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Clinicopathological characteristics, treatment patterns and outcomes in patients with HER2-positive breast cancer based on hormone receptor status: a retrospective study

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Abstract

Background Different hormone receptor (HR) expression patterns have significant biological and therapeutic implications in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer. However, the distinction between HR-positive /HER2-positive (HR+/HER2+) and HR-negative/HER2-positive (HR-/HER2+) subtypes remains unclear.

Methods This retrospective study analyzed 828 patients with HER2-positive breast cancer at the First Affiliated Hospital of Xi'an Jiaotong University from 2012 to 2022. Baseline characteristics were compared by chi-square test. Survival outcomes were estimated by Kaplan-Meier method.

Results In total, 56.3% ($n=466$) had HR-positive and 43.7% ($n=362$) had HR-negative disease. Comparatively, HR+/HER2 + breast cancers presented favorable clinicopathological features. At a median follow-up of 49 months, 199 disease-free survival (DFS) events and 99 deaths were observed. HR+/HER2 + patients had significantly better survival outcomes than HR-/HER2 + patients. HR-positive status was an independent protective factor for overall survival (OS) [$P=0.032$; hazard ratio, 0.61; 95% confidence interval (CI), 0.39–0.96] and DFS ($P=0.001$; hazard ratio, 0.61; 95% CI, 0.46–0.81). HR+/HER2 + patients were significantly less sensitive to neoadjuvant therapy than HR-/HER2 + patients. In the first-line treatment for HR+/HER2 + advanced breast cancer, receiving endocrine therapy significantly improved advanced-OS ($P<0.001$; hazard ratio, 0.33; 95% CI, 0.18–0.59) and progression-free survival (PFS) ($P<0.001$; hazard ratio, 0.38; 95% CI, 0.25–0.58) compared with not receiving endocrine therapy. Moreover, maintenance endocrine therapy after HER2-targeted therapy and chemotherapy is associated with significant advanced-OS and PFS benefits compared with no maintenance endocrine therapy (advanced-OS: $P<0.001$; hazard ratio, 0.05; 95% CI, 0.03–0.12; PFS: $P<0.001$; hazard ratio, 0.35; 95% CI, 0.21–0.57).

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Conclusions This study reveals the high heterogeneity of HER2-positive breast cancer related to HR status in clinicopathological features, metastasis patterns, and outcomes. Large randomized controlled trials are warranted to optimize treatment strategies for the HER2-positive breast cancer population.

Keywords HER2-positive breast cancer, Hormone receptor, HER2-targeted therapy, Endocrine therapy, Survival.

Background

Breast cancer is the most common malignant tumor and the leading cause of death in women, with an estimated 297,790 new cases and 43,170 deaths in 2023 [1]. Breast cancer has been well recognized as a heterogeneous disease with multiple histologic and molecular subtypes. Based on the expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), breast cancer can be classified into four different molecular subtypes to guide precise treatment and prognosis estimation [2]. HER2 overexpression occurs in approximately 20–25% of breast cancers, which are prone to early recurrence and distant metastasis, resulting in a poor prognosis [3]. About half of HER2-positive breast cancers also express hormone receptors (HRs), including ER and/or PR [4]. A growing body of evidence suggests that biological behavior, clinical features, therapeutic response, and prognosis of HER2-positive breast cancer vary by HR status [5]. According to molecular intrinsic subtypes, HR-negative/HER2-positive (HR-/HER2+) breast cancers are more likely to be categorized as HER2-enriched (HER2-E), 75% compared with 30% in HR+/HER2+tumors [6]. About 70% of HR+/HER2+tumors are luminal A or B, which is biologically similar to HR+/HER2- tumors that are associated with low response to anti-HER2 treatment but relatively good prognosis [7]. In neoadjuvant settings, HR+/HER2+tumors showed a lower pathologic complete response rate (pCR) than HR-/HER2+tumors [8]. In terms of relapse patterns, HR+/HER2+breast cancer had a lower risk of recurrence than HR-/HER2+breast cancer in the first 5 years, whereas the risk of recurrence of HR+/HER2+breast cancer is increased and similar to that of HR-/HER2+in years 6 to 10 [9]. Previous studies have demonstrated that complex crosstalk between HR and HER2 signaling pathways can induce resistance to endocrine therapy or HER2-targeted therapy [10]. Dual inhibition of HR and HER2 pathways may provide long-term disease control, particularly in patients who cannot tolerate the toxicity of chemotherapy and require maintenance of disease stability [11]. However, limited data from randomized, double-blind, controlled trials for HR+/HER2+breast cancer has resulted in a lack of standardized treatment regimens for these patients. To date, the impact of HR status on survival outcomes and treatment options for patients with HER2-positive breast cancer has not yet been clarified.

In this retrospective cohort study, based on the large-scale Asian population, we investigated the clinicopathological features, metastatic patterns, and clinical outcomes of patients with HER2-positive breast cancer associated with HR status. These real-world data are aimed to provide support and references for a better understanding of tumor behavior and further develop personalized treatment strategies for patients with HER2-positive breast cancer.

Methods

Patient selection

Patients with breast cancer admitted to the First Affiliated Hospital of Xi'an Jiaotong University from January 2012 to June 2022 were retrospectively enrolled. Clinicopathological, treatment, and follow-up information were retrieved from Xi'an Jiaotong University Breast Cancer Database. Patients who met the inclusion and exclusion criteria were finally included in this study for further analysis (Fig. 1). The inclusion criteria were as follows: (1) Female gender; (2) Pathologically confirmed HER2-positive invasive breast cancer; (3) ER and PR status known; (4) complete clinical and follow-up data. The exclusion criteria were as follows: (1) Male gender; (2) HER2-negative or HER2 status unknown; (3) ER and/or PR status unknown; (4) Combined second primary tumor; (5) Bilateral breast cancer; (6) Incomplete clinical information; (7) Missing or unknown cause of death. This study was reviewed and approved by the independent Ethical Committees of The First Affiliated Hospital Xi'an Jiaotong University.

Histopathological assessments and related definitions

Histopathologic assessment was conducted by the Department of Pathology, the First Affiliated Hospital of Xi'an Jiaotong University. The methods and criteria for immunohistochemistry (IHC) assessment of ER, PR, HER2, and Ki-67 were made from paraffin-embedded tumor samples from open excision biopsy and core needle biopsy. All IHC and fluorescence in situ hybridization (FISH) results were reviewed by two senior pathologists. ER-positivity and PR-positivity were defined as at ≥1% positive tumor cells with nuclear staining [12]. HER2 status was firstly determined by IHC and scored as 0 to 3+according to ASCO/CAP (American Society of Clinical Oncology/College of American Pathologists) guidelines [13]. Tumors with IHC HER2 2+were further examined by FISH, and the tumor was considered to have

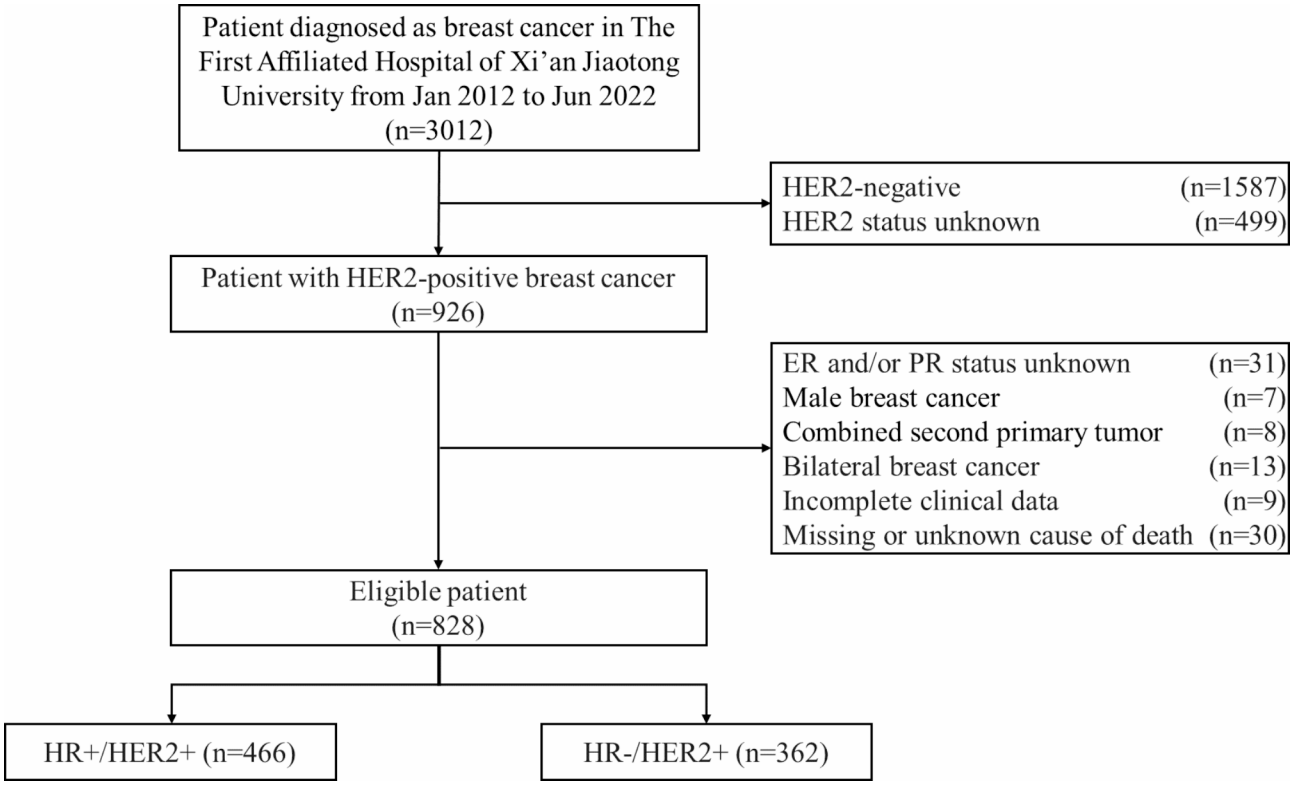


Fig. 1 Flowchart of the 828 patients included in the study. Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2

HER2 amplification if the ratio of HER2 gene signals to chromosome 17 signals was ≥2.2. HER2 positivity was defined as IHC HER2 3+or FISH-proven HER2 amplified [14]. Ki-67 expression was scored as the percentage of positive invasive tumor cells with any nuclear staining and recorded as the mean percentage of positive cells. HR-positive disease was defined as ER-positive and/or PR-positive tumors in early breast cancer (EBC) or metastatic breast cancer (MBC). De novo MBC was defined as an initial breast cancer diagnosis with distant metastases observed concurrently or confirmed within 30 days.

The Miller-Payne (MP) grading system was used to evaluate pathological responses to neoadjuvant therapy [15].

Grade 1: No change or some alteration to individual malignant cells but no reduction in overall cellularity.

Grade 2: A minor loss of tumor cells but overall cellularity is still high; up to 30% loss;

Grade 3: Between an estimated 30% and 90% reduction in tumor cells;

Grade 4: A marked disappearance of tumor cells such that only small clusters or widely dispersed individual cells remain; more than 90% loss of tumor cells;

Grade 5: No malignant cells identifiable in sections from the site of the tumor, only vascular fibroelastic stroma remains often containing macrophages. However, ductal carcinoma in situ may be present.

pCR was defined as no histological evidence of malignancies or only in situ residuals in breast tissue after surgery and complete disappearance of lymph node metastasis.

Criteria for menopause: (a) bilateral ovariectomy; (b) age<60 years, follicle-stimulating hormone and estradiol in the postmenopausal range and have natural amenorrhea for one year or more; (c) age≥60 years.

Follow-up

All patients were followed up by outpatient visit or called every 3 months for the first 2 years after surgery, every 6 months between the 3rd and 5th years, then annually until death. Disease-free survival (DFS) was computed from the date of surgery to the date of the following events: locoregional recurrence, contralateral breast cancer, secondary non-breast malignancy, distant recurrence at any site, and death for any cause. Progression-free survival (PFS) was defined as the time from the receipt of a particular treatment regimen to the occurrence of breast cancer progression or death for any cause. Overall survival (OS) was defined as the period from the date of surgery to the date of death for any cause. Advanced-OS was defined as the period from diagnosis of breast cancer recurrence or metastasis to death for any cause. The diagnosis of recurrence or metastasis was usually based on the patient's radiological images and/or available

pathological biopsies. The data cutoff date was December 31, 2022.

Statistical analysis

Descriptive characteristics of categorical variables were tested using the chi-square test or Fisher's exact test. Kaplan-Meier survival curves were used to assess the OS, DFS, and PFS. Log-rank tests were used to evaluate differences in survival. Multivariate survival analyses were performed using the Cox proportional hazards model, and the results were reported as hazard ratios with 95% confidence intervals (CIs). All statistical procedures were performed using SPSS software, version 24.0. $P<0.05$ was considered statistically significant.

Results

Clinicopathological characteristics and early treatment patterns

From January 2012 to June 2022, a total of 3012 breast cancer patients were admitted to the First Affiliated Hospital of Xi'an Jiaotong University. Among 828 patients who met eligibility criteria, 466 (56.3%) were HR+/HER2+patients and 362 (43.7%) were HR-/HER2+patients. Main baseline characteristics were reported in Table 1. The median follow-up duration for all enrolled patients was 49 months (range 3–196 months). The median follow-up duration was longer in the HR+/HER2+group than in the HR-/HER2+group (53 months vs. 41 months, $P<0.001$). The median age was 49 years for HR+/HER2+group and 50 years for HR-/HER2+group ($P=0.472$). Compared to HR-/HER2+group, HR+/HER2+breast cancer had a lower histological grade (I-II: 41.1% vs. 30.4%, $P=0.025$). In terms of HER2 status, HR+/HER2+group showed lower HER2 immunohistochemical staining and the proportion of IHC 3+positivity in HR+/HER2+tumors was significantly lower than that in HR-/HER2+tumors (75.1% vs. 83.7%, $P=0.003$). Moreover, Ki67 values in HR+/HER2+breast cancers were significantly lower than that in HR-/HER2+tumors (Ki67 ≤ 30%: 45.9% vs. 37.6%, $P=0.034$). Concerning early treatment options, HR+/HER2+patients were more preferred to receive breast-conserving surgery (BCS) and other procedures (38.6% vs. 29.6%, $P=0.025$), as well as adjuvant endocrine therapy (80.5% vs. 6.4%, $P<0.001$), and less inclined to receive neoadjuvant therapy (36.5% vs. 43.9%, $P=0.030$) compared with HR-/HER2+patients (Table 2). However, there was no significant difference between HR+/HER2+and HR-/HER2+groups in the age at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status, menopausal status at diagnosis, affected breast, family history of tumor, histological type, T-staging, N-staging, TNM staging at diagnosis, neoadjuvant HER2 targeted therapy, adjuvant therapy, adjuvant radiotherapy, adjuvant chemotherapy, and adjuvant HER2-targeted therapy.

Relapse and metastatic patterns

By the end of the follow-up, among the 828 eligible patients, 263 patients had local recurrence or distant metastasis, including 132 patients in HR+/HER2+group and 131 patients in HR-/HER2+group (Table 3). Compared with HR-/HER2+patients, HR+/HER2+patients tend to have bone metastasis (61.4% vs. 38.9%, $P<0.001$) and have bone as the first metastatic site (46.2% vs. 25.2%, $P<0.001$). HR-/HER2+patients tend to have lung metastasis (51.1% vs. 35.6%, $P=0.011$) and have the lung as the first metastatic site (37.4% vs. 25.8%, $P=0.042$) and have other sites (including soft tissues, pleura, peritoneum, etc.) as the first metastatic site (39.7% vs. 28.0%, $P=0.046$) than HR+/HER2+patients. However, there was no significant difference between HR+/HER2+and HR-/HER2+groups in MBC diagnosis type, visceral involvement, the number of visceral involvements, liver metastasis, brain/central nervous system (CNS) metastasis, distant lymph node metastasis, other site metastasis, whether the first metastatic site involved viscera, brain/CNS, liver, and distant lymph node.

Neoadjuvant treatment and efficacy

Among the 828 HER2-positive patients included, a total of 329 patients had received preoperative neoadjuvant therapy, of which 170 cases (51.7%) were in the HR+/HER2+group and 159 cases (48.3%) were in the HR-/HER2+group. Based on ER and PR status, 329 HER2-positive patients who had received neoadjuvant therapy were further classified into four subgroups, ER+/PR+, ER+/PR-, ER-/PR+, and ER-/PR-, of which there were 110 cases (33.4%) in the ER+/PR+subgroup, 45 cases (13.7%) in the ER+/PR- subgroup, 15 cases (4.6%) in the ER-/PR+subgroup, and 159 cases (48.3%) in the ER-/PR- subgroup. HR+/HER2+group had a significantly lower pCR rate (the percentage of Grade 5) than that of HR-/HER2+group (34.7% vs. 45.9%, $P<0.001$) (Fig. 2b). Likewise, the pCR rate was considerably lower in ER+/PR+subgroup than in ER+/PR-, ER-/PR+, and ER-/PR-subgroups (32.7% vs. 37.8% vs. 40.0% vs. 45.9%, all P value <0.05) (Fig. 2a).

Depending on the neoadjuvant therapy regimes, 329 patients with HER2-positive breast cancer who had received neoadjuvant therapy were divided into three groups, chemotherapy (CT) only group, trastuzumab+CT group, and trastuzumab+pertuzumab+CT group. As shown in Fig. 3b and Table S1, chemotherapy combined with HER2-targeted therapy in neoadjuvant therapy significantly improved the pCR rate of HER2-positive patients compared with CT alone, regardless of HR status (all P values <0.001). The dual HER2-targeted

Table 1 Baseline clinicopathological characteristics in HER2-positive patients

Characteristics	All patients (*n* = 828) (%)	HR+/HER2+ (*n* = 466) (%)	HR-/HER2+ (*n* = 362) (%)	*P* value
Follow-up time (month)				
Median (range)	49 (3-196)	53 (3-174)	41 (6-196)	< 0.001
Age at diagnosis (years)				
Median (range)	50 (20–92)	49 (20–84)	50 (22–92)	0.472
Age group at diagnosis, years				0.134
< 50	410 (49.5)	241 (51.7)	169 (46.7)	
≥ 50	418 (50.5)	225 (48.3)	193 (53.3)	
ECOG PS				0.726
0–1	719 (86.8)	406 (87.1)	313 (86.5)	
2+	47 (5.7)	25 (5.4)	22 (6.1)	
Unknown	62 (7.5)	35 (7.5)	27 (7.5)	
Menopausal status at diagnosis				0.413
Premenopausal	498 (60.1)	286 (61.4)	212 (58.6)	
Postmenopausal	330 (39.9)	180 (38.6)	150 (41.4)	
Affected breast				0.544
Left	443 (53.5)	245 (52.6)	198 (54.7)	
Right	385 (46.5)	221 (47.4)	164 (45.3)	
Family history of tumor				0.523
Yes	110 (13.3)	65 (13.9)	45 (12.4)	
No	718 (86.7)	401 (86.1)	317 (87.6)	
Histological type				0.332
IDC	742 (89.6)	413 (88.6)	329 (90.9)	
Non-IDC	86 (10.4)	53 (11.4)	33 (9.1)	
Histological grade				0.025
I/II	297 (35.8)	187 (40.1)	110 (30.4)	
III	370 (44.7)	199 (42.7)	171 (47.2)	
Unknown	161 (19.4)	80 (17.2)	81 (22.4)	
HER2 status				0.003
IHC 3+	653 (78.9)	350 (75.1)	303 (83.7)	
IHC 2 + and FISH + [a]	175 (21.1)	116 (24.9)	59 (16.3)	
ER				< 0.001
< 10%	438 (52.9)	76 (16.3)	362 (100.0)	
10–49%	105 (12.7)	105 (22.5)	0 (0.0)	
≥ 50%	285 (34.4)	285 (61.2)	0 (0.0)	
PR				< 0.001
< 20%	634 (76.6)	272 (58.4)	362 (100.0)	
≥ 20%	194 (23.4)	194 (41.6)	0 (0.0)	
Ki-67				0.034
≤ 30%	350 (42.3)	214 (45.9)	136 (37.6)	
>30%	472 (57.0)	250 (53.6)	222 (61.3)	
Unknown	6 (0.7)	2 (0.4)	4 (1.1)	
T-staging				0.134
T1	224 (27.1)	138 (29.6)	86 (23.8)	
T2	492 (59.4)	277 (59.4)	215 (59.4)	
T3	60 (7.2)	28 (6.0)	32 (8.8)	
T4	42 (5.1)	19 (4.1)	23 (6.4)	
Tx	10 (1.2)	4 (0.9)	6 (1.7)	
N-staging				0.084
N0	308 (37.2)	180(38.6)	128 (35.4)	
N1	301 (36.4)	177 (38.0)	124 (34.3)	
N2	107 (12.9)	59 (12.7)	48 (13.3)	
N3	110 (13.3)	50 (10.7)	60 (16.6)	

Table 1 (continued)

Characteristics	All patients (*n* = 828) (%)	HR+/HER2+ (*n* = 466) (%)	HR-/HER2+ (*n* = 362) (%)	*P* value
Nx	2 (0.2)	0 (0.0)	2 (0.6)	
TNM staging at diagnosis				0.677
I-III	763 (92.1)	431 (92.5)	332 (91.7)	
IV	65 (7.9)	35 (7.5)	30 (8.3)	

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; IDC, invasive ductal carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; PR, progesterone receptor

[a] Patients with IHC 2+positivity was fluorescence in situ hybridization (FISH)-proven HER2 amplified

Table 2 Early treatment patterns in HER2-positive patients

Characteristics	All patients (*n* = 828) (%)	HR+/HER2+ (*n* = 466) (%)	HR-/HER2+ (*n* = 362) (%)	*P* value
Surgery				0.025
Radical mastectomy	490 (59.2)	258 (55.4)	232 (64.1)	
BCS and other	287 (34.7)	180 (38.6)	107 (29.6)	
No surgery	51 (6.2)	28 (6.0)	23 (6.4)	
Neoadjuvant therapy				0.030
Yes	329 (39.7)	170 (36.5)	159 (43.9)	
No	499 (60.3)	296 (63.5)	203 (56.1)	
Neoadjuvant HER2 targeted therapy				0.087
Yes	289 (34.9)	151 (32.4)	138 (38.1)	
No	539 (65.1)	315 (67.6)	224 (61.9)	
Adjuvant therapy				0.386
Yes	745 (90.0)	423 (90.8)	322 (89.0)	
No	83 (10.0)	43 (9.2)	40 (11.0)	
Adjuvant radiotherapy				0.545
Yes	401 (48.4)	230 (49.4)	171 (47.2)	
No	427 (51.6)	236 (50.6)	191 (52.8)	
Adjuvant chemotherapy				0.822
Yes	534 (64.5)	299 (64.2)	235 (64.9)	
No	294 (35.5)	167 (35.8)	127 (35.1)	
Adjuvant HER2 targeted therapy				0.992
Yes	623 (75.2)	350 (75.1)	273 (75.4)	
No	205 (24.8)	116 (24.9)	89 (24.6)	
Adjuvant endocrine therapy				< 0.001
Yes	398 (48.1)	375 (80.5)	23 (6.4)	
No	430 (51.9)	91 (19.5)	339 (93.6)	

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; BCS: breast-conserving surgery

therapy group with the addition of pertuzumab further improved the pCR rate compared with the trastuzumab+CT group ($P<0.001$). However, the pCR rate was significantly lower in HR+/HER2+patients compared to HR-/HER2+patients treated with either trastuzumab+CT or trastuzumab+pertuzumab+CT (both P values <0.05). Similarly, as illustrated in Fig. 3a and Table S2, the combination of HER2-targeted therapy with neoadjuvant therapy significantly improved the pCR rate in all subgroups of HER2-positive patients, regardless of ER and PR status. The dual anti-HER2 therapy with trastuzumab plus pertuzumab further significantly improved the pCR rate in all subgroups compared with trastuzumab alone (all P values <0.05). In the trastuzumab+CT group, the pCR rate of the ER+/PR+subgroup was significantly lower than that in the ER+/PR- and ER-/PR- subgroups (14.3% vs. 28.6% vs. 30.2%, all P values <0.05). In the trastuzumab+pertuzumab+CT group, the pCR rate in the ER+/PR+subgroup was also significantly lower than that in the ER-/PR+and ER-/PR- subgroups (53.7% vs. 66.7% vs. 62.1%, both P values <0.05), whereas there was no significant difference in the pCR rate between the ER+/PR+and ER+/PR- subgroups (53.7% vs. 55.0%, $P=0.921$). Table S3 describes the detailed neoadjuvant therapy regimens by HR status.

Table 3 Metastatic patterns in HER2-positive MBC patients

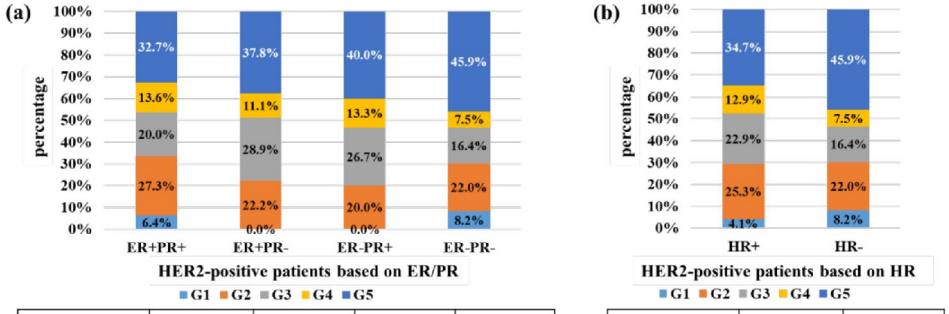
Characteristics	All patients (*n* = 263) (%)	HR+/HER2+ (*n* = 132) (%)	HR-/HER2+ (*n* = 131) (%)	*P* value
MBC diagnosis type				0.497
Recurrent	198 (75.3)	97 (73.5)	101 (77.1)	
De novo[a]	65 (24.7)	35 (26.5)	30 (22.9)	
Metastatic sites				
Visceral involvement [b]	188 (71.5)	90 (68.2)	98 (74.8)	0.234
Lung	114 (43.3)	47 (35.6)	67 (51.1)	0.011
Liver	93 (35.4)	52 (39.4)	41 (31.3)	0.170
Brain/CNS	74 (28.1)	35 (26.5)	39 (29.8)	0.557
Bone	132 (50.2)	81 (61.4)	51 (38.9)	< 0.001
Distant lymph node	130 (49.4)	64 (48.5)	66 (50.4)	0.758
Other sites [c]	116 (44.1)	52 (39.4)	64 (48.9)	0.122
Number of visceral metastases				0.332
0	75 (28.5)	42 (31.8)	33 (25.2)	
1	104 (39.5)	52 (39.4)	52 (39.7)	
2	65 (24.7)	27 (20.5)	38 (29.0)	
3	19 (7.2)	11 (8.3)	8 (6.1)	
First metastatic site				
Visceral involvement	140 (52.8)	67 (50.8)	73 (55.7)	0.419
Lung	83 (31.6)	34 (25.8)	49 (37.4)	0.042
Liver	55 (20.9)	34 (25.8)	21 (16.0)	0.052
Brain/CNS	21 (8.0)	10 (7.6)	11 (8.4)	0.806
Bone	94 (35.7)	61 (46.2)	33 (25.2)	< 0.001
Distant lymph node	86 (32.7)	44 (33.3)	42 (32.1)	0.826
Other sites	89 (33.8)	37 (28.0)	52 (39.7)	0.046

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; CNS, central nervous system

[a] *De novo* (as opposed to recurrent) MBC indicates < 30 days between EBC and MBC diagnoses

[b] Visceral involvement includes metastasis of lung, liver central nervous system, and other visceral sites

[c] Metastasis of other sites refers to the metastasis of soft tissue, pleura, peritoneum, etc



Neoadjuvant therapy efficacy	ER+/PR+ (n=110) (%)	ER+/PR- (n=45) (%)	ER-/PR+ (n=15) (%)	ER-/PR- (n=159) (%)
pCR (%)	36 (32.7)	17 (37.8)	6 (40.0)	73 (45.9)

Neoadjuvant therapy efficacy	HR+ (n=170) (%)	HR- (n=159) (%)
pCR (%)	59 (34.7)	73 (45.9)

Fig. 2 Efficacy of neoadjuvant therapy by HR status (**a**) and ER/PR status (**b**) in HER2-positive patients. Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor, pCR: pathological complete remission

Clinical outcomes and prognostic factors

Up to the latest follow-up date, 9.9% (46/466) of patients in the HR-positive cohort and 14.6% (53/362) of patients in the HR-negative cohort had died. The median OS of all enrolled patients was 135 months (Fig. 4a). The median OS of patients in HR-positive cohort was not reached, compared with 116 months of patients in HR-negative cohort. Kaplan-Meier estimated curves showed that OS was significantly better in HR+/HER2+patients than in HR-/HER2+patients (P=0.047; hazard ratio, 0.67; 95% CI, 0.45-1.00) (Fig. 4b). In addition, ER+/PR+subgroup had significantly better OS than ER-/PR- subgroup (P=0.025; hazard ratio, 0.59; 95% CI, 0.38–0.92), whereas

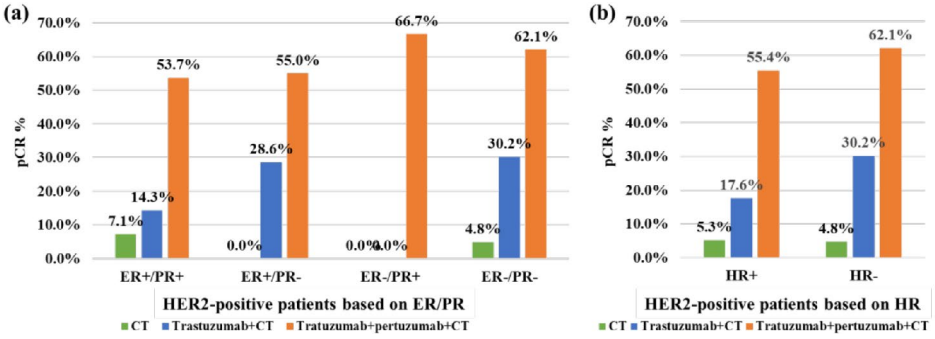


Fig. 3 The pCR rates by HR status (**a**) and ER/PR status (**b**) in HER2-positive patients. Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; pCR, pathological complete remission; CT, chemotherapy

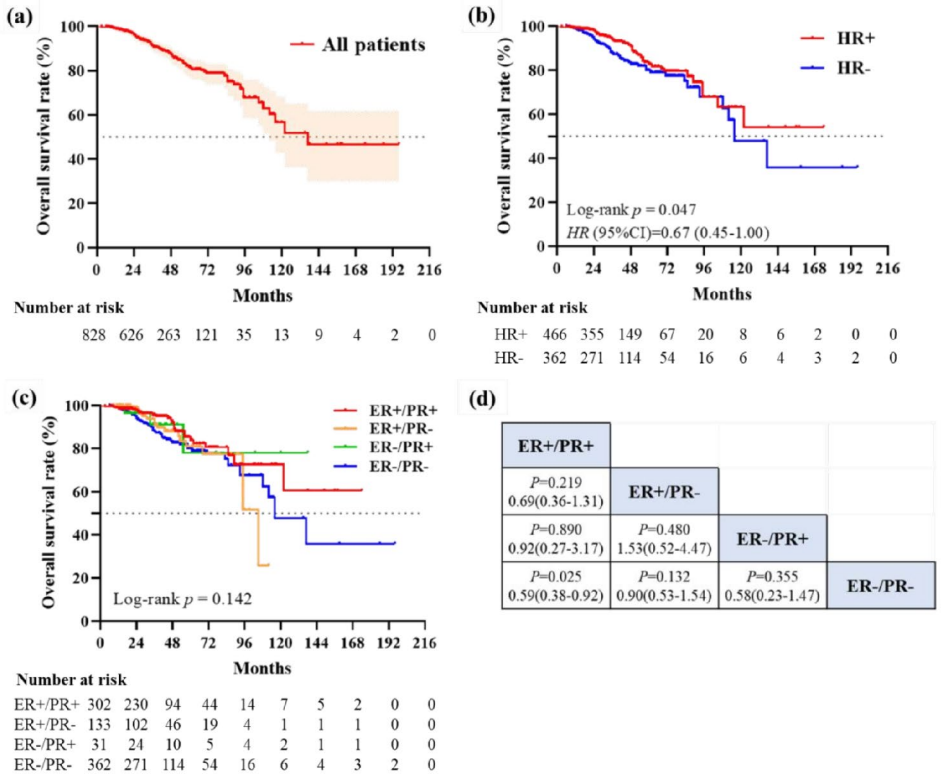


Fig. 4 OS by HR status and ER/PR status in HER2-positive patients. (**a**) Kaplan-Meier estimated OS in all HER2-positive patients included. (**b**) Kaplan-Meier estimated OS by HR status in HER2-positive patients. (**c**) Kaplan-Meier estimated OS by ER/PR status in HER2-positive patients. (**d**) Data are presented as *P* value and hazard ratios (95% CI). Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; OS, overall survival rate; *HR*, hazard ratio; CI, confidence intervals

no significant difference in OS was observed among other subgroups based on ER and PR (Fig. 4c and d).

By data cutoff, a total of 199 DFS events occurred in 762 patients (excluding 65 patients with de novo MBC and 1 patient who did not undergo surgery), including 23.0% (99/431) of patients in the HR-positive cohort and 30.2% (100/331) of patients in the HR-negative cohort had progressed or died. The median DFS of 762 patients was 76 months (Fig. 5a). Kaplan-Meier estimated curves showed that DFS was significantly better in HR+/HER2+patients than in HR-/HER2+patients ($P=0.010$; hazard ratio, 0.70; 95% CI, 0.53–0.93) (Fig. 5b). In the first 6 years after diagnosis of breast cancer, HR+/HER2+patients had a lower risk of recurrence than HR-/HER2+patients, but after 6 years, the recurrence risk of HR-/HER2+patients decreased rapidly and was lower than that of HR+/HER2+patients. In addition, ER+/PR+subgroup had significantly better DFS than ER-/PR- subgroup ($P<0.001$; hazard ratio, 0.37; 95% CI, 0.27–0.51) and ER-/PR+subgroup ($P=0.042$; hazard ratio, 0.49; 95% CI, 0.19–1.25),

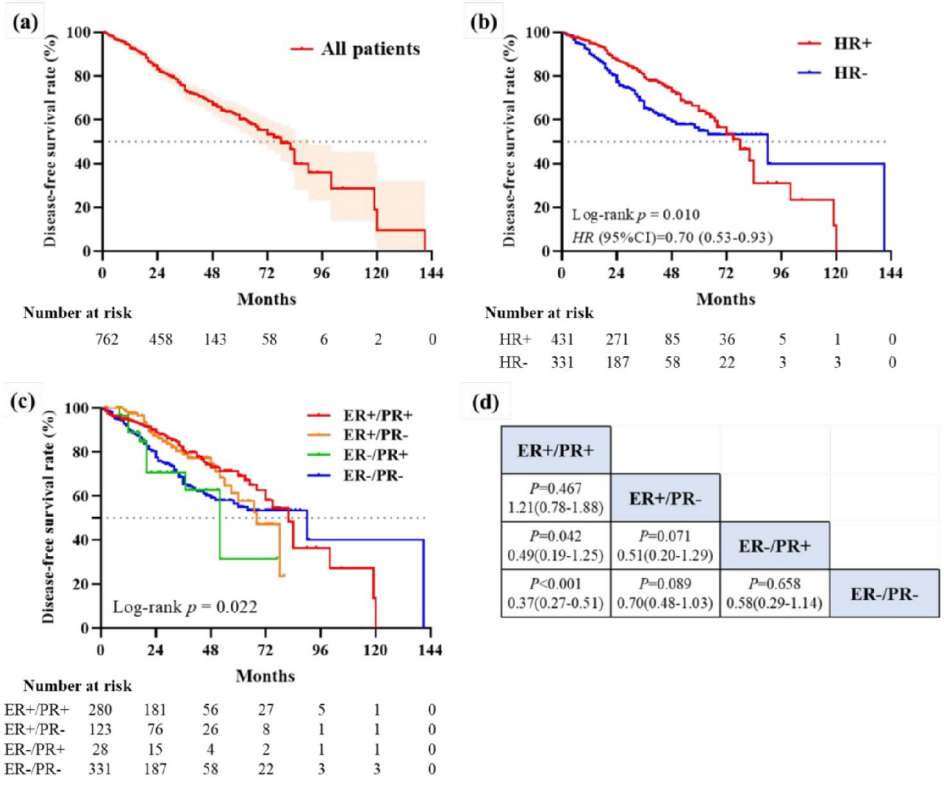


Fig. 5 DFS by HR status and ER/PR status in HER2-positive patients. (**a**) Kaplan-Meier estimated DFS in all HER2-positive patients included. (**b**) Kaplan-Meier estimated DFS by HR status in HER2-positive patients. (**c**) Kaplan-Meier estimated DFS by ER/PR status in HER2-positive patients. (**d**) Data are presented as *P* value and hazard ratios (95% CI). Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor; DFS, disease-free survival rate; *HR*, hazard ratio; CI, confidence intervals

whereas no significant difference in DFS was observed among other subgroups based on ER and PR (Fig. 5c and d).

Of all patients enrolled, 263 patients were diagnosed with advanced breast cancer by the end of follow-up. Among them, 132 patients with HR+/HER2+, 33.3% (44/132) died, and 131 patients with HR-/HER2+, 40.5% (53/131) died. The median advanced-OS of all patients with advanced breast cancer was 55 months (Fig. 6a). The median advanced-OS of patients in both the HR-positive and HR-negative cohorts was 55 months (Fig. 6b). Kaplan-Meier analysis showed no significant difference in advanced-OS between HR+/HER2+patients and HR-/HER2+patients ($P=0.378$), and similarly, there was no significant difference in advanced-OS between subgroups based on ER and PR (Fig. 6c and d).

The results of univariate Cox regression analysis suggested that HR was associated with OS and DFS and was a protective factor. Considering potential bias, we performed multivariate Cox regression analysis adjusting for baseline characteristics and confirmed that HR-positive status was an independent protective factor for OS ($P=0.032$; hazard ratio, 0.61; 95% CI, 0.39–0.96) and DFS ($P=0.001$; hazard ratio, 0.61; 95% CI, 0.46–0.81). Moreover, Ki-67>30%, HER2 heterogeneity, HER2 status of IHC 2+and FISH +, positive axillary lymph nodes (ALNs), neoadjuvant therapy, no adjuvant HER2-targeted therapy, liver metastasis, and brain/CNS metastasis were independent risk factors for OS. Positive ALNs, no adjuvant radiotherapy, and no adjuvant HER2-targeted therapy were independent risk factors for DFS (Table S5 and Table S6).

First-line treatment patterns and outcomes in HER2-positive patients with MBC

At data cutoff, 99.2% (131/132) of the HR-positive cohort and 99.2% (130/131) of the HR-negative cohort had received first-line systemic treatment for MBC. As shown in Table 4, in the HR-positive cohort, the most common first-line regimen was HER2-targeted therapy plus chemotherapy, administered to 63 (47.7%) patients, with single-targeted HER2 therapy [trastuzumab only or a tyrosine kinase inhibitor (TKI)] more common than dual-targeted HER2 therapy [28.0% (37/132) vs. 19.7% (26/132)]. The second most common regimen was HER2-targeted therapy plus chemotherapy sequential endocrine therapy, received by 34 (25.8%) patients, with single-targeted HER2 therapy (trastuzumab only or

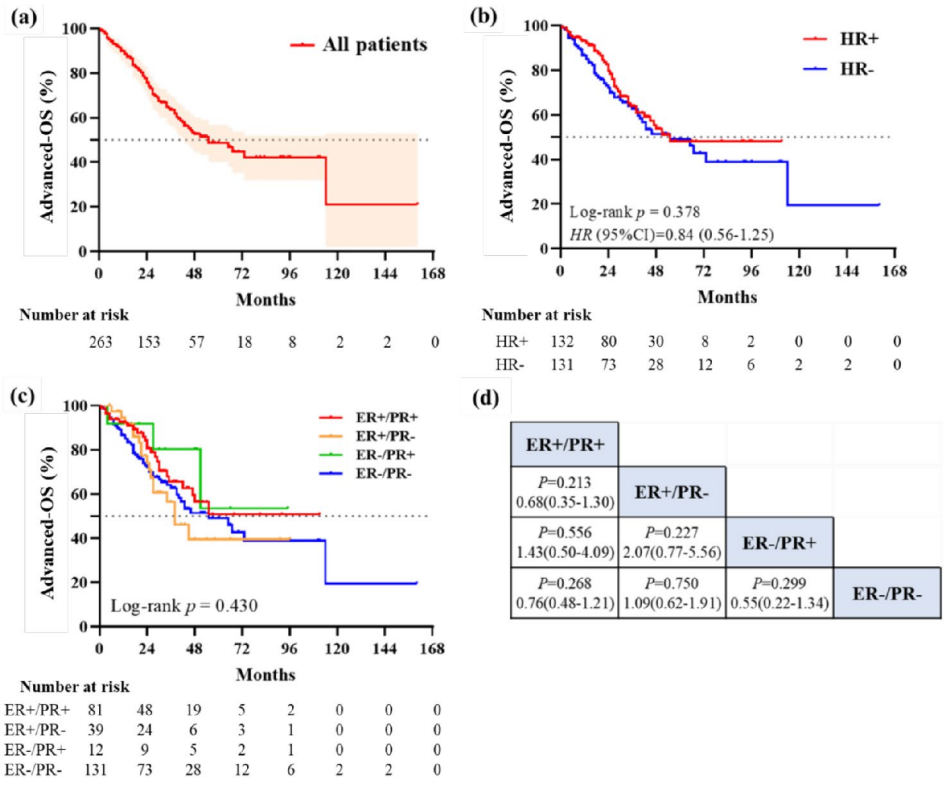


Fig. 6 Advanced-OS by HR status and ER/PR status in HER2-positive patients with advanced breast cancer. (**a**) Kaplan-Meier estimated advanced-OS in all HER2-positive patients with advanced breast cancer. (**b**) Kaplan-Meier estimated advanced-OS by HR status in HER2-positive patients with advanced breast cancer. (**c**) Kaplan-Meier estimated advanced-OS by ER/PR status in HER2-positive patients with advanced breast cancer. (**d**) Data are presented as *P* value and hazard ratios (95% CI). Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PR, progesterone receptor, OS: overall survival rate; *HR*, hazard ratio; CI, confidence intervals

Table 4 First-line treatment by HR status in HER2-positive MBC patients

Systemic therapy regimens	HR+/HER2+ (*n* = 132) (%)	HR-/HER2+(*n* = 131) (%)
HER2-targeted therapy + chemotherapy → endocrine therapy	34 (25.8)	6 (4.6)
Single-target therapy [a] + chemotherapy → endocrine therapy	22 (16.7)	5 (3.8)
Dual-target therapy [b] + chemotherapy → endocrine therapy	12 (9.1)	1 (0.8)
HER2-targeted therapy + chemotherapy	63 (47.7)	94 (71.8)
Single-target therapy + chemotherapy	37 (28.0)	52 (39.7)
Dual-target therapy + chemotherapy	26 (19.7)	42 (32.1)
HER2-targeted therapy + endocrine therapy	9 (6.8)	0 (0.0)
Single-target therapy + endocrine therapy	6 (4.5)	0 (0.0)
Dual-target therapy + endocrine therapy	3 (2.3)	0 (0.0)
Chemotherapy → endocrine therapy	6 (4.5)	0 (0.0)
Chemotherapy only	6 (4.5)	20 (15.3)
HER2-targeted therapy only	5 (3.8)	10 (7.6)
Endocrine therapy only	8 (6.1)	0 (0.0)
No systemic treatment received	1 (0.8)	1 (0.8)

Abbreviations: HR, hormone receptor; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer

[a] Single-target therapy refers to the use of only one HER2-targeted agent, such as trastuzumab or a small-molecule tyrosine kinase inhibitor (TKI, including lapatinib, neratinib, tucatinib, or pyrotinib)

[b] Dual-target therapy refers to the combination of two HER2-targeted agents, such trastuzumab combined with pertuzumab or trastuzumab plus a TKI

"→" represent sequential treatment

a TKI) more common than dual-targeted HER2 therapy [16.7% (22/132) vs. 9.1% (12/132)]. In addition, only 6.8% (9/132) of patients were treated with HER2-targeted therapy plus endocrine therapy, and similarly, single-targeted HER2 therapy (trastuzumab only or a TKI) was more common than dual-targeted HER2 therapy [4.5% (6/132) vs. 2.3% (3/132)]. In the HR-negative cohort, the most common first-line regimen was HER2-targeted therapy plus chemotherapy [74.8% (94/131)]. Likewise, single-targeted HER2 therapy (trastuzumab only or a TKI) was more common than dual-targeted HER2 therapy [39.7% (52/131) vs. 32.1% (42/131)]. Patients with HR-positive and HR-negative disease received HER2-targeted therapies in similar proportions [84.1% (111/132) vs. 84.0% (110/131)], but patients with HR-positive disease were treated with chemotherapy less commonly than those with HR-negative disease [82.6% (109/132) vs. 90.9% (120/131)].

To investigate the effect of receiving endocrine therapy in first-line treatment on the survival outcomes of HR+/HER2+patients with MBC, HR+/HER2+patients were divided into two groups. Patients who received endocrine therapy in first-line treatment were categorized as those who received endocrine therapy in first-line treatment, regardless of whether they received targeted therapy or chemotherapy or a combination of both ($n=57$). Patients who had not used any endocrine therapy in first-line but had received chemotherapy or targeted therapy or a combination of both in first-line treatment were classified as the group that did not receive endocrine therapy in first-line treatment ($n=75$). Kaplan-Meier survival curves of the two groups showed that the advanced-OS and PFS in the endocrine therapy group were significantly longer than those in the non-endocrine therapy group. Median advanced-OS was not yet estimable in the endocrine therapy group and 38 months in the non-endocrine therapy group ($P<0.001$; hazard ratio, 0.33; 95% CI, 0.18–0.59). Median PFS was 24 months and 9 months in the endocrine therapy group and non-endocrine therapy group, respectively ($P<0.001$; hazard ratio, 0.38; 95% CI, 0.25–0.58) (Fig. 7).

To explore the effect of sequential endocrine therapy after receiving HER2-targeted therapy plus chemotherapy in first-line treatment on the survival outcome of HR+/HER2+patients with MBC, HR+/HER2+patients were divided into two groups, namely, sequential endocrine therapy group ($n=34$) and non-sequential endocrine therapy group ($n=62$). Kaplan-Meier survival curves of the two groups showed that the advanced-OS and PFS in the sequential endocrine therapy group were significantly longer than those in the non-sequential endocrine therapy group. Median advanced-OS was not yet estimable in the sequential endocrine therapy group and 34 months in the non-sequential endocrine therapy group ($P<0.001$; hazard ratio, 0.05; 95% CI, 0.03–0.12). Median PFS was 29 months and 10 months in the sequential endocrine therapy group and non-sequential endocrine therapy group, respectively ($P<0.001$; hazard ratio, 0.35; 95% CI, 0.21–0.57) (Fig. 8).

Receptor status heterogeneity and outcomes in HER2-positive patients

Among the patients with recurrent disease, the receptor status of both metastatic and primary tumors was known in 131 patients. As shown in Table S7, inconsistent ER and PR status was observed in 13.7% and 25.2% of cases, respectively. Tumor ER status converted from ER-positive primary to ER-negative metastatic in 7.6% of patients, versus 6.1% who converted from ER-negative to ER-positive. Tumor PR status is more commonly converted from PR-positive primary to PR-negative metastatic (18.3%) than from PR-negative to PR-positive (6.9%). Moreover, inconsistent HER2 status in primary and metastatic tumors was observed in 25.2% of cases. Conversion of HER2 status from primary HER2-positive to metastatic HER2-negative (12.2%) was roughly the

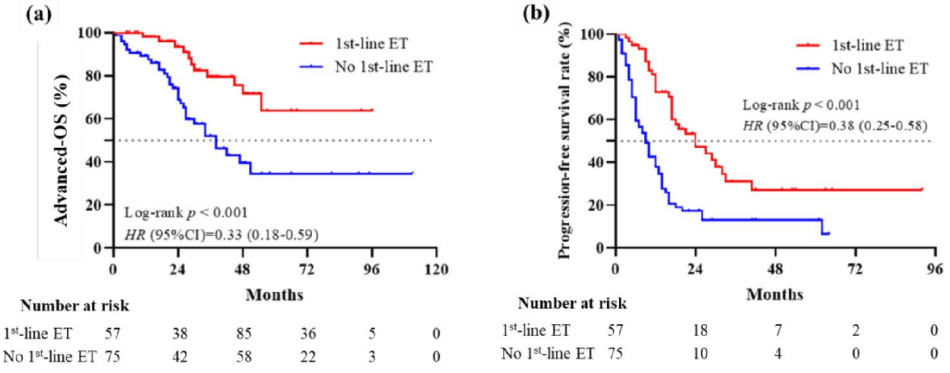


Fig. 7 Advanced-OS (**a**) and PFS (**b**) in HR+/HER2+patients with or without endocrine therapy in the first line treatment. Abbreviations: OS: overall survival rate; PFS, progression-free survival; ET: endocrine therapy; *HR*, hazard ratio; CI, confidence intervals

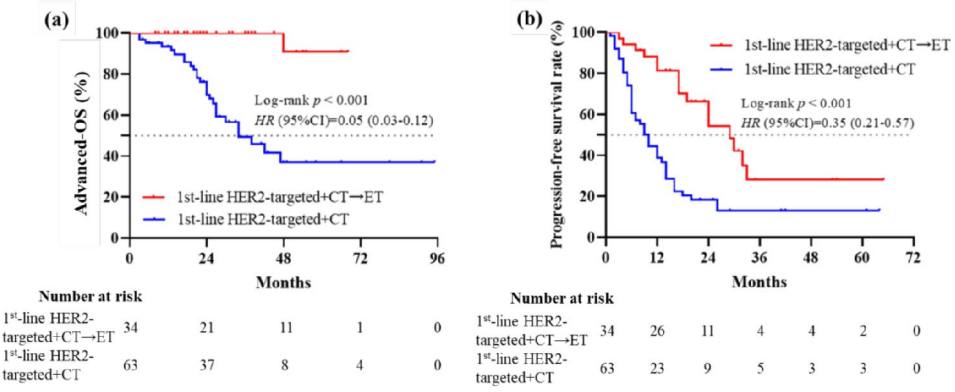


Fig. 8 Advanced-OS (**a**) and PFS (**b**) in HR+/HER2 + patients with or without sequential endocrine therapy in the first line treatment. Abbreviations: HER2, human epidermal growth factor receptor 2; OS: overall survival rate; PFS, progression-free survival; ET: endocrine therapy; CT: Chemotherapy; *HR*, hazard ratio; CI, confidence intervals

same proportion as HER2-negative to HER2-positive (13.0%).

To investigate the impact of HER2 heterogeneity on the prognosis of HER2-positive breast cancer, patients with HER2-positive advanced breast cancer who had undergone at least two HER2 assays of tumor tissues (n=182) were divided into two groups with HER2 heterogeneity (n=42) and without HER2 heterogeneity (n=140). Survival analysis showed no significant difference in advanced-OS between the two groups (P=0.108; hazard ratio, 0.65; 95% CI, 0.37–1.17). Median advanced-OS was 67 and 40 months in the group with and without HER2 heterogeneity, respectively. However, patients with HER2 heterogeneity tended to have worse PFS than those without HER2 heterogeneity (P=0.058; hazard ratio, 0.70; 95% CI, 0.46–1.07). Median PFS was 12 and 12 months in the group with and without HER2 heterogeneity, respectively (Figure S1).

To explore the effect of HR status on the prognosis of patients with HER2 heterogeneity, patients with HER2 heterogeneity (n=42) were divided into two groups of HR-positive (n=28) and HR-negative (n=14) according to HR status. The proportion of patients with HER2 heterogeneity was significantly higher in the HR-positive group than in the HR-negative group (30.1% vs. 15.7%, P=0.021) (Table S3). Survival analysis showed no significant difference in advanced-OS between the two groups (P=0.890; hazard ratio, 0.94; 95% CI, 0.37–2.37). Median advanced-OS was 38 and 41 months in the HR-positive and HR-negative group, respectively. However, the HR-positive group tended to have better PFS than the HR-negative group (P=0.056; hazard ratio, 0.92; 95% CI, 0.45–1.90). Median PFS was 12 and 9 months in the HR-positive and HR-negative group, respectively (Figure S2).

Discussion

In this retrospective study, we found that HR status had a significant impact on clinicopathological features and metastatic patterns as well as survival outcomes in patients with HER2-positive breast cancer. HR+/HER2+tumors exhibited a comparatively lower histological grade, lower Ki67 level, and lower HER2 immunohistochemical staining, indicative of favorable clinical characteristics. These were consistent with previous studies reporting that HR-/HER2+tumors behave more aggressively, including a higher proportion of advanced and high-grade tumors compared to HR+/HER2+tumors [16]. Concerning the pattern of metastatic spread, HR+/HER2+patients presented an extremely high frequency of bone metastases at 61.4%, whereas HR-/HER2+tumors tended to metastasize to viscera, including the brain and lungs. Several studies reported significant correlations between breast cancer molecular subtypes and metastatic sites [17–21], with bone metastases being the most prevalent in HR+/HER2- tumors (79.7%), followed by HR+/HER2+tumors (61.0%), while brain metastases were more frequent in patients with HR-/HER2+and triple-negative breast cancers, accounting for 25–46% and 30–55% of all brain metastases from breast cancer, respectively [22]. These results suggested that the HR+/HER2+subtype is associated with milder tumor behavior compared to the HR-/HER2+subtype and represents an independent biological subtype.

Our results demonstrated that the relapse patterns of HR+/HER2+and HR-/HER2+tumors differed over time. During the first 6 years, HR-/HER2+tumors recurred more frequently than HR+/HER2+tumors. However, the risk of recurrence in HR+/HER2+tumors remained relatively stable and surpassed that of HR-/HER2+patients after 6 years. Similar to previous published clinical trials in HER2-positive breast cancer, superior outcomes of HR-positive patients were only observed in the first five

years and the differences disappeared over time [23, 24]. Therefore, personalized follow-up strategies are vital to address the different early recurrence patterns of HR+/HER2+and HR-/HER2+patients.

In terms of prognostic profiles, our study showed that HR+/HER2+breast cancer was significantly associated with improved OS and DFS over HR-/HER2+breast cancer, which was in line with previously published reports [25–27]. However, no significant difference in advanced-OS was observed between these two subtypes. In the multivariate analysis, HR positivity is associated with better survival outcomes than HR negativity. According to PAM50-defined intrinsic subtypes, HER2-E is the predominant subtype in HR-/HER2+breast cancers (75%), whereas it accounts for only 30% of HR+/HER2+, the majority of which are luminal subtypes [6]. This genomic profile reveals the heterogeneity of biological behavior in HR+/HER2+and explains the reduced pCR rate after anti-HER2 neoadjuvant therapy, however with better survival outcomes.

Regarding treatment options, HR+/HER2+patients more commonly underwent breast-conserving surgery, which may be related to the fact that the smaller size and lower malignancy of HR+/HER2+tumors than HR-/HER2+tumors [26]. Additionally, HR+/HER2+patients were less likely to receive neoadjuvant therapy, which may be associated with poorer efficacy of neoadjuvant therapy in HR+/HER2+patients compared to HR-/HER2+patients. Our analysis confirmed that HR+/HER2+patients had a significantly lower pCR rate than HR-/HER2+patients, regardless of the neoadjuvant regimen received. However, in the neoadjuvant setting, irrespective of HR status, HER2-targeted therapy plus chemotherapy significantly improved the pCR rate in HER2-positive patients compared with chemotherapy alone, and trastuzumab plus pertuzumab can further enhance efficacy. These findings were consistent with previous clinical studies (NeoSphere [28] and PEONY study [29]). At present, major guidelines recommend the TCbHP (docetaxel, carboplatin, trastuzumab, pertuzumab) regimen as the first choice for neoadjuvant treatment of HER2-positive breast cancer. However, both preclinical and clinical data have indicated that extensive crosstalk between the ER and HER2 signaling pathways leading to dual inhibition of both pathways may be essential to prevent resistance. PerELISA study [30] demonstrated that HR+/HER2+patients with reduced Ki67 after 2 weeks of preoperative letrozole treatment achieved meaningful pCR rates without chemotherapy. PAM50 intrinsic subtypes further enhance the ability to identify a subset of patients who may be spared from chemotherapy.

In the first-line setting, our results confirmed that HER2-targeted therapy plus chemotherapy and sequential endocrine therapy significantly improved survival in patients with HR+/HER2+breast cancer, only 25.8% of patients in this real-world setting received such treatment. Currently, HER2-targeted therapy-based combination (trastuzumab, pertuzumab, and a taxane) is still recommended as first-line treatment for patients with HER2-positive MBC, irrespective of HR status [31, 32]. Generally, endocrine therapy is offered to HR+/HER2+patients as maintenance therapy after the cessation of chemotherapy. Observational studies registHER [33] and SystHERs [34] suggested that HER2-targeted therapy plus chemotherapy followed by sequential endocrine maintenance therapy significantly prolonged PFS and OS in HR+/HER2+patients in the first-line setting, but only 29.4% and 34.9% of patients received sequential endocrine therapy, respectively. Compared to Western countries, the proportion of HR+/HER2+patients receiving sequential endocrine therapy in the first-line setting was relatively lower at 25.8% in this study. This indicated that some HR+/HER2+patients in the real world may be under-treated with endocrine therapy. With increasing research on the de-escalated treatment for HR+/HER2+subset, it remains controversial which is the optimal partner for anti-HER2 therapy, endocrine therapy or chemotherapy. A real-world study [35] based on the US National Cancer Database showed that endocrine therapy plus anti-HER2 therapy as first-line treatment significantly improved the 5-year survival rate (47.5% vs. 39.8%, $P<0.001$) compared with chemotherapy plus anti-HER2 therapy. The phase III SYSUCC-002 study [36] confirmed that trastuzumab plus endocrine therapy was non-inferior to trastuzumab plus chemotherapy (PFS: 19.2 months vs. 14.8 months; hazard ratio, 0.88; 95% CI, 0.71–1.09; $P<0.0001$) but with reduced toxicity. Hence, HER2-targeted therapy combined with endocrine therapy may be a more appropriate first-line treatment option for low-risk patients with HR+/HER2+MBC, illustrating a potential modality shift toward a chemotherapy-sparing regimen. Moreover, both the PERTAIN [37] and ALTERNATIVE [38] studies have demonstrated that dual HER2 blockade therapy (trastuzumab plus pertuzumab or lapatinib) combined with endocrine therapy significantly improved PFS in HR+/HER2+patients compared to trastuzumab plus endocrine therapy. A recent network meta-analysis [39] including 20 randomized controlled trials (RCTs) suggested that for HR+/HER2+MBC, the regimens containing dual HER2 blockade, either in combination with chemotherapy (CT) or endocrine therapy (ET), displayed better efficacy. Compared with CT-containing regimens, ET-containing regimens have superior efficacy and similar safety profiles. ASCO guidelines state that for selected patients with low disease burden, the presence of comorbidities, and long disease-free intervals, clinicians may recommend either endocrine therapy

plus HER2-targeted therapy or endocrine therapy alone [31]. With the wide application of CDK4/6 inhibitors in HR-positive breast cancer, CDK4/6 inhibitors in HR+/HER2+patients have emerged as a focus in clinical studies. The phase II monarcHER trial [40] suggested that in patients with HR+/HER2+MBC, the combination of abemaciclib, fulvestrant, and trastuzumab significantly improved PFS versus standard-of-care chemotherapy plus trastuzumab (8.3 vs. 5.7 months; hazard ratio, 0.67; $P=0.051$) and numerically prolonged OS (31.1 months vs. 20.7 months). The phase II PLEASURABLE study [41] demonstrated the efficacy and safety of pyrotinib and dalpiciclib plus endocrine therapy (letrozole or fulvestrant) in HR+/HER2+MBC. The objective response rate (ORR) was 68.1% and the disease control rate was 100%. The novel fully oral triplet combination has been proven to be safe and effective, potentially providing a total oral chemotherapy-free regime for patients with HR+/HER2+MBC. Therefore, the combination of CDK4/6 inhibitors based on the dual blockade of HER2 and HR pathways provides an alternative promising therapeutic option in heavily pretreated patients with HR+/HER2+MBC.

In the aspect of HER2 status, we found that equivocal HER2 immunohistochemistry results (2+) were more frequent in HR-positive tumors and discordance between two HER2 assays (defined as HER2 heterogeneity in this study) was more common in HR-positive tumors. Furthermore, discordant HER2 status in primary and metastatic tumors was observed in 25.2% of cases, which was similar to the 25% previously reported in the literature [14]. Survival analysis showed that patients with HER2 heterogeneity tended to have worse PFS. Multiple lines of evidence indicated that HER2 heterogeneity was closely related to clinical outcomes in breast cancer patients. A phase II clinical trial [42] assessed the impact of HER2 heterogeneity on the efficacy of neoadjuvant therapy with trastuzumab emtansine (T-DM1) plus pertuzumab in patients with HER2-positive breast cancer.10% of patients were assessed as HER2 heterogeneous, and 81% of these patients were also HR-positive. The results showed that the pCR rate was 55% in the non-heterogeneous subgroup and 0% in the heterogeneous group ($P<0.0001$, adjusted for HR status). HER2 heterogeneity may reduce the response of neoadjuvant HER2-targeted therapies. In addition, the status of HER2 in breast cancer may change in response to treatment. A study of HER2-positive patients with residual lesions after neoadjuvant treatment with trastuzumab plus chemotherapy showed that one-third of tumors showed loss of HER2 amplification, which was associated with poor recurrence-free survival [43]. The PAMELA study [44] performed gene sequencing of HER2-E tumors before and after neoadjuvant treatment with lapatinib plus trastuzumab. The results showed that the proportion of luminal A subtypes increased from baseline at day 14 of treatment, while the proportion of HER2-E and luminal B subtypes decreased from baseline. These conversions were more pronounced in the HR+/HER2+versus HR-/HER2+subgroups, and the switch from HER2-E to the luminal A was significantly associated with a decrease in the pCR rate. The above studies illustrated that alterations in HER2 expression after HER2-targeted therapy can exert a profound impact on patient prognosis. Therefore, it is crucial to reassess HER2 status in tissue biopsy samples from residual lesions after neoadjuvant therapy as well as recurrent or metastatic sites.

This study has several limitations. Firstly, this study is retrospective and single-centered, which may lead to inevitable biases in characteristics and treatment patterns between different groups. Well-designed large prospective clinical studies are required to validate the findings. Secondly, treatment choices based on clinical features and tumor aggressiveness could lead to selection bias in the outcome of specific treatments. For example, after induction chemotherapy, those patients with more aggressive disease may be switched to other chemotherapy regimens after disease progression rather than sequential endocrine therapy. This removes such patients with invasive disease from the group receiving sequential treatment, thus potentially selecting for better outcomes among the remaining patients. Thirdly, reimbursement conditions for targeted therapies limit the availability of anti-HER2 agents and restrict the use of anti-HER2 agents in combination with other medications.

In the real world, clinicians tend to focus more on the application of chemotherapy combined with targeted therapies to control disease progression in HR+/HER2+breast cancers, while neglecting the importance of endocrine therapy. With the breakthroughs in the efficacy of various innovative endocrine agents such as CDK4/6 inhibitors and antibody-drug conjugates (ADCs), an increasing number of studies will be performed on endocrine therapy plus HER2-targeted therapy or multi-targeted combination regimens for HR+/HER2+patients. Biomarkers of populations that could benefit from de-escalated therapy will gradually be revealed, with the goal of better balancing survival outcomes with quality of life for patients.

Conclusions

In conclusion, this study illustrates the dramatic differences in clinical outcomes related to HR status in HER2-positive breast cancer, including clinicopathological features, metastatic patterns, and overall prognosis. Furthermore, we observed that the addition of maintenance endocrine therapy following HER2-targeted therapy and chemotherapy was associated with improved survival in

HR+/HER2+patients, but some patients had inadequate endocrine therapy. To optimize disease management in this subset of HR+/HER2+breast cancer, more large-scale RCTs are warranted to explore the optimal combination and sequencing of multiple treatments, in order to tailor personalized therapeutic strategies.

Abbreviations

HR	Hormone receptor
HER2	Human epidermal growth factor receptor 2
HER2-E	HER2-enriched
HR+/HER2+	HR-positive /HER2-positive
HR-/HER2+	HR-negative/HER2-positive
CI	Confidence interval
HR	Hazard ratio
DFS	Disease-free survival
OS	Overall survival
PFS	Progression-free survival
ER	Estrogen receptor
PR	Progesterone receptor
pCR	Pathologic complete response rate
ASCO/CAP	American Society of Clinical Oncology/College of American Pathologists
IHC	Immunohistochemistry
FISH	Fluorescence in situ hybridization
EBC	Early breast cancer
MBC	Metastatic breast cancer
MP	Miller-Payne
IDC	Invasive ductal carcinoma
ECOG	Eastern Cooperative Oncology Group
BCS	Breast-conserving surgery
CNS	Central nervous system
RCTs	Randomized controlled trials
T-DM1	Trastuzumab emtansine
TKI	Tyrosine kinase inhibitor
ADCs	Antibody-drug conjugates
HER2-E	HER2-enriched
CT	Chemotherapy
ET	Endocrine therapy
ALNs	Axillary lymph nodes
ORR	Objective response rate

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-12974-4.

Supplementary Material 1

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Author contributions

RR carried out the study conception and design. RR and SDZ performed the data analysis, study interpretation and draft the manuscript. DFD and JY reviewed and revised the manuscript. YZ, XYH, HW, YF, YSZ and YFQ participated in data collection. All authors read and approved the final manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

This article does not contain any studies with human participants performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was reviewed and approved by the independent Ethical Committees of the First Affiliated Hospital of Xi'an Jiaotong University.

Consent for publication

Not applicable.

Informed consent

Informed consent was obtained from all participants or, if participants are under 18, from a parent and/or legal guardian.

Competing interests

The authors declare no competing interests.

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