Hospital and tissue samples were obtained from the pathology archives of the hospital.

HER2 status analysis. According to the guidelines (23) for HER2 testing in gastric cancer and other malignancies, HER2 1+ and HER2 2+/FISH- are defined as negative, while HER2 2+/FISH+ and HER2 3+ are defined as positive. Targeted therapy is recommended for patients with HER2-positive status (28). To broaden the scope of treatment and improve patient prognosis, the present study population was divided into groups. Patient tumor samples were tested using IHC and FISH methods. The detection results were used to classify patients by HER2 status into the following groups based on IHC alone and the traditional combined IHC/FISH method: i) IHC alone, patients were divided into the HER2 zero expression (IHC 0) group and the HER2 expression (IHC 1+, 2+ and 3+) group;

and ii) traditional combined IHC/FISH classification, patients were categorized as HER2-negative (IHC 0, IHC 1+ or IHC 2+/FISH-) or HER2-positive (IHC 3+ or IHC 2+/FISH+).

IHC. Paraffin-embedded samples were fixed with 10% neutral formalin for 24 h at room temperature. IHC was performed on 3-μm thick sections obtained from formalin-fixed, paraffin-embedded tissue blocks. The immunohistochemistry images were captured using a light microscope. PD-L1 and HER2 were targeted using specific primary antibodies. The gold standard for detecting PD-L1 expression is IHC (29), which utilizes the high specificity of antibody-antigen binding to display the location and intensity of antigen-antibody binding through histochemical techniques, thereby detecting the expression levels of PD-L1 on the surface of tumor cells or immune cells. In the present study, PD-L1 expression levels were assessed using slides stained for PD-L1 22C3 (catalog number M3666; Dako, Agilent Technologies, Inc.) and the combined positive score (CPS) method was applied for evaluation. The procedure was performed according to the manufacturer's instructions. CPS was calculated as: (Number of PD-L1-positive tumor cells + number of PD-L1-positive immune cells)/total number of viable tumor cells x100. A CPS threshold of ≥1 was used to determine PD-L1 positivity (30). CPS=0 indicated that PD-L1 expression was negative (Fig. S1) with no brown staining observed in tumor cells or immune cells. By contrast, when PD-L1 was positively expressed in tumor cells or immune cells, partial brown staining was observed (Fig. S2). This indicates a certain level of PD-L1 expression in the tumor microenvironment, providing a reference for the evaluation of immunotherapy. In addition, the present study adhered to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines (31) for gastric cancer to establish HER2 IHC scoring criteria. These criteria were defined as follows: 0, no staining or <10% of tumor cell membranes stained; 1+, ≥10% of tumor cells with faint or barely perceptible membrane staining, with only part of the membrane stained; 2+, ≥10% of tumor cells with weak to moderate complete, basolateral or lateral membrane staining; and 3+, ≥10% of tumor cells with strong complete, basolateral or lateral membrane staining. Based on HER2 expression scoring standards in gastric and gastroesophageal adenocarcinoma, HER2 staining was categorized as: 0, negative; 1+, negative; 2+, equivocal; and 3+, positive (32). Cases with equivocal HER2 upregulation (2+) results were further analyzed using FISH (33).

FISH. FISH tests were conducted using the Vysis PathVysion HER2 DNA Probe Kit (Abbott Pharmaceutical Co. Ltd.), according to the manufacturer's protocol. The dual-color FISH method, involving two labeled DNA probes, was performed on sections cut from the same tissue microarray block. The LSI HER2 probe, which spans the entire HER2 gene, was labeled in Spectrum Orange, while the CEP17 probe (chromosome-17 centromere probe for chromosome 17 enumeration) was labeled in Spectrum Green. These probes hybridized to the a satellite DNA located at the centromere of chromosome 17 (17p11.1-q11.1). For analysis, two separate fields comprising ≥20 cells each were counted. The HER2 signal ratio was calculated by tallying red (HER2 gene) and green (chromosome 17) signals in preselected tumor areas. Tumor cells from the same sites analyzed by IHC were typically assessed for signal counts. Images were captured using an ECLIPSE 80i (Nikon Corporation) fluorescence microscope with a PlanFluor (Nikon Corporation) 100X oil objective and a double band-pass filter enabling simultaneous visualization of green and red colors.

IHC and FISH interpretation and quality control. Representative images of different levels of HER2 expression using IHC and FISH are shown in Figs. 1 and 2, respectively, and data presented in Tables I and II. For quality control of IHC/FISH analysis, two pathologists with >5 years of experience independently interpreted the results. In cases of disagreement and the inability to reach a consensus, a third senior reviewer made the final judgment.

Statistical analysis. Statistical analyses were conducted using SPSS (version 25; IBM Corp.). Clinical and pathological characteristics were compared using the χ^2 test or Fisher's exact test as appropriate. Survival analysis was performed using the Kaplan-Meier method and comparisons were made using log-rank tests. Multivariate analysis was performed using the Cox proportional hazards regression model to identify independent prognostic factors. All reported P-values were two-sided. P<0.05 was considered to indicate a statistically significant difference.

Results

HER2 expression levels in cervical adenocarcinoma. The present study included 179 patients with cervical adenocarcinoma who underwent radical surgery, and HER2 expression was evaluated through IHC and FISH results (Figs. 1 and 2). A novel classification method specifically designed to evaluate HER2 expression using IHC alone was utilized (Fig. 3). In the IHC alone group, the expression rates of IHC 1+, 2+ and 3+ were 27.4% (49/179), 12.8% (23/179) and 3.9% (7/179), respectively, which indicated that 44.1% of samples exhibited HER2 expression. In the traditional combined IHC/FISH method group, there were 7 HER2 3+ cases and 23 HER2 2+ cases (data not shown). After FISH testing, only 2 of the 23 cases were FISH-positive. Therefore, the total number of HER2-positive patients was 9, accounting for only 5% of included patients.

Association of HER2 expression and clinical factors in the IHC group. There were 100 patients with HER2 zero expression and 79 patients with HER2 expression. As shown in Table III, the age distribution between the HER2 zero expression group and the HER2 expression group was generally similar and showed no statistically significant difference among patients with cervical adenocarcinoma who underwent radical surgery. However, the mean age at onset was 49.75±11.40 years for patients in the HER2 zero expression group and 47.97±10.72 years for those in the HER2 expression group among patients with cervical adenocarcinoma who underwent radical surgery (Table III). HER2 expression was significantly associated with advanced FIGO stages (P=0.001) and higher recurrence rates (P=0.032). Among the

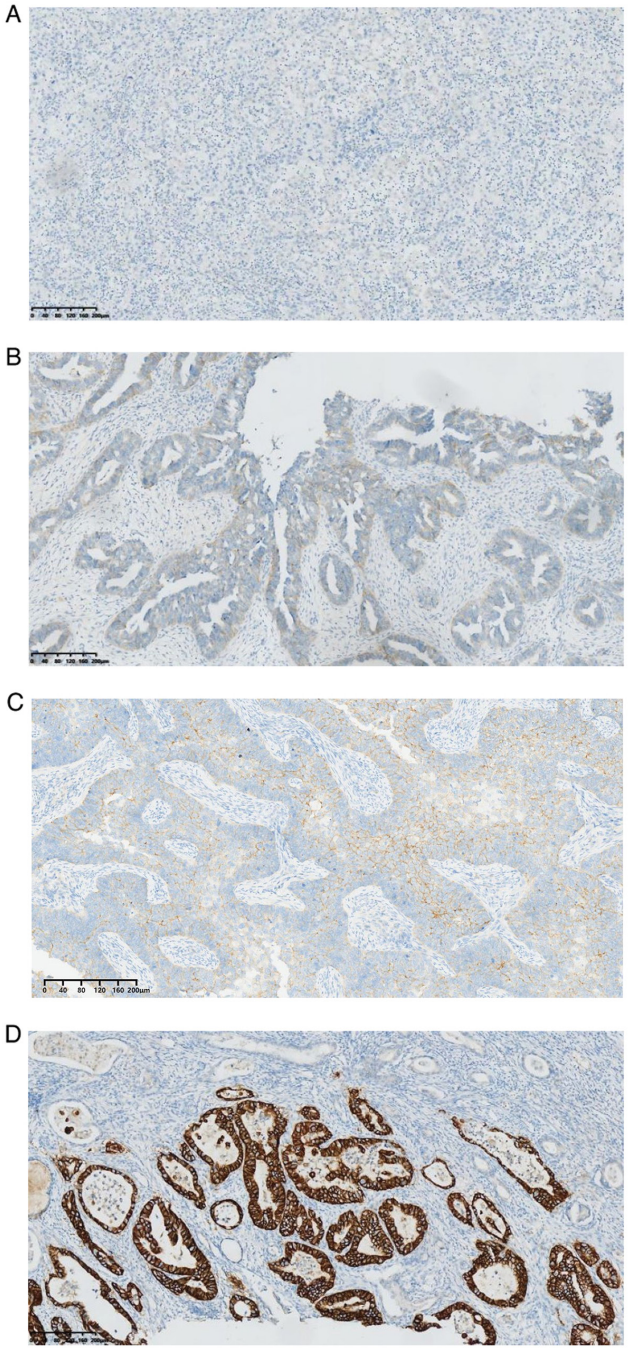

Figure 1. Representative images of human epidermal growth factor receptor 2 status assessed by immunohistochemistry for scores (A) 0, (B) 1+, (C) 2+ and (D) 3+. Scale bar, 200 μm.

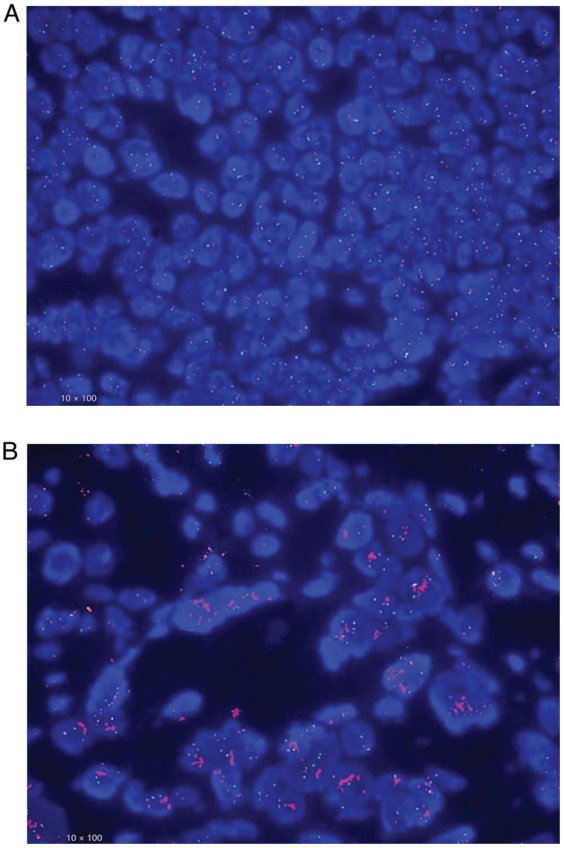

Figure 2. Human epidermal growth factor receptor 2 status assessed by fluorescence *in situ* hybridization for (A) signal ratio <2.0 and (B) signal ratio ≥2.0.

tumor markers, abnormal pre-treatment CA-125 levels were significantly associated with HER2 expression (P=0.023), whereas pre-treatment CA19-9 levels did not reach statistical significance (P=0.15).

Patients in the HER2 zero expression group exhibited a survival rate of 57.7% and a mortality rate of 46.7%, compared with a survival rate of 42.3% and a mortality rate of 53.3% for the HER2 expression group, suggesting a trend towards improved prognosis for patients without HER2 expression, although this was not statistically significant (P=0.266). When excluding the 10 patients who had received neoadjuvant chemotherapy, postoperative pathological findings indicated that HER2 expression was significantly associated with vascular or perineural invasion (P=0.029) and lymph node metastasis (P=0.002), with no significant differences observed in tumor size or invasion depth.

Association between HER2 expression and prognosis. IHC alone and combined IHC/FISH both indicated that patients with HER2 expression experienced significantly poorer PFS times compared with those without HER2 expression. In the IHC alone group, the PFS time was 56.01±2.22 months for the HER2 IHC 0 group and 51.02±2.75 months for the HER2 expression group, with a statistically significant difference when compared [hazard ratio (HR), 0.559; 95% confidence interval (CI), 0.313-0.998; P=0.049; Fig. 4]. Kaplan-Meier survival curves were used to evaluate OS based on HER2 status, which demonstrated that the OS time of the patients with HER2 expression was slightly lower compared with that of the patients without HER2 (Fig. 5). Specifically, the OS was 69.47±1.93 months for the HER2 zero expression group and 58.47±2.22 months for the HER2 expression group, although this difference did not reach statistical significance (HR, 0.657; 95% CI, 0.318-1.356; P=0.255).

In the traditional method group, which employed combined IHC/FISH, the PFS time was 55.17±1.78 months for the HER2-negative group, compared with 36.44±7.85 months for the HER2-positive group, showing a statistically significant difference (HR, 0.125; 95% CI, 0.03033-0.5156; P=0.004; Fig. 6). The present study showed that the risk of poor survival in HER2-negative patients was significantly

Table I. Description of representative images of HER2 expression using IHC.

IHC status, score	Characteristics of IHC	IHC results
0	The cells appear blue, with no significant membrane staining observed in the glandular cells.	Fig. 1A
1+	The cells in the glandular structures show slight staining.	Fig. 1B
2+	Some glandular structures exhibit an incomplete membranous staining pattern (basolateral or 'U-shaped').	Fig. 1C
3+	The membranous staining of glandular cells is relatively complete, displaying a pattern that encircles the glands.	Fig. 1D

Table II. Description of representative images of HER2 2+ using FISH.

Category	HER2/CEP17 signal ratio	FISH results
Non-amplification	<2.0	Fig. 2A
Amplification	≥2.0	Fig. 2B

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization.

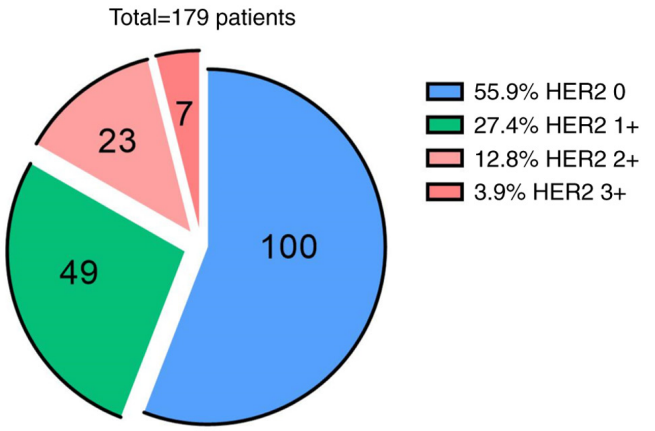

Figure 3. Distribution of patient numbers and detection rates across different HER2 expression levels (IHC 0, 1+, 2+ and 3+) assessed using IHC alone. HER2 zero expression (IHC 0) was the most common (100 cases, 55.9%), followed by HER2 1+ (49 cases, 27.4%), HER2 2+ (23 cases, 12.8%) and HER2 3+ (7 cases, 3.9%), indicating a relatively high proportion of positive HER2 expression in the present study cohort. HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

lower compared with that of HER2-positive patients, with an HR of 0.1250, which indicated that the survival risk in the HER2-negative group was only 12.5% of that in the HER2-positive group. Therefore, HER2 negativity was associated with an improved prognosis. Kaplan-Meier survival curves comparing HER2 positivity and OS indicated an OS time of 68.06±1.60 months for the HER2-negative group and 54.11±7.48 months for the HER2-positive group, with no statistically significant difference observed (OS; HR, 0.628; 95% CI, 0.114-3.465; P=0.593; Fig. 7).

Association between HER2 and PD-L1 expression in cervical adenocarcinoma. The association between HER2 expression and PD-L1 expression in 37 cases of cervical adenocarcinoma with fatal outcomes was analyzed (Table IV). Among these cases, 21 (56.8%) exhibited PD-L1 expression. The data suggested a statistically significant association between HER2 expression and increased levels of PD-L1 expression (χ^2, 4.259; P=0.039). Furthermore, the overlap in HER2 and PD-L1 expression was found to be 40.5%. Specifically, among the 16 PD-L1-negative patients, 6 cases (37.5%) showed HER2 expression. By contrast, among the 21 PD-L1-positive patients, 15 cases (71.4%) showed HER2 expression. The proportion of HER2-positive patients in the PD-L1-positive group was higher compared with that in the PD-L1-negative group.

Multivariate analysis of factors associated with disease progression in patients. In the multivariate Cox regression analysis of factors influencing disease progression in 179 patients with cervical adenocarcinoma after radical surgery, factors such as LVSI, depth of invasion, tumor size, pre-treatment levels of CA19-9 and CA-125, HER2 expression, age, staging and lymph node metastasis were included. These factors were selected as they are commonly considered relevant in cancer prognosis and disease progression (34). Patient prognosis was significantly associated with LVSI (P=0.003), but not HER2 expression (P=0.401), age (P=0.520), depth of invasion (P=0.284), tumor size (P=0.261) or the tumor markers CA19-9 (P=0.654) and CA-125 (P=0.630) (Table V). The confidence intervals for staging and lymph node metastasis were excessively wide.

Discussion

Although numerous studies have reported that HER2 expression may impact the prognosis of patients with various types of cancer (35,36), data specific to cervical cancer remains limited. According to the latest National Comprehensive Cancer Network guidelines (version 1, 2024), HER2 IHC testing is recommended for patients with advanced recurrent or metastatic cervical cancer (37). However, a standardized protocol for HER2 testing and interpretation in cervical cancer has yet to be established. In gynecological tumors, HER2 testing often references guidelines for breast cancer, which report very low rates of high HER2 expression and gene amplification in cervical cancer, with rates of 5.7 and 1.2%, respectively (38). In the present study, 179 patients with cervical adenocarcinoma

Table III. Association between HER2 status and characteristics in 179 cases in the HER2 zero expression (n=100) and HER2 expression (n=79) groups.

A, Total patient cohort

Variables	HER2 zero expression	HER2 expression	χ^2	P-value
No. of patients	100	79		
Age, n (%)			1.735	0.188
≤60 years	83 (53.9)	71 (46.1)		
>60 years	17 (68.0)	8 (32.0)		
FIGO stage, n (%)			10.116	0.001
I-IIB	78 (63.9)	44 (36.1)		
III-IV	22 (38.6)	35 (61.4)		
Recurrence status, n (%)			4.581	0.032
No progression	80 (60.6)	52 (39.4)		
Progression	20 (42.6)	27 (57.4)		
Survival status, n (%)			1.237	0.266
Survival	86 (57.7)	63 (42.3)		
Death	14 (46.7)	16 (53.3)		
Pre-treatment CA19-9 levels, n (%)			2.072	0.15
Normal	69 (59.0)	48 (41.0)		
Abnormal	26 (47.3)	29 (52.7)		
Not available	5 (71.4)	2 (28.6)		
Pre-treatment CA-125 levels, n (%)			5.141	0.023
Normal	76 (60.8)	49 (39.2)		
Abnormal	20 (41.7)	28 (58.3)		
Not Available	4 (66.7)	2 (33.3)		

B, Excluding 10 patients who received neoadjuvant chemotherapy

Variables	HER2 zero expression	HER2 expression	χ^2	P-value
No. of patients	94	75		
Vascular or perineural invasion, n (%)			4.751	0.029
Negative	62 (62.6)	37 (37.4)		
Positive	32 (45.7)	38 (54.3)		
Lymph node metastasis, n (%)			9.979	0.002
Negative	77 (63.1)	45 (36.9)		
Positive	17 (36.2)	30 (63.8)		
Depth of invasion, n (%)			1.180	0.277
Not infiltrated into deep muscle layer	48 (60.0)	32 (40.0)		
Infiltration into the deep muscle layer	46 (51.7)	43 (48.3)		
Tumor size, n (%)			0.629	0.428
≤4 cm	69 (53.9)	59 (46.1)		
>4 cm	25 (61.0)	16 (39.0)		

P-values were calculated using the χ^2 test, with percentages showing the expression ratio of HER2-positive or HER2-negative patients for each item. CA19-9, carbohydrate antigen 19-9; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; HER2, human epidermal growth factor receptor 2.

were evaluated using breast cancer guidelines, which identified only 9 HER2-positive cases. Based on the traditional combined IHC/FISH classification, the HER2 positivity rate was 5%. Meanwhile, using the ASCO/CAP gastric cancer guidelines, IHC alone has shown higher rates of high HER2 expression in cervical cancer, at 27.0% (38). In the present

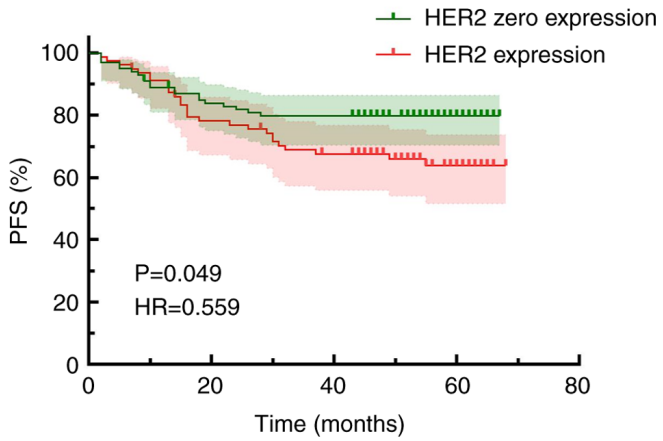

Figure 4. Kaplan-Meier estimates for PFS according to HER2 status assessed by IHC alone. The IHC alone patients were stratified into the HER2 zero expression (IHC 0) and HER2 expression (IHC 1+, 2+ or 3+) groups. The PFS time in the HER2 zero expression group was significantly improved compared with that in the HER2 expression group (HR,0.559; P=0.049), indicating that HER2 expression was associated with an increased risk of progression. PFS, progression-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry.

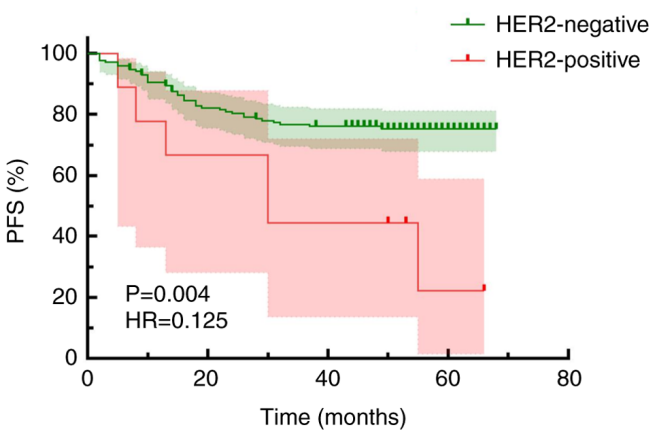

Figure 6. Kaplan-Meier estimates for PFS and according to HER2 status assessed by the traditional combined IHC/FISH method. Patients were divided into the following groups: HER2-negative (IHC 0, IHC 1+ or IHC 2+/FISH-) or HER2-positive (IHC 3+ or IHC 2+/FISH+) assessed by the traditional combined IHC/FISH method. HER2-negative patients demonstrated significantly improved PFS times compared with HER2-positive patients (HR, 0.125; P=0.004). PFS, progression-free survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization.

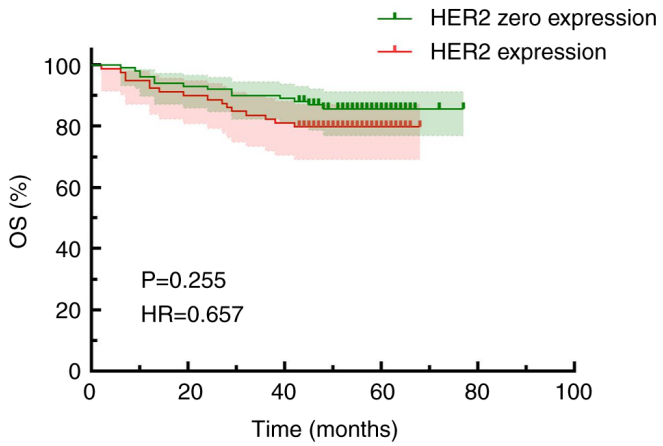

Figure 5. Kaplan-Meier estimates for OS according to HER2 status assessed by IHC alone. The IHC alone patients were stratified into the HER2 zero expression (IHC 0) and HER2-expression (IHC 1+, 2+ or 3+) groups. Patients in the HER2 zero expression group exhibited improved OS times compared with those with HER2 expression; however, the difference did not reach statistical significance (HR, 0.657; P=0.255). OS, overall survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry.

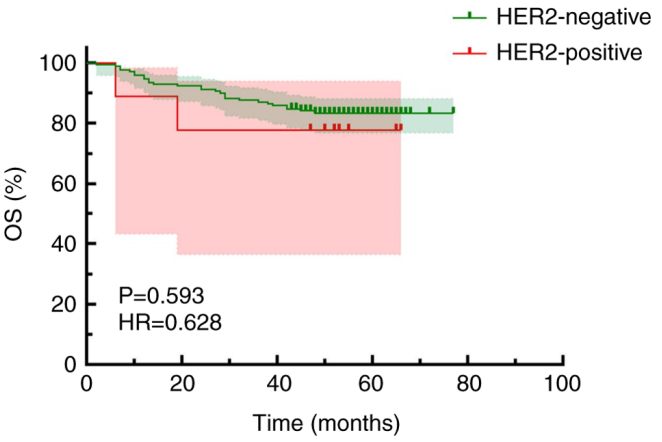

Figure 7. Kaplan-Meier estimates for OS according to HER2 status assessed by traditional combined IHC/FISH. Patients were divided into the following groups: HER2-negative (IHC 0, IHC 1+ or IHC 2+/FISH-) or HER2-positive (IHC 3+ or IHC 2+/FISH+) assessed by the traditional combined IHC/FISH method. Although HER2-negative patients show a numerically improved OS time compared with HER2-positive patients, the difference was not statistically significant (HR, 0.628; P=0.593). OS, overall survival; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IHC, immunohistochemistry; FISH, fluorescence *in situ* hybridization.

study, when assessed by gastric cancer guidelines, IHC alone (1+ to 3+) identified 72 cases of low HER2 expression (40.2%), with an overall HER2 expression rate of 44.1%. In a study by Shi *et al* (17), involving 209 patients with cervical adenocarcinoma, 123 were identified as HER2-positive, resulting in a positivity rate of 58.9%. Among these, 100 patients (47.8%) exhibited low HER2 expression. The study also observed higher HER2 expression in gastric-type adenocarcinoma compared with ordinary adenocarcinoma, which was potentially associated with poor prognosis. These findings were consistent with the present results. Additionally, a previous study indicated that HER2 staining in cervical adenocarcinoma frequently exhibits incomplete membrane patterns (such as basolateral or U-shaped) in 12.2% of cases (15/123) and intratumoral staining heterogeneity in 17.1% of cases (21/123), resembling patterns observed in gastric and gastroesophageal adenocarcinomas (17). Given these similarities, the HER2 assessment criteria that aligned with those used for gastric cancer were adopted in the present study.

HER2, a receptor tyrosine kinase, exerts its effects through several key biological pathways. First, the PI3K/AKT/mTOR pathway serves a pivotal role in cell survival, proliferation and metabolic regulation, with its aberrant activation frequently observed in various types of cancer (39). The MAPK signaling

Table IV. Expression rates of PD-L1 and HER2.

PD-L1 expression	HER2 expression, n (%)	HER2 zero expression, n (%)	χ^2	P-value
Negative	6 (37.5)	10 (62.5)	4.259	0.039
Positive	15 (71.4)	6 (28.6)		

PD-L1, PD-L1, programmed death-ligand; HER2, human epidermal growth factor receptor 2.

Table V. Multivariate analysis of factors associated with disease progression in 179 patients after radical surgery for cervical adenocarcinoma.

Subgroup	HR (95% CI)	P-value
Age, years		
≤60	1.000	
>60	0.751 (0.313-1.799)	0.520
FIGO stage		
I-IIB	1.000	
III-IV	1407.350 (0-1.006x10^{55})	0.905
Tumor size, cm		
≤4	1.000	
>4	1.505 (0.738-3.068)	0.261
Vascular or perineural invasion		
Negative	1.000	
Positive	0.279 (0.12-0.651)	0.003
Depth of invasion		
Not infiltrated into deep muscle layer	1.000	
Infiltration into the deep muscle layer	0.592 (0.227-1.544)	0.284
Pre-treatment CA19-9 levels		
Normal	1.000	
Abnormal	1.161 (0.604-2.231)	0.654
Pre-treatment CA-125 levels		
Normal	1.000	
Abnormal	1.187 (0.59-2.389)	0.630
HER2 expression status		
Negative	1.000	
Positive	0.752 (0.386-1.462)	0.401
Lymph node metastasis		
Negative	1.000	
Positive	0.000 (0-1.937x10^{48})	0.893

CA19-9, carbohydrate antigen 19-9; CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth factor receptor 2.

pathway contributes to tumor development and progression by promoting cell proliferation, differentiation and survival (40). Additionally, the JAK2/STAT3 pathway facilitates uncontrolled cancer cell growth, resistance to apoptosis and regulation of cell survival. These pathways are not only integral to tumor biology but also serve as potential therapeutic targets (41). With increasing focus on HER2 expression in cervical cancer, the use of ADCs in metastatic HER2-expressing cervical cancer has emerged as a key area of interest. Current clinical trial data on ADCs in cervical cancer treatment shows promising outcomes for patients. The open-label phase II study, DESTINY-PanTumor02 (42), aimed to evaluate the efficacy and safety of trastuzumab deruxtecan (T-DXd; 5.4 mg/kg) as a second-line treatment for HER2-expressing solid tumors. In the cervical cancer cohort, 40 patients were enrolled and T-DXd demonstrated significant antitumor activity, with an ORR of

50%. Additionally, the RC48-C018 study included a cervical cancer cohort of patients with HER2-expressing recurrent or metastatic disease who had undergone at least one prior line of treatment. As of October 2023, 25 patients with cervical cancer were enrolled, with 22 being evaluable for efficacy. The ORR was 36.4% (including 1 complete response), the disease control rate was 86.4%, the median duration of response was 5.52 months and the median PFS time was 4.37 months (25). The advent of ADCs represents a novel treatment strategy for cervical cancer, making the detection of HER2 (especially IHC 1+ and 2+/FISH-) particularly important.

In recent years, the emergence of immunotherapy has brought new hope to some patients with advanced cervical cancer. PD-L1 is a critical co-stimulatory molecule in immune responses and exhibits a high expression rate in cervical cancer (43). This characteristic suggests that PD-L1 may serve an important role in the immune regulation of cervical cancer. Additionally, numerous studies have shown a potential synergy between the expression levels of HER2 and PD-L1. Oki *et al* (44) found that in gastric cancer cells, HER2 expression levels were positively correlated with PD-L1 expression levels. Among patients with HER2 3+ status, 72.4% demonstrated high levels of PD-L1 expression. Furthermore, when HER2 expression was downregulated using siRNA, PD-L1 protein levels were significantly reduced, indicating that HER2 signaling pathways might directly or indirectly regulate PD-L1 expression. Similarly, Chaganty *et al* (45) proposed that a combination of anti-HER2 therapy and anti-programmed cell death protein 1/PD-L1 therapy could be a potential strategy to improve therapeutic outcomes in breast cancer. In the present study, data from 37 patients who died were analyzed. The results showed that among the 21 PD-L1-positive patients, 15 (71.4%) also demonstrated HER2 expression, indicating a high level of co-expression between the two markers. Furthermore, the overlap in HER2 and PD-L1 expression was found to be 40.5%, and the present results demonstrated a statistically significant association between HER2 expression and PD-L1 expression levels (χ^2, 4.259; P=0.039), suggesting a potential association between these two markers in the tumor microenvironment. These findings provide an important basis for further investigation into the synergistic effects of HER2 and PD-L1 and their potential application in dual-targeted therapy. This observation was consistent with previous studies in gastric, esophageal and esophago-gastric cancer, which supported dual HER2 and PD-L1 targeting, showing clinical benefits (46,47). Such evidence offers a foundation for more individualized treatment strategies for patients with cervical cancer with dual HER2 and PD-L1 expression.

Univariate analysis in the present study demonstrated a significant association between HER2 expression in patients with cervical adenocarcinoma and adverse clinicopathological characteristics, such as advanced FIGO stage, lymph node metastasis, presence of vascular cancer thrombus, nerve invasion and abnormal CA-125 levels. Patients with HER2 expression typically exhibited multiple poor prognostic factors, contributing to an overall worse prognosis. The present study indicated HER2 to be a potentially key biomarker for prognostic evaluation in patients with cervical adenocarcinoma. However, the multivariate analysis did not show consistent results. The absence of statistical significance between HER2 expression and disease progression may be attributed to insufficient sample size or collinearity among variables, potentially masking its effect. Although HER2 failed to demonstrate independent prognostic significance, this does not exclude its potential role, and further investigations with larger sample sizes are essential to validate these findings. Numerous studies have demonstrated that adverse clinicopathological factors significantly impact the prognosis of patients with cervical cancer. These high-risk factors include lymph node metastasis, vascular or perineural invasion and FIGO staging (48,49). The present study suggests that HER2 expression may be associated with a poorer prognosis. Martinho *et al* conducted a pathological study using IHC techniques to analyze HER2 expression in cancer tissues from 229 patients with cervical cancer, including 194 adenocarcinomas and 35 squamous carcinomas (20). Univariate analysis suggested a notable but non-significant trend toward an association between HER2 positivity and poor prognosis (P=0.07). Kaplan-Meier curve analysis further associated HER2 upregulation with adverse prognosis (P=0.014). Multivariate analysis confirmed metastasis and HER2 upregulation as independent prognostic factors for patients with cervical cancer (20). In the present analysis, PFS time for patients in the HER2 zero expression group was increased compared with that of patients with HER2 expression, with an HR of 0.559, indicating a ~44.1% reduction in the risk of disease progression or death. The 95% CI (0.313-0.998) and a P-value of 0.049 further supported the statistical significance of this observation.

In summary, patients with HER2 expression exhibited worse PFS time compared with those in the HER2 zero expression group. Moreover, OS time for patients in the HER2 zero expression group appeared improved compared with that for patients with HER2 expression, with an HR of 0.656, indicating a potential 34.4% reduction in mortality risk. However, the 95% CI (0.318-1.356) and a non-significant P-value of 0.255 suggested uncertainty in these results. Although the OS in HER2 zero expression shows a better trend compared to HER2 expression, it did not reach statistical significance, and longer-term studies may elucidate significant differences. Therefore, HER2 status holds significant implications for assessing disease progression and could potentially serve as a pivotal biomarker for treatment and prognosis monitoring in cervical adenocarcinoma.

The present study had several limitations that warrant consideration. First, the analysis of HER2 expression in the samples was conducted retrospectively. Due to the extended time between surgery and sample collection, samples that originally expressed HER2 may have lost the protein over time, leading to insufficient staining. Therefore, the actual HER2 expression rate may be higher. Second, due to the lack of established HER2 assessment guidelines specifically for cervical adenocarcinoma, the present study, similar to others (42), referenced guidelines originally developed for breast or gastric cancer. HER2 assessment standards can differ significantly across such different cancer types (50). Third, the present study was limited by its retrospective design, and insufficient available data and sample size, which made conducting sensitivity analyses challenging and

resulted in the absence of sensitivity analysis. Larger-scale studies or clinical trials are needed to validate and generalize these findings.

In summary, the present study evaluated HER2 IHC expression in patients with cervical adenocarcinoma using gastric cancer assessment criteria. HER2 expression was analyzed based on both traditional and newly established standalone IHC classification methods. The findings underscore the association between HER2 expression and adverse prognostic factors in patients undergoing radical surgery for cervical adenocarcinoma. HER2-positive patients experienced poorer PFS times, emphasizing the critical role of early HER2 status assessment in guiding treatment decisions for cervical adenocarcinoma. Tumor patients expressing HER2 who have died may also exhibit higher PD-L1 expression levels, and the combined expression of these markers could help physicians develop personalized treatment strategies. This approach holds promise for predicting patient outcomes and optimizing therapeutic strategies to improve treatment efficacy.

Future research will explore the pathological characteristics of cervical cancer in greater depth, particularly focusing on the association between HER2 expression and cervical squamous cell carcinoma. This effort aims to develop tailored treatment approaches that could ultimately enhance survival rates and improve the quality of life for patients with cervical cancer.

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Availability of data and materials

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

Authors' contributions

QX, ZY, YL, XZ and JN were responsible for data collection, processing, and interpretation. QX was responsible for methodology, software, formal analysis and manuscript writing. ZY partook in formal analysis and investigation. YL performed formal analysis. XZ contributed to the study design and data analysis, as well as to the processing of data images. JN contributed to study conception and design, and reviewed and edited the manuscript. HL undertook study conceptualization, resources, project administration, funding acquisition and supervision. All authors read and approved the final manuscript. QX and JN confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki with the approval of the Medical Ethics Committee of Zhejiang Cancer Hospital (Hangzhou, China; approval no. IRB-2023-656). Patients signed an informed consent form at admission, which included consent for their samples to be used for research.

Patient consent for publication

Patients provided written informed consent for publication of their data.

Competing interests

The authors declare that they have no competing interests.

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